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Cortisol-related hippocampal-extrastriate functional connectivity explains the adverse effect of cortisol on visuospatial retrieval

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ABSTRACT

Cortisol is known to affect visuospatial memory through its major binding site in the brain, the hippocampus. The synchronization of neural activity between the hippocampus, prefrontal cortex (PFC), and visual cortex is presumed to be essential for the formation of visuospatial memory because of their visuospatial learning-dependent neuroplasticity. However, it remains unclear how hippocampal connectivity with the PFC and visual cortex is involved in the relationship between cortisol and visuospatial memory in humans. We thus investigated whether functional connectivity (FC) of the hippocampus, specifically its rostral and caudal subdivisions, mediates the relationship between visuospatial memory and endogenous cortisol. One-hundred sixty-six healthy young adults underwent standard neuropsychological tests to assess visuospatial construction (a complex figure copying test) and retrieval (the corresponding recall test) and collected their saliva at 6-time points across 2 consecutive days for measurement of daily cortisol concentrations (dCOR). Ninety of them received resting-state fMRI scans. Greater dCOR was significantly associated with better figure copying performance, but contrastingly with poorer figure recall. In proportion to dCOR, the rostral hippocampus (rHC) showed significantly increased FC with the PFC (including its dorsolateral and medial parts) and the inferior lateral occipital cortex (iLOC), while the caudal hippocampus had increased FC with the anterior middle temporal cortex. Of the cortisol-related hippocampal connectivity, the rHC-iLOC FC was specifically correlated with figure recall and showed complete mediation for the negative relationship of dCOR with figure recall. These results suggest that cortisol might have enhancing effects on visuospatial encoding as well as impairing effects on visuospatial retrieval, possibly due to its occupancy patterns of corticosteroid receptors. Cortisol's adverse effects on visuospatial retrieval might be explained through cortisol-related rostral hippocampal connectivity with the iLOC, which is a part of the extrastriate cortex implicated in visuospatial perception. Thorough dissection of hippocampal-prefrontal-extrastriate connectivity might facilitate the understanding of neural mechanisms underlying cortisol's contrasting effects on encoding (or consolidation) and retrieval of visuospatial information.

Abbreviations: FC, functional connectivity; rHC, rostral hippocampus; iLOC, inferior occipital cortex; dl/mPFC, dorsolateral/medial prefrontal cortex

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1. Introduction

Glucocorticoids (mainly cortisol in humans) are a class of steroid hormones that are synthesized in the adrenal cortex. Cortisol specifically binds to glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs), both of which are abundantly expressed in the hippocampus (Reul and de Kloet, 1985). Cortisol exerts a regulatory effect on the homeostasis of cardiovascular, metabolic, and immunologic responses for general adaptation to stress through the hypothalamic-pituitary-adrenal (HPA) axis (McEwen, 2000); however, chronic exposure to excessive amounts of cortisol is known to destroy neurons in the hippocampus (McEwen et al., 2016; Sapolsky, 1992).

The hippocampus plays a critical role in memory. It contains neuronal assemblies responding distinctly to different spatial locations (OKeefe and Dostrovsky, 1971) and exhibits neuronal firing as well as functional activation during three-dimensional spatial memory tasks (Ekstrom et al., 2003; Hartley et al., 2003), which indicates its predominant involvement in spatial memory. Although previous lesion studies have reported that selective damage of the hippocampus causes amnesia of not only spatial but also non-spatial memory (for review, see Spiers et al., 2001), recent meta-analyses of functional magnetic resonance imaging (fMRI) studies have revealed that the hippocampus shows differential functions for its subdivisions (*e.g.*, anterior vs. posterior parts), as well as different types of memory (*e.g.*, spatial vs. non-spatial) (Persson and Söderlund, 2015; Robinson et al., 2015; Kühn and Gallinat, 2014)

Due to the fact that cortisol is highly relevant to the hippocampus, there has been extensive investigation into whether cortisol affects memory functions. There is ample evidence indicating that psychologically or pharmacologically stimulated cortisol release causes deterioration in performance of memory retrieval (Shields et al., 2017; Het et al., 2005; Sauro et al., 2003), despite inconsistent findings on encoding or consolidation (Shields et al., 2017; Het et al., 2005; Roozendaal, 2002; Wolf, 2009). Cortisol's negative effects on memory retrieval are generally associated with the occupancy of GRs (Wolf et al., 2016), which have a lower affinity to cortisol than MRs and thereby are phasically activated by exogenous cortisol elevation (Reul and de Kloet, 1985). However, in contrast to such exogenously stimulated cortisol, little research has been done on the unstimulated (endogenous) cortisol that substantially occupies and tonically activates the MRs under non-stimulation conditions (De Kloet et al., 1998). In studies investigating patients with Cushing's disease, which is characterized by excessive endogenous cortisol secretion, it has been observed that smaller hippocampal volumes are correlated with the severity of visuospatial memory impairments and length of hypercortisolemia (Resmini et al., 2012). In addition, Cushing's disease patients have been found to have more diminished functional activity in the hippocampus, dorsolateral parts of the prefrontal cortex (PFC), and the visual cortex (specifically the inferior lateral occipital cortex: iLOC) during a visual memory task than healthy controls (Ragnarsson et al., 2017). Above all, the PFC and iLOC, which similarly express GRs and involve spatial processing (Malikovic et al., 2016; Funahashi et al., 1989; Reul and de Kloet, 1985), show distinguished deactivation during encoding and retrieval (Ragnarsson et al., 2017). Furthermore, using the resting-state fMRI to detect intrinsic functional connectivity (FC) representing cortisol's tonic release more specifically, a couple of previous studies have demonstrated that the connectivity comprising these brain regions is altered as it depends on unstimulated cortisol levels even in healthy individuals (Soares et al., 2013; Veer et al., 2012). These findings suggest that greater circulation amount of endogenous cortisol could generally affect the construction and recall of visuospatial memory through such task-irrelevant and relatively static connectivity of the hippocampus with the PFC and visual cortex.

Indeed, the hippocampus is not a solitary structure in terms of its contributions to memory. It interacts with other brain regions such as the visual cortex and PFC, depending on the sensory modality of memory. For example, the visual cortex, specifically the inferior temporal gyrus (ITG) projecting to the PFC (Ungerleider et al., 1989) as well as the hippocampus (Webster et al., 1991), is known to show enhancement of selectivity for specific visual stimuli in the process of learning (McKee et al., 2014; Ranganath and DEsposito, 2005). In addition, the learning-dependent neuroplasticity in the visual cortex that is responsible for visual perception, such as the iLOC, is essential for the construction and retrieval of visual memory (Wheeler et al., 2000). Similarly, synchronization of neural activity between the hippocampus and PFC (including its medial part) has been shown to be crucial in spatial memory processing (Wang and Cai, 2006; Jones and Wilson, 2005). Therefore, the PFC and visual cortex conceivably synchronize with the hippocampus to implement visuospatial memory, and endogenous cortisol may affect the visuospatial aspect of memory by mediating the connectivity between these regions. However, no study has investigated how the hippocampal FC, as an index of its neural synchronization, could mediate the relationship between endogenous cortisol and visuospatial memory in humans, focusing on its intrinsic functional aspects.

The aim of the present study was three-fold: to determine 1) which cognitive functions, including the construction and retrieval of visuospatial memory, are specifically associated with endogenous cortisol, 2) with which hippocampal connectivity the endogenous cortisol is associated, and 3) whether the identified cortisol-associated hippocampal connectivity explains the relationship of cortisol with the cognitive function. We obtained a sizable sample of healthy young adults and used resting-state fMRI to measure intrinsic FC and neuropsychological tests to comprehensively assess cognitive functions, including visuospatial memory. We hypothesized that 1) greater levels of unstimulated cortisol concentrations measured through daily life would be associated with altered intrinsic FC of the hippocampus with PFC and visual cortex, as well as poorer performance in the construction and retrieval of visuospatial memory; and 2) such cortisol-associated hippocampal FC with PFC and visual cortex would explain the relationship between cortisol and visuospatial memory. Additionally, we explored whether FC throughout the whole brain would predict visuospatial memory, which may provide a clue to understanding the systematic neural network underlying visuospatial memory.

2. Methods

2.1. Participants

The present study was carried out under the approval of the Kitasato University Medical Ethics Organization (No. C11-690), and in accordance with the ethical guidelines determined by the National Ministry of Health, Labour and Welfare and the Declaration of Helsinki. Participants were recruited via advertisements in a local magazine and billboards at Kitasato University. The eligibility criteria of the study were (1) age from 20 to 35, (2) no Axis-I psychiatric disorders or substance-abuse history as determined using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), (3) no major medical illnesses, (4) no regular intake of psychotropics, steroids, or opioids, and (5) no regular intake of tobacco. One hundred and sixty-six individuals who met the criteria provided written informed consent: 94 women, mean age = 21.9 years, range = 20–35, standard deviation (SD) = 2.7.

For MRI scans, the inclusion criteria were (1) no metal embedded in the body or any medical appliance attached to the body, (2) able to remain in an MRI scanner (*e.g.*, no claustrophobia), (3) no history of brain injury or trauma with loss of consciousness over 10 min, (4) no regular use of psychotropics, steroids, opioids, or cold medicine that could affect blood-oxygen-level dependent (BOLD) signals. Of 166 participants, 10 were excluded due to a dental implant (n = 1), a past history of brain injury/trauma with loss of consciousness (n = 4), subarachnoid hemorrhage (n = 2), epilepsy (n = 2), and hydrocephalus

(n = 1). Of the remaining participants, who met the MRI inclusion criteria, 90 provided written informed consent for MRI scans: 51 women, mean age = 21.6 years, range = 20–33, SD = 2.1, and 93% right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. Study procedures

All participants underwent psychological assessment and saliva collection. The following demographic and physical status data were acquired: age, sex, body mass index (BMI), monthly alcohol consumption, and years of education, in addition to the results of neuropsychological tests. Women were asked to disclose the presence of menstrual irregularity, their typical menstrual period, and last menstruation date. None used oral contraceptives. Within 2 weeks after the assessment, participants were instructed to collect their saliva at home for 2 consecutive typical weekdays. The scoring methods for BMI, monthly alcohol consumption, and menstrual period are detailed in the Supplementary material.

Ninety participants who provided informed consent for MRI were scheduled to receive MRI scans within 2 weeks after the initial assessment. The average time interval between saliva collection and MRI scans was 0.9 ± 6.4 days. Thirty-four percent of these participants provided saliva samples prior to MRI scans. Of these participants, 46 (51%) performed a cognitive task, and then underwent resting-state fMRI sequence after 5 min break. The task, in which participants attended to a non-emotional target stimulus with emotional distractors, had no significant effect on hippocampal connectivity (see Supplementary material).

2.3. Neuropsychological assessment

Multiple domains of cognitive function were assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, 1998). The RBANS is standardized for the Japanese population and well established both in reliability and validity (Matsui et al., 2010). RBANS is a clinician-administered neuropsychological test for adults aged between 20 and 89 years and calculates age-adjusted scores according to each age group: 20–39, 40 s, 50 s, 60 s, 70 s, and 80 s. It includes the following 12 standard cognitive subtests: 1) list learning, 2) story memory, 3) figure copying, 4) line orientation, 5) picture naming, 6) semantic fluency, 7) digit span, 8) digit symbol coding, 9) list recall, 10) list recognition, 11) story recall, and 12) figure recall. The total scores of these subtests have high correlational coefficients in both test-retest and parallel-test methods (r = 0.94 and r = 0.84, respectively), indicating sufficient reliability (Matsui et al., 2010). The figure copying and figure recall tests are specifically relevant to visuospatial memory: participants are asked to carefully observe and copy a complex figure and then to recall and redraw the figure without any clue after the elapsing of a certain period of time. These tests are closely associated with visual memory facets but not with any verbal memory facet of the Wechsler Memory Scale – Revised (Wechsler, 1987) (specifically, figural memory and visual memory span for the figure copying, and figural memory, visual reproduction, and visual paired associates for the figure recall, which supports their construct validity (Matsui et al., 2010). RBANS's subtests comprise of five cognitive domains: immediate memory (subtests 1–2), visuospatial construction (3–4), language (5–6), attention (7–8), and delayed memory (9–12). The total index obtained from all the subtests provides an estimate of the overall intelligence quotient and shows a normal distribution, with mean ± SD = 100 ± 15.

In addition to RBANS, the trail-making test (TMT) was used (Reitan, 1992). In the TMT, Part A assesses selective attention and processing speed, and Part B assesses divided attention and set-shifting. Response time (RT) was measured as each performance score. Additionally, the ratio of Part B / Part A, called the TMT quotient (TMTQ), gives an estimate of executive functioning (Arbuthnott and Frank, 2000). Larger TMTQ values indicate poorer performance.

These neuropsychological tests were administered by experienced qualified clinical psychologists (Y.H. and N.M.) mostly in the afternoon (mean ± SD of the administration time = 1:35 pm ± 1:42).

2.4. Saliva collection and cortisol assay

Salivary cortisol was measured 3 times daily: upon awakening, 30 min after awakening, and at bedtime. At the first meeting with a participant, an experimenter fully explained the procedures and demonstrated saliva collection in front of the participant. Each participant was instructed to gently chew a swab in his/her mouth for approximately 1 min, and encouraged to practice taking his/her saliva using a sample tube, referring to a handout of detailed collection procedures. Saliva was collected on 2 consecutive typical weekdays using personalized kits with 6 tubes containing Salimetric Oral Swabs (Salimetrics, Inc., State College, PA), each labeled in a unique color with date and time of measurement (*e.g.*, *The 1 st day, at bedtime* in green). Participants were allowed to choose the day on which they would start saliva collection, provided it was a typical weekday within 2 weeks after the initial assessment, but were instructed never to collect saliva on the days when they would be engaged in any special activity or take a rest.

During the consecutive 2 days and 1 night before starting, the participants were required not to consume any alcohol. Similarly, taking any food or drink besides water, exercising, tooth-brushing, and showering or bathing was not allowed within 30 min after awakening or 1 h before bedtime. At awakening, participants were instructed to record the time they went to bed and woke up and to rate sleep quality and perceived stress on a 4-point scale (*i.e.*, 0–3). Collected saliva was stored in participants' house refrigerator during the 2 days of saliva collection. Within 24 h after completing saliva collection, the refrigerated samples were transported to the National Institute of Occupational Safety and Health (to author S. I.).

For the salivary assay, slowly thawed samples were centrifuged at 3000 rpm (G-force = 1710) for 15 min. Enzyme-linked immunoassay kits (IBL International, Hamburg, Germany) was used to determine salivary cortisol concentrations. Inter-assay and intra-assay concentration variations were below 7.3% and 9.3%, respectively. Based on the previous studies in which cortisol was assessed at three time points per day (*e.g.*, Short et al., 2016; Barnett et al., 2005), we focused on the sum of all the time points averaged across the 2 days as an index of daily cortisol concentration (dCOR), as it was shown to be a potent predictor of FC between HPA-axis regulatory regions such as the amygdala and hippocampus in our previous study focusing on emotional processing (Hakamata et al., 2017). Additionally, the area under the curve with respect to ground (AUC) was calculated as a reference index of dCOR, based on the following formula: $[(T1 + T2) \times Time_{T2\text{-}T1\ (h)} / 2] + [(T2 + T3) \times Time_{T3\text{-}T2\ (h)} / 2]$ (Pruessner et al., 2003). When these measures did not follow a normal distribution, as determined by the Shapiro-Wilk test, they were square-root transformed.

2.5. MRI acquisition

Anatomical and functional MRI scans were acquired using a 1.5-Tesla GE Signa scanner (Signa HDxt; GE Healthcare, Waukesha, WI, USA) with an 8-channel phased-array head coil. Participants were asked to lie down and stay motionless with their eyes closed, and not to move or fall asleep in the MRI scanner. Structural images were acquired using a 3D T1-weighted sequence (slice thickness without slice gap = 1.2 mm, field of view (FOV) = 240 mm, matrix = 288 × 256, repetition time (TR) = 13.5 ms, echo time (TE) = 5.8 ms, and flip angle (FA) = 20°). For functional images, data were acquired using fast-gradient echo-planar T2*-weighted imaging with 5 dummy volumes at the beginning of the session. Each functional volume consisted of 30–34

transverse slices (slice thickness = 4.0 mm, slice gap = 1.0 mm, FOV = 260 mm, matrix = 128 × 128, TR = 3000 ms, TE = 40 ms, and FA = 90°).

2.6. fMRI preprocessing

We used the CONN Functional Connectivity Toolbox version 17c (http://www.nitrc.org/projects/conn), which is compatible with SPM12 (Institute of Neurology, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12), for pre-processing and statistical analyses. Pre-processing included the following procedures: segmentation of the T1 structural volume image, slice-time correction of functional images, co-registration of the structural image to the functional images, spatial normalization to Montreal Neurological Institute (MNI) space based on the co-registered structural image, Gaussian spatial smoothing of functional images (full width at half maximum = 6 mm), and outlier detection ("scrubbing" to eliminate excessive head motion). Three confounders were removed by principal-component-based noise-correction ("CompCor" method) (Murphy et al., 2009): signal noise from the white matter and cerebrospinal fluid, within-subject covariates including head-motion artifacts and scrubbing parameters, and the main condition effect convolved with a hemodynamic response function. Band-pass filtering was applied with a frequency window of 0.008 to 0.09 Hz, the default setting for resting-state fMRI in CONN.

2.7. Psychological data analysis: identification of cognitive functions associated with cortisol

First, to exclude a confounding effect on cortisol, we examined whether dCOR was significantly associated with any of the following potential confounders: age, sex, BMI, monthly alcohol consumption, RBANS total index score, menstrual period, sleep duration, sleep quality, or perceived stress. Menstrual period was examined with an analysis of variance (ANOVA), and sex with an independent t-test. Correlation analyses were used for the other quantitative variables (see Supplementary material).

Next, a multiple regression analysis using the enter method was performed for figure copying (or figure recall) as a dependent variable, with dCOR and figure recall (or figure copying) as explanatory variables. To explore which cognitive components would be the most relevant to dCOR among different cognitive functions, we further performed a forward-selection stepwise regression analysis in which the 12 subtest scores and 5 cognitive domains of RBANS and TMT indices were considered together (see Supplementary material for the detailed procedures). Any confounder identified in the above-mentioned analysis was incorporated into the regression model as well.

These analyses were performed with SPSS version 24.0 J (IBM, Inc., Tokyo, Japan). The statistical significance threshold was set at $p < 0.025$ (2-sided) by considering the number of regression analyses (*i.e.*, 2 for figure copying and recall).

2.8. fMRI data analysis

2.8.1. Seed-to-voxel analysis: cortisol-associated hippocampal functional connectivity

We performed a hippocampus-seeded correlation analysis between dCOR and averaged values of time series of BOLD signals in each voxel of the whole brain, in order to identify neural correlates of cortisol. The effects of subject and potential confounders of cortisol, if any, were entered into the model as covariates of no interest.

As the seed regions, two divisions of the hippocampus were employed: the rostral and caudal parts (also referred to as the anterior and posterior parts), which are correlated with distinct cognitive functions (Persson and Söderlund, 2015; Robinson et al., 2015; Kühn and Gallinat, 2014). These regions of interest (ROI) were defined using the Brainnetome atlas (http://www.brainnetome.org/) (Fig. S1), which is a fine-grained, cross-validated human brain atlas with finely parcellated subcortical regions (Fan et al., 2016).

We set the regions of interest (ROI) as the target brain regions functionally connected to the hippocampal seeds. The ROIs were selected from the regions that have been reported to be involved in endogenous cortisol and visuospatial memory: the dorsolateral PFC including the superior frontal gyrus (SFG), inferior frontal gyrus (IFG) including pars triangularis and opercularis, and middle frontal gyrus (MFG) [as the regions are reported to be associated with endogenous cortisol (Ragnarsson et al., 2017; Kremen et al., 2010)]; the medial PFC including medial parts of the superior frontal gyrus (mSFG) and orbitofrontal gyrus (mOFG) [as the regions are indicated to be involved in spatial memory processing (Wang and Cai, 2006; Jones and Wilson, 2005) in addition to endogenous cortisol (Kremen et al., 2010) (Fig. S2a)]; and the visual cortices including the iLOC [as demonstrated to be relevant to endogenous cortisol (Ragnarsson et al., 2017)] and anterior, posterior, and temporo-occipital divisions of the ITG (aITG, pITG, and toITG) [presumed to have learning-dependent response selectivity to spatial visual stimuli (McKee et al., 2014; Ranganath and DEsposito, 2005) (Fig. S2b)]. As little is known about the possible involvement of the visual cortex in visuospatial memory due to the exclusive focus on the hippocampus and the PFC in previous research, we also included the following visual cortices in addition to the above-mentioned ROIs: occipital pole (OP), anterior, posterior, and temporo-occipital divisions of the middle temporal cortex (aMTG, pMTG, and toMTG, respectively) [the regions that comprehensively encompass all the visual cortices in the ventral pathway (Mishkin et al., 1983); see Supplementary material for the details]. Anatomical definitions of the visual cortices were based on the CONN default atlas [comprised of the FSL Harvard-Oxford atlas (http://www.cma.mgh.harvard.edu/fsl atlas.html) and the Automated Anatomical Labeling (AAL) atlas (http://www.gin.cnrs.fr/AAL)]. The PFC ROIs were selected based on the AAL atlas, which more comprehensively covers that area. Small volume correction (SVC) was applied to the ROIs. According to the number of ROIs and seed regions (*i.e.*, 14 × 2), the height threshold at cluster level was set at $p < 0.0018$ with family wise error (FWE) corrections for multiple tests to satisfy $^{FWE-corrected}p < 0.05$, and with extent threshold $k > 10$ voxels. The FWE is the most conservative correction method for multiple comparisons, and has costs such as an increase in type II errors and bias towards obvious large effects (Lieberman and Cunningham, 2009). We therefore applied a $p < 0.05$ threshold with false discovery error (FDR) corrections to these results as well, in which the number of seed regions as well as ROIs were corrected, preventing the inflation of both type I and type II errors. The estimated values (βs) of clusters surviving SVC with FWE-/FDR-correction were extracted with MarsBar 0.43 (http://marsbar.sourceforge.net/) for subsequent analyses.

2.8.2. Exploratory whole-brain analysis: neural correlates of visuospatial construction and retrieval

As an additional analysis, we conducted a whole-brain analysis to explore which brain regions were involved in visuospatial construction (figure copying) and retrieval (figure recall) processes. The detailed analysis is described in Supplementary material.

2.9. Correlation analysis between cortisol-related hippocampal FC values and cognitive functions

We used the hippocampal FC values that were correlated with cortisol in order to clarify which cortisol-related hippocampal connectivity would represent the relationship of cortisol with cognitive function. Provided the presence of a significant correlation between the extracted hippocampal FC values and cortisol-associated cognitive function was confirmed, a mediation analysis was applied to investigate whether the hippocampal FC would explain the association between the cognitive function and cortisol.

2.10. Mediation analysis: relationship between cortisol, cognitive function, and cortisol-related hippocampal FC

Mediation effects of cortisol-related hippocampal FC on the relationship between a cognitive function and cortisol were examined using AMOS version 22.0 J (IBM, Inc., Tokyo, Japan). We estimated bias-corrected 95% confidence intervals of the indirect effect using the parametric bootstrap method for maximum likelihood estimators (2000 samples). Statistical significance was defined as $p < 0.05$ (2-sided). The independent variable was cortisol (independent variable = X), and the dependent variable was the associated cognitive function (dependent variable = Y). Hippocampal FC was assigned as the mediator (M). Effects of any confounders were controlled for in the mediation analyses using unstandardized residuals for cortisol that was predicted by these variables. Paths from X to M, from M to Y, and from X to Y were represented as *a*, *b*, and *c'*, respectively. *c* indicates the path from X to Y when M is excluded. A mediation effect was inferred if (1) we would observe a statistically significant indirect effect (*ab*) of the variable X on Y through the mediator M, whose 95% Cl did not include 0, and (2) the significance of the direct effect *c*' was reduced or nullified (*i.e.*, partial or complete mediation, respectively) in the mediation model (in contrast to the direct effect *c*).

Additionally, as reference analyses, we performed mediation analyses using the values of hippocampal FC with the identified regions defined by the default atlas.

3. Results

3.1. Participants' characteristics on cognitive performance and cortisol

Descriptive statistics for participants' age, sex, years of education, cognitive test scores, and cortisol are presented in Table 1. No significant group difference was found in these variables between all participants ($n = 166$) and the participants who underwent MRI scans ($n = 90$), as shown in Table 1. The cognitive test performance of the participants was commensurate with that of a normative sample (Lezak, 2012; Randolph, 1998). None were engaged in shift work or had jet lag. As the greatest commonality was observed between dCOR and AUC ($r = 0.96$, $p < 0.001$), we focused on dCOR in the following analyses. The dCOR for the whole sample did not meet the assumption of normality determined by the Shapiro-Wilk test ($W = 0.92$, $df = 166$, $p < 0.001$), and thus it was square-root transformed.

The average time interval (days) between neuropsychological assessment and saliva collection was 6.2 ± 5.9 (range: 1 − 42). Of 166 participants, 157 (95%) collected saliva within 2 weeks from neuropsychological assessment. Additionally, the time interval between MRI acquisition and neuropsychological assessment was 6.3 ± 9.8 (range: 1 − 46). Of the 90 participants, 72 (80%) underwent both MRI scans and saliva collection within 2 weeks from neuropsychological assessment. Thus, the effects of the day intervals between neuropsychological assessment, saliva collection, and MRI acquisition were controlled for subsequent analyses.

The following potential confounders were not significantly associated with dCOR: age, menstrual period, BMI, monthly alcohol consumption, years of education, sleep duration, sleep quality, and perceived stress during the 2 saliva collection days (see Supplementary material). The effect of sex was significant, and thus, was controlled for in subsequent analyses as well.

3.2. Identification of cognitive functions associated with cortisol

Multiple regression analysis revealed that the regression model for figure copying with sex, measurement-related time differences, figure recall, and dCOR as independent variables was significant: $F(4,161) = 12.83$, adjusted $R^2 = 0.22$, $p < 0.001$. In the model, dCOR positively predicted figure copy performance ($\beta = 0.31$, $p < 0.001$), with figure recall ($\beta = 0.39$, $p < 0.001$). As for the measurement-related time differences and sex, the effects were not significant ($\beta = 0.00$, $p = 0.96$; $\beta = 0.04$, $p = 0.60$; respectively). In addition, the regression model for figure recall with sex, measurement-related time differences, figure copying, and dCOR was significant as well: $F(4,161) = 10.18$, adjusted $R^2 = 0.18$, $p < 0.001$. In the model, dCOR negatively predicted figure recall performance (β = -0.22, $p = 0.003$), with figure copying and sex ($\beta = 0.41$, $p < 0.001$; $\beta = 0.16$, $p = 0.03$; respectively). The effect of measurement-related time differences was not significant (β = -0.02, $p = 0.81$).

Furthermore, we confirmed the comparable results when the 12 subtest scores and 5 cognitive domains of RBANS and TMT indices were incorporated into the regression model together. Figure copying and figure recall were the most relevant functions to cortisol among different cognitive functions (figure copying: $\beta = 0.35$, $p < 0.001$ and figure recall: β = -0.24, $p = 0.003$, the other results are reported in Supplementary material).

These results indicate opposite findings for figure copying and recall, such that, greater daily circulating cortisol was associated with better construction, but contrastingly with poorer recall of visuospatial information.

Table 1
Descriptive statistics of participants' years of education, cognitive test scores, and cortisol of whole sample ($n = 166$) and MRI subsample ($n = 90$).

	$n = 166$		$n = 90$		test statistics (t or χ^2)	p
	Mean	SD	Mean	SD		
Age	21.9	2.7	21.6	2.1	1.08	0.28
Sex (% of females)		56.6		56.7	0.00	1.00
Years of education	14.7	1.1	14.7	1.1	0.00	1.00
RBANS						
Immediate memory	104.2	13.4	107.1	11.0	−1.80	0.07
List learning	32.4	3.7	33.1	3.2	−1.31	0.19
Story memory	20.4	2.9	21.0	2.5	−1.55	0.12
Visuospatial construction	98.3	9.3	97.8	9.3	0.42	0.68
Figure copy	19.3	0.8	19.2	0.9	1.34	0.18
Line orientation	18.3	1.7	18.4	1.5	−0.18	0.85
Language	97.2	11.9	98.0	10.7	−0.53	0.60
Picture naming	9.9	0.3	9.9	0.3	−0.20	0.84
Semantic fluency	17.0	3.8	17.2	3.6	−0.35	0.73
Attention	102.1	13.8	103.3	12.5	−0.71	0.48
Digit span	12.0	2.2	12.1	2.1	−0.32	0.75
Digit symbol coding	64.3	9.5	65.3	9.0	−0.82	0.41
Delayed memory	104.0	14.6	104.1	14.7	−0.07	0.94
List recall	8.2	1.6	8.3	1.5	−0.27	0.78
List recognition	19.8	0.6	19.7	0.6	0.24	0.81
Story recall	11.2	1.2	11.4	1.0	−1.16	0.25
Figure recall	17.5	2.4	17.5	2.4	0.18	0.86
Total index	102.0	13.2	103.5	11.7	−0.91	0.36
TMT						
Part A	24.6	6.8	24.6	6.8	1.45	0.15
Part B	49.8	12.9	48.3	11.6	0.90	0.37
Parta B / Part A (TMTQ)	2.1	0.6	2.1	0.5	−0.38	0.70
Cortisol (nmol/L)						
dCOR	37.2	20.1	33.5	21.1	1.40	0.16
AUC	233.1	126.6	211.0	131.1	1.32	0.19
Time 1 (at awakening)	12.6	8.2	11.2	8.4	1.30	0.20
Time 2 (30 min after awakening)	21.2	11.5	19.3	11.1	1.30	0.19
Time 3 (bedtime)	3.4	4.2	3.0	4.7	0.68	0.50

3.3. Seed-to-voxel analysis: cortisol-associated hippocampal functional connectivity

Seed-to-voxel correlation analysis demonstrated that dCOR was significantly correlated with increased FC of the right rostral hippocampus (rHC) with two PFC clusters: left SFG (MNI peak coordinate:

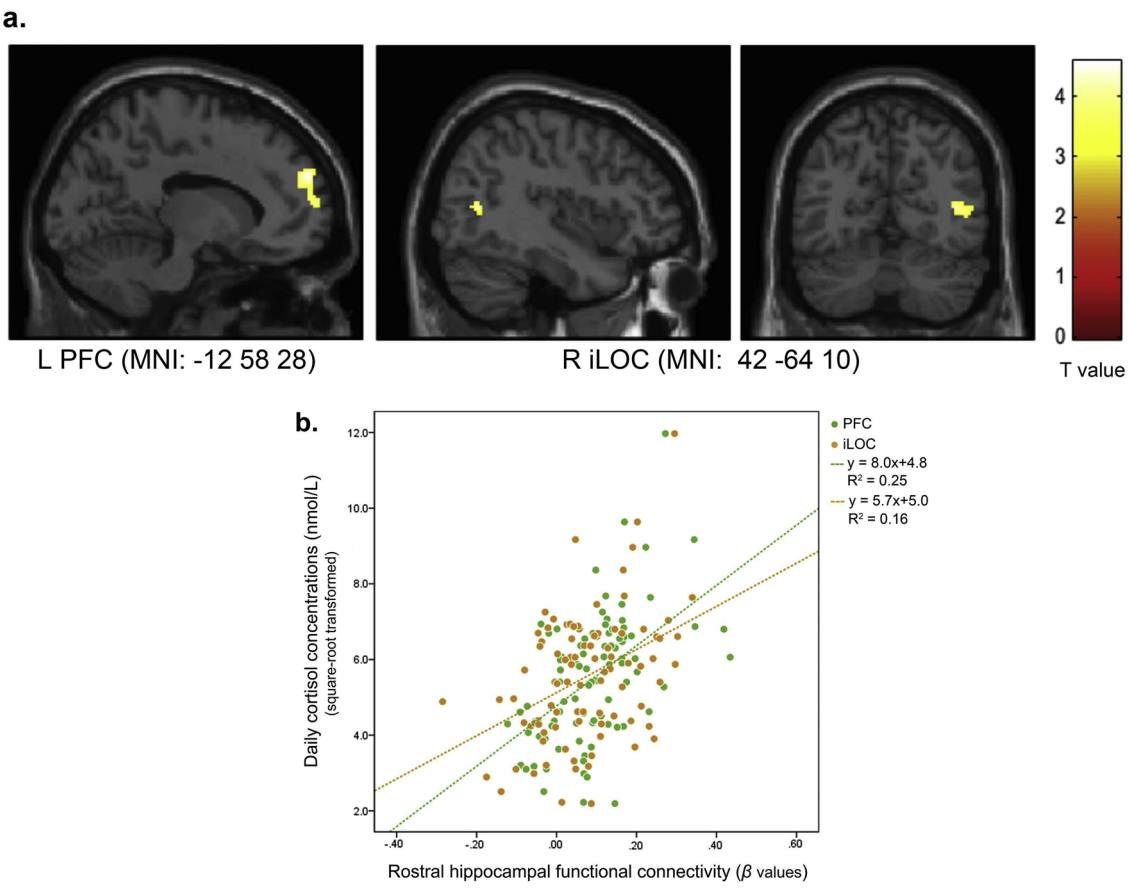

Fig. 1. Rostral hippocampus FC with PFC and iLOC were positively correlated with dCOR. The right rostral hippocampus showed significantly increased FC with the following two clusters as a function of dCOR: **a.)** Left PFC; MNI coordinates -12 58 28, cluster size: 1688 mm^3, $T = 4.56$, $^{FWE-corrected}p < 0.001$; and right iLOC; MNI coordinates: 42 −64 10, cluster size: 512 mm^3, $T = 4.10$, $^{FWE-corrected}p = 0.005$. b). Scatter plots of the relationship between dCOR and rostral hippocampus FC.

Abbreviations: dCOR, daily cortisol concentration; FC, functional connectivity; PFC, prefrontal cortex; iLOC, inferior lateral occipital cortex; MNI, Montreal Neurological Institute.

-12 58 28, cluster size: 624 mm^3, $T = 4.56$, $^{FWE-corrected}p = 0.004$, $^{FDR-corrected}p = 0.047$) and medial SFG (MNI peak coordinate: -10 56 24, cluster size: 712 mm^3, $T = 4.22$, $^{FWE-corrected}p = 0.002$, $^{FDR-corrected}p = 0.047$). For simplicity in subsequent analyses, these clusters were united into one PFC cluster (MNI peak coordinate: -12 58 28, cluster size: 1688 mm^3, $T = 4.56$, $^{FWE-corrected}p < 0.001$) (Fig. 1a). Moreover, increased FC between the rHC and iLOC (both on the right side) was significantly correlated with dCOR (MNI peak coordinate: 42 −64 10, cluster size: 512 mm^3, $T = 4.10$, $^{FWE-corrected}p = 0.005$, $^{FDR-corrected}p = 0.047$) (Fig. 1a). Scatter plots of these PFC and iLOC clusters are presented in Fig. 1**b**. Additionally, dCOR was also correlated with increased FC of the left caudal hippocampus (cHC) with the right aMTG (MNI peak coordinate: 54 2 −28, cluster size: 512 mm^3, $T = 4.23$, $^{FWE-corrected}p = 0.007$, $^{FDR-corrected}p = 0.049$). No other region showed significant FC with the hippocampal seeds in relation to dCOR (FC values of nonsignificant clusters are reported in Table S3). We thus focused on the right rHC FC with the left PFC and right iLOC and the left cHC FC with the right aMTG in the subsequent correlation analysis.

3.4. Correlation analysis between cortisol-related hippocampal FC and cognitive functions

Controlling for the effect of sex and measurement-related time differences, we confirmed significant correlations between the dCOR-associated cognitive functions (*i.e.*, figure copying and recall) and the rHC FC with both the PFC and iLOC, but not the cHC FC with the aMTG. The rHC-PFC FC was positively correlated with figure copying ($r = 0.27$, $p = 0.01$), but not with recall ($r = -0.08$, $p = 0.48$). When the PFC clusters were analyzed independently for the SFG and medial SFG, the correlation coefficients were the same as those of the united PFC cluster due to the proximity of these clusters. In contrast, the rHC-iLOC FC was negatively correlated with figure recall ($r = -0.32$, $p = 0.002$) but not with copying ($r = 0.06$, $p = 0.56$). The rHC-iLOC FC was significantly correlated with the rHC-PFC FC ($r = 0.28$, $p = 0.009$). There was no significant correlation between the cHC-aMTG FC and either figure copying ($r = -0.10$, $p = 0.37$) or figure recall ($r = -0.17$, $p = 0.13$).

3.5. Mediation analysis: relationship between cortisol, cognitive function, and cortisol-related hippocampal FC

We performed two mediation analyses to examine 1) the mediation effect of the rHC-PFC FC (M) on the relation between cortisol (X) and figure copying (Y) (Fig. 2a) and 2) the mediation effect of the rHC-iLOC FC (M) on the relation between cortisol (X) and figure recall (Y) (Fig. 2b), controlling for the effects of sex and measurement-related time differences. Although an indirect effect of cortisol on figure copying through the rHC-PFC failed to reach significance ($ab = 0.09$, $p = 0.09$; 95% Cl: −0.01 − 0.23; Fig. 2a), we observed a significant indirect effect of cortisol on figure recall through the rHC-iLOC FC ($ab = -0.13$, $p = 0.003$; 95% Cl: −0.24 −0.04; Fig. 2b), with 51.6% of cortisol's total effect on figure recall explained. In this model, the statistical significance of the direct effect ($c = -0.24$, $p = 0.02$) disappeared after considering M ($c' = -0.11$, $p = 0.30$), indicating complete mediation by the rHC-iLOC FC. Additionally, an integrative

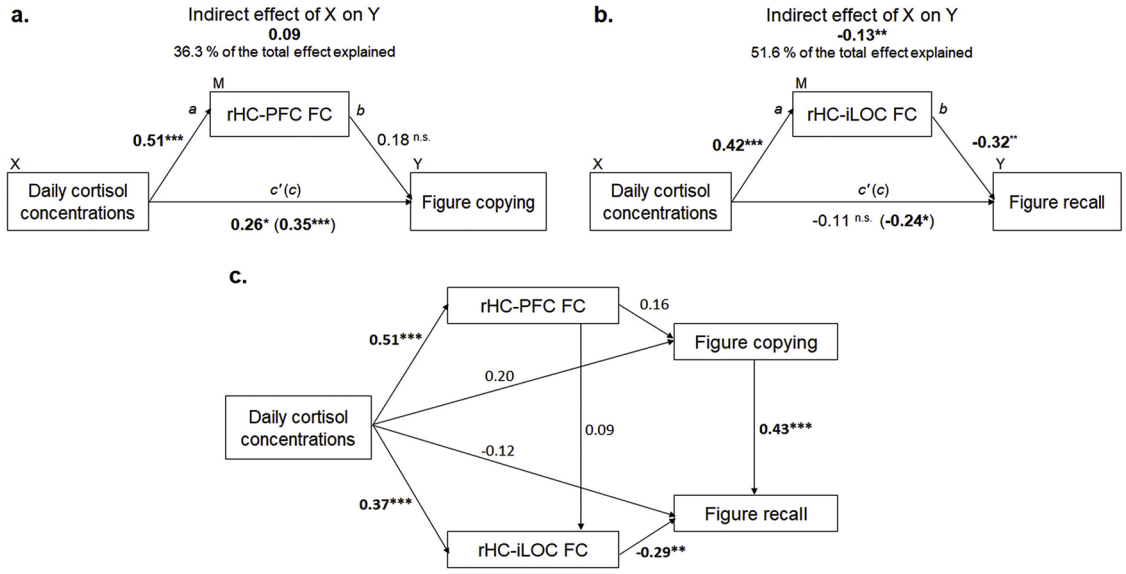

Fig. 2. Results of mediation analyses. a.) Mediation model for figure copying. **b.**) Mediation model for figure recall. X (independent variable) = daily cortisol concentration (adjusted for the effects of sex and measurement-related time differences), M (mediator) = hippocampal FC, and Y (dependent variable) = figure copying / figure recall (each adjusted for the other paired function). **c.**) Unified model of **a.** and **b.**: results of path analysis. All path coefficients are standardized regression weights. In model **a.**, the indirect effect explained 36.3% of the total effect of cortisol on figure copying, whereas 51.6% of the total effect of cortisol on figure recall was explained in model **b**. Abbreviations: PFC; prefrontal cortex; iLOC; inferior lateral occipital cortex; FC, functional connectivity. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

model incorporating all the variables (*i.e.*, dCOR, rHC-PFC FC, rHC-iLOC FC, and figure copy and recall) supported a substantial contribution of the rHC-iLOC FC to figure recall (Fig. 2**c**; $\chi^2 = 0.98$, $df = 2$, $p = 0.61$; GFI = 1.00, AGFI = 0.97, RMR = 0.03, NFI = 0.99, RMSEA = 0.00; The analytic procedures are detailed in Supplementary material).

Additionally, in mediation analyses using the FC values of rHC with the default atlas-defined SFG, medial SFG, and iLOC, no significant mediation effect was observed (see Supplementary material).

3.6. Exploratory whole-brain analysis: neural correlates of visuospatial construction and retrieval

Finally, a whole-brain analysis showed that figure copying (visuospatial construction) was negatively associated with FC between the amygdala, OFC, and anteroventral nucleus (AV) (Fig. 3a), whereas figure recall (visuospatial retrieval) was positively associated with FC of the iITG with the iLOC, but negatively with FC of the iITG with the hypothalamus (Fig. 3**b**) (Table 2).

4. Discussion

We found that higher daily cortisol levels were associated with poorer performance in a complex figure recall test, but with better performance in a preceding copying test. The current findings are partly consistent with those of previous large-scale neuropsychological studies that showed a negative association between endogenous cortisol and figure recall performance in older adults (Franz et al., 2011; Lee et al., 2007); however, we identified a positive association between endogenous cortisol and figure copying performance. Furthermore, of the cortisol-related hippocampal connectivity, we demonstrated that FC between the rHC and iLOC specifically mediated the negative relationship between cortisol and figure recall. The present study is the first to show that cortisol-related rostral hippocampal connectivity with visual cortex explains endogenous cortisol's involvement in visuospatial retrieval.

Most importantly, cortisol had an adverse effect on visuospatial retrieval that was completely mediated by increased FC between the right rHC and right iLOC. The lateral occipital cortex (LOC), which belongs to the extrastriate cortex, is implicated in visual perception and recognition of objects and faces (for meta-analytic review, see Malikovic et al., 2016). In addition, types of spatial processing such as spatial location discrimination and mental rotation strongly activate the LOC (Malikovic et al., 2016). Similarly, as mentioned earlier, the hippocampus is crucially involved in spatial processing in terms of memory (Ekstrom et al., 2003; Hartley et al., 2003; OKeefe and Dostrovsky, 1971). Its rostral part (the anterior hippocampus), which is dominated by the CA1 region and subiculum (Zeidman and Maguire, 2016), is closely linked to stress-related behaviours and the HPA axis (Chase et al., 2015; Robinson et al., 2015; Bannerman et al., 2014), and the right rostral part has intrinsic FC with the ipsilateral LOC (Robinson et al., 2015). Although the caudal part (the posterior hippocampus) is implicated more in spatial processing (*e.g.*, spatial navigation), the anterior hippocampus involves general memory processes including both encoding and retrieval (Robinson et al., 2015; Carr et al., 2010). Thus, the anterior hippocampus might be specifically relevant to the relationship between cortisol and memory. GRs, which have a lower affinity and thus easier binding to cortisol under conditions of its greater circulating amount in comparison to MRs, are distributed in both the hippocampus (including CA1) and visual cortex (as well as other parts of the cerebral cortex) (Reul and de Kloet, 1985). Therefore, higher levels of endogenous cortisol might interfere with visuospatial retrieval through anterior hippocampal-extrastriate connectivity responsible for visuospatial perception, possibly via GRs. Given the comparability of resting-state FC with task-related FC (Laird et al., 2011), the increased rHC-iLOC FC might imply effortful (or possibly compensatory) engagement—as a form of greater synchronization—by neurons in these two regions for visuospatial memory retrieval. Additionally, we found no significant mediation effect of rHC FC with the default atlas-defined iLOC, conceivably because such extensive ROI contains functionally quite heterogeneous regions and might have made it difficult to identify the exact neural correlates bridging a gap between cortisol and visuospatial memory. Future research would benefit from more detailed dissection of a brain region to approach the complicated relationship between cortisol and behavior.

In contrast, rather unexpectedly, cortisol showed a positive

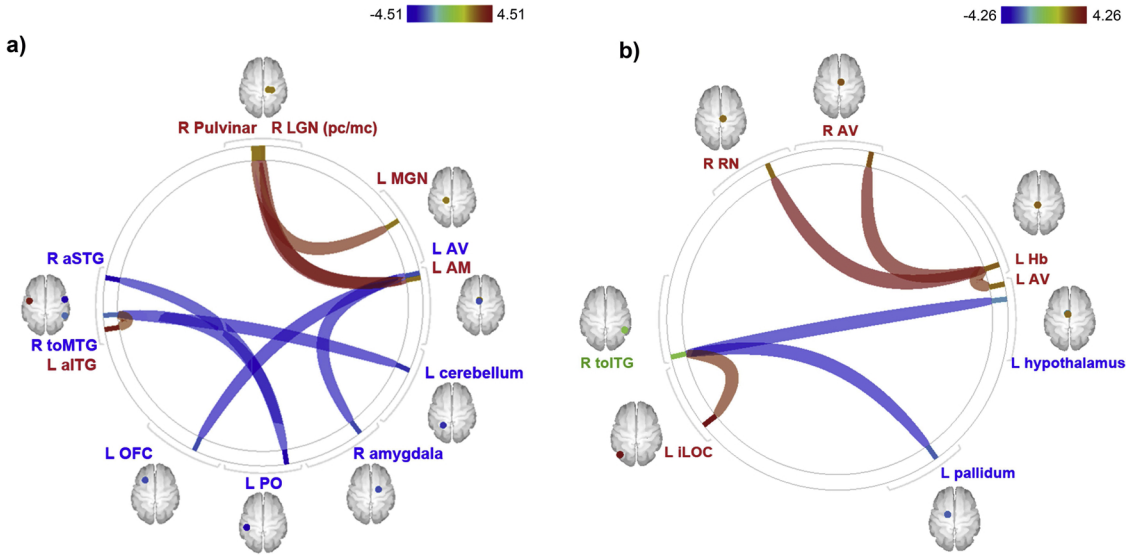

Fig. 3. FC significantly correlated with visuospatial construction and retrieval. Results of ROI-based whole-brain analyses. **a.**) Visuospatial construction. **b.**) Visuospatial retrieval. Blue: negative correlation with figure copying / recall performance. Red: positive correlation with figure copying / recall performance. $^{FDR-corrected}$ $p < 0.05$ (2-sided). Thickness of bundles is proportional to *T* values. The color bars indicate *T* values. Abbreviations: FC: functional connectivity; ROI: region of interest; LGN (mc), lateral geniculate body (magnocellular area); LGN (pc), lateral geniculate body (parvocellular area); AM, anteromedial thalamic nucleus; MGN, medial geniculate body; aITG, anterior part of inferior temporal gyrus; toMTG, temporo-occipital part of middle temporal gyrus; AV, anteroventral thalamic nucleus; OFC, orbitofrontal fortex; PO, parietal operculum; aSTG, anterior part of superior temporal gyrus; RN, thalamic reticular nucleus; Hb, habenular nucleus; toITG, temporo-occpital part of inferior temporal gyrus; iLOC, inferior part of lateral occipital cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

relationship with visuospatial construction (figure copying), as well as rHC's FC with the dorsolateral and medial PFC. It is noteworthy that endogenous cortisol had distinct effects on visuospatial memory—better construction and poorer retrieval of visuospatial stimuli. Although cortisol's negative effects on memory retrieval has been established (Shields et al., 2017; Het et al., 2005; Sauro et al., 2003), its effects on encoding (or consolidation) remain elusive (Shields et al., 2017; Het et al., 2005; Roozendaal, 2002; Wolf et al., 2009). Such inconsistency might be partly addressed by taking the timing of cortisol stimulation and the activation of MRs into consideration. For example, a meta-analytic study has revealed that cortisol elevation does not deteriorate encoding processing, as long as the time interval between them is distant (Shields et al., 2017). In addition, it has been reported that cortisol can rather promote context-dependent emotional memory consolidation (van Ast et al., 2013) and working memory (Henckens et al., 2011) with reduced hippocampal and PFC local activity (Henckens et al., 2012), but only when memory performance was measured after a long time delay from cortisol stimulation (*i.e.*, reflecting cortisol's slow effects that alter gene expressions). The present study is different from these previous studies in that cortisol was measured under ordinary circumstances, without specific imposition of stress, and visuospatial stimuli with no emotional valence were used. Even so, endogenous cortisol might reflect, at least partly, stress-related fluctuations or purely physiological variations as a result of gene expressions in everyday life (*i.e.*, slow genomic effects) (Ross et al., 2014).

As for the activation of MRs, several studies have demonstrated that an intake of fludrocortisone, which specifically occupies MRs, enhanced memory consolidation (Groch et al., 2013) and improved working memory both in healthy individuals and psychiatric patients (Hinkelmann et al., 2015; Otte et al., 2015; Wingenfeld et al., 2015). Similarly, an animal study using gene transfer vectors has showed that the overexpression of MRs together with corticosterone administration, which results in a prominent decrease in the number of the corticosterone-bound GRs, enhanced memory consolidation and attenuated retrieval deficits (Ferguson and Sapolsky, 2007). These findings suggest that cortisol might have some positive effects on memory consolidation or encoding when it activates a substantial number of MRs (and possibly a small number of GRs); however, the binding to a greater number of GRs itself might still impair memory retrieval, as indicated in previous studies (for a systematic-review, see Wolf et al., 2016). Particularly, not only GRs but also MRs are expressed in the PFC of humans (López et al., 1998), and its expressed amount (especially in the dorsolateral and medial parts) is found to be significantly lower in psychiatric patients than in healthy controls (Patel et al., 2016; Qi et al., 2013; Xing et al., 2004). An endogenous cortisol-related increase in rHC's intrinsic FC with the dorsolateral and medial PFC might represent the dominant activation of MRs therein, which is relevant to stress-ameliorating effects (ter Heegde et al., 2015). Although the mediation effect of rHC-PFC FC on the positive relationship between cortisol and figure copying remained at trend level, endogenous cortisol might possibly have enhancing effects on a facet of visuospatial encoding more directly involving spatial working memory, through the rHC-PFC connectivity essential for it (Spellman et al., 2015; Wang and Cai, 2006; Jones and Wilson, 2005). In contrast, a cortisol-related increase in rHC's FC with the iLOC, where the expression of MRs has not been reported, might reflect that endogenous cortisol might bind to a greater number of GRs therein, and thereby have an adverse effect on visuospatial retrieval. Future research focusing on the balance between MRs and GRs, according to their distribution in specific brain regions, would facilitate the understanding of cortisol's contrasting effects on memory consolidation and retrieval, providing relevant implications for possible improvement of memory decline in psychiatric disorders.

Additionally, in the whole-brain analysis, poorer figure recall performance was observed to be correlated with decreased FC between the iLOC and the ITG, whereas better figure copying performance was correlated with decreased FC between the amygdala, OFC, and AV, which suggests that the iLOC and PFC each participates in broader neural networks involved in visuospatial construction and retrieval, respectively. In particular, the ITG, whose potential importance in visuospatial memory was mentioned earlier, showed increased FC with the hypothalamus; but at the same time, decreased FC with iLOC as it pertains to poorer figure recall performance. The ITG might be involved in visuospatial retrieval through its key role in the integration of visuospatial information (*e.g.*, Tomita et al., 1999). In addition, the

Table 2
Functional connectivity associated with visuospatial encoding and retrieval (n = 90).

Side	Seed region	Side	Target region	T	$^{FDR-corrected}p$
Visuospatial encoding					
Positive correlation with figure copying					
R	LGN (pc)	L	AM	4.51	0.004
R	LGN (mc)			4.07	0.01
R	pulvinar	L	MGN	3.97	0.03
L	aITG	R	toMTG	3.60	0.04
Negative correlation with figure copying					
R	amygdala	L	AV	−4.00	0.02
L	OFC			−3.86	0.02
L	cerebellum	R	toMTG	−3.92	0.03
L	PO			−3.77	0.03
		R	aSTG	−3.71	0.04
Visuospatial retrieval					
Positive correlation with figure recall					
R	RN	L	Hb	4.26	0.01
R	AV			4.04	0.01
L	AV			3.59	0.04
R	toITG	L	iLOC	3.64	0.04
Negative correlation with figure recall					
R	toITG	L	pallidum	−3.73	0.04
		L	hypothalamus	−3.58	0.04

Abbreviations: LGN (mc), lateral geniculate body (magnocellular area); LGN (pc), lateral geniculate body (parvocellular area); AM, anteromedial thalamic nucleus; MGN, medial geniculate body; aITG, anterior part of inferior temporal gyrus; toMTG, temporo-occipital part of middle temporal gyrus; AV, anteroventral thalamic nucleus; OFC, orbitofrontal fortex; PO, parietal operculum; aSTG, anterior part of superior temporal gyrus; RN, thalamic reticular nucleus; Hb, habenular nucleus; toITG, temporo-occpital part of inferior temporal gyrus; iLOC, inferior part of lateral occipital cortex.

hypothalamus governs the secretion of corticotropin-releasing hormone (CRH) as a part of the hypothalamic-pituitary-adrenal axis, which regulates cortisol. The rHC-iLOC FC might be ancillary to this systematic network; however, neural connectivity specifically between these two regions might be under the predominant influence of cortisol.

Limitations of this study should be considered when interpreting the results. First, we used cortisol measurements from 3 time points per day, across 2 consecutive days. The index dCOR might be similar to total cortisol output, as unstimulated cortisol levels at a single time are reported to be significantly correlated with total cortisol output (Edwards et al., 2001), but it is not equal. Cortisol measurements from multiple time points are needed for further clarification. Second, the figure copying subtest is relatively easier than the other cognitive tests, because it only requires participants to copy a complex figure while carefully examining it. Although the current sample data was comparable to the original normative data for the same age group (Randolph, 1998), visuospatial construction and its related encoding should be assessed in a more detailed manner. Third, the immunoassay has some limitation in its sensitivity and specificity to cortisol, although many previous studies have employed this method for salivary cortisol measurement. Finally, the causality between hippocampal-extrastriate-PFC connectivity, cortisol, and cognitive test performance remains unaddressed. Future longitudinal studies assessing endogenous cortisol levels across typical consecutive weekdays, intrinsic functional connectivity, and then cognitive performance should further unravel the exact relationship between cortisol, memory, and the brain. Furthermore, the causal direction of connectivity between the hippocampus, PFC, and extrastriate cortex should be also determined using the dynamic causal modeling in a visuospatial task design (Friston et al., 2003). Despite these limitations, we determined that endogenous cortisol, which was measured in a natural setting, was differentially involved in visuospatial construction and retrieval through rostral hippocampal connectivity, using standard neuropsychological tests in a sizable sample of healthy young adults who were intact in terms of aging-related cognitive decline.

In conclusion, we showed that endogenous cortisol is differentially involved in visuospatial memory—better construction and poorer retrieval of visuospatial information. In proportion to endogenous cortisol levels, the rostral hippocampus strengthens its connectivity with the dorsolateral and medial PFC and the iLOC. Specifically, the cortisol-related rostral hippocampal connectivity with the iLOC, an area implicated in visuospatial perception, completely mediated cortisol's negative effect on visuospatial retrieval. The distribution pattern and activation balance between MRs and GRs might generate differential effects on visuospatial construction and retrieval. Thus, future research focusing on the activation balance between the different corticosteroid receptors according to their distribution in specific brain regions would facilitate the understanding of cortisol's contrasting effects on memory consolidation and retrieval, providing relevant implications for possible memory improvement in psychiatric disorders.

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Declaration of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.04.013.

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