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Study of the Hippocampal Adaptation to Hypoxia in Freedivers: Insights from Multimodal Neuroimaging and Memory Function

Par Julia MICAUX

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Dirigée par **Marion NOULHIANE**

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Devant un jury composé de :

Pr. **Nikolaï AXMACHER**	Ruhr University Bochum, Allemagne	Rapporteur
Pr. **Séverine SAMSON**	Université de Lille, France	Rapportrice
Pr. **Christophe PIERARD**	IRBA, France	Examinateur
Pr. **Sophie DUPONT**	Université Paris Sorbonne, France	Examinatrice
Pr. **Martine GAVARET**	Université Paris Cité, France	Examinatrice
Dr. **Marion NOULHIANE**	Université Paris Cité, France	Directrice de thèse

Titre : Etude de l'adaptabilité de l'hippocampe à l'hypoxie chez les plongeurs en apnée : une étude par neuroimagerie multimodale et évaluation de la mémoire épisodique

Résumé :
L'hypoxie (i.e., le manque d'oxygène), lorsqu'elle survient accidentellement, peut avoir des effets délétères sur le cerveau, conduisant à des pathologies neurologiques comme les accidents vasculaires cérébraux, l'hypoxie néonatale, les troubles liés à la haute altitude ou encore l'apnée du sommeil. Les sous-champs hippocampiques, essentiels à la mémoire épisodique, sont particulièrement vulnérables à l'hypoxie. Pourtant, les plongeurs apnéistes (PA), régulièrement exposés à des épisodes d'hypoxie volontaires lors de leurs entraînements, ne présentent pas de troubles majeurs de la mémoire épisodique. Quels marqueurs neuronaux sous-tendent cette apparente résilience chez les PA ? Au moyen de la neuroimagerie multimodale par résonance magnétique (IRM), nous avons étudié l'évolution mnésique, neuroanatomique, et neurofonctionnelle d'un groupe de PA entrainés sur une saison d'apnée (7 mois) en les comparant à un groupe de sportifs pratiquant des sports en aérobie. Trois axes ont guidé cette étude : (1) AXE COGNITIF : la tâche de séparation de patterns HippoPS, évaluant l'implication distinctive des sous-champs hippocampiques dans les processus de la mémoire épisodique, a montré une stabilité des performances mnésiques dans les deux groupes (Micaux *et al.*, 2025). (2) AXE NEUROANATOMIQUE : l'outil HSF (Hippocampal Segmentation Factory©), dédié à la segmentation automatique en IRM anatomique, a été utilisé pour examiner l'intégrité des volumes des sous-champs hippocampiques. L'analyse a révélé des volumes comparables entre les deux groupes, ce qui suggère une préservation de l'intégrité anatomique malgré une exposition prolongée à l'hypoxie (Micaux *et al.*, 2025). (3) AXE NEUROFONCTIONNEL : l'IRMf de repos, acquise à la fois en normoxie et en apnée, a montré les effets aigus de l'hypoxie sur la connectivité cérébrale et a montré une réorganisation fonctionnelle spécifique de la connectivité de l'hippocampe, dont une diminution de la connectivité avec les régions sensori-motrices, et une augmentation avec les régions cérébelleuses et visuelles, notamment en fin de saison d'entraînement. De plus, des corrélations positives entre la connectivité fonctionnelle hippocampique et les performances mnésiques suggèrent un mécanisme compensatoire reposant sur une plasticité fonctionnelle adaptative (Micaux *et al.*, In Prep).
En conclusion, ces résultats révèlent que l'exposition répétée à l'hypoxie volontaire, dans un cadre d'entraînement physique contrôlé en sport de loisir, n'induit ni altération anatomique des sous-champs hippocampiques, ni déficit mnésique significatif. Cette résilience serait sous-tendue par une réorganisation cérébrale fonctionnelle liée aux sous-champs hippocampiques assumant le maintien des fonctions de la mémoire épisodique. Ce travail positionne l'apnée comme un modèle naturel pour étudier les mécanismes de résilience cérébrale à l'hypoxie, ouvrant ainsi des perspectives thérapeutiques pour les pathologies neurologiques survenant dans un tel contexte.

Mots clefs : Apnée, Hypoxie, Plasticité Cérébrale, Hippocampe, Mémoire Episodique, Neuroimagerie, Segmentation Anatomique, Connectivité Fonctionnelle

Title: Study of the Hippocampal Adaptation to Hypoxia in Freedivers: Insights from Multimodal Neuroimaging and Memory Function

Abstract:
Accidental hypoxia (i.e., the lack of oxygen) can have detrimental effects on the brain, leading to neurological pathologies such as stroke, neonatal hypoxia, high-altitude-related disorders, or sleep apnea. The hippocampal subfields, essential for episodic memory, are particularly vulnerable to hypoxia. However, freedivers (FD), who are regularly exposed to voluntary hypoxic episodes during their training, do not seem to present major episodic memory impairments. What neural markers underlie this apparent resilience in FD? Using multimodal magnetic resonance imaging (MRI), we investigated the memory, neuroanatomical, and neurofunctional evolution of a group of trained FD over a freediving season (7 months). Results were compared to those of a group of athletes engaged in aerobic exercise training. The study was structured along three axes: (1) COGNITIVE AXIS: the HippoPS pattern separation task, assessing the involvement of hippocampal subfields in episodic memory processes, showed stable memory performance in both groups (Micaux *et al.*, 2025). (2) NEUROANATOMICAL AXIS: the HSF tool (Hippocampal Segmentation Factory©), dedicated to automatic segmentation in anatomical MRI, was used to examine the integrity of hippocampal subfield volumes. This analysis revealed comparable volumes between the two groups, suggesting anatomical integrity is maintained despite prolonged hypoxia. (Micaux *et al.*, 2025). (3) NEUROFUNCTIONAL AXIS: resting-state fMRI, acquired both in normoxia and during apnea, showed the acute effects of hypoxia on brain connectivity and revealed a specific functional reorganization of hippocampal networks, including a decrease in connectivity with sensorimotor regions and an increase in connectivity with cerebellar and visual regions, particularly at the end of the training season. Additionally, positive correlations between hippocampal functional connectivity and memory performance suggest a compensatory mechanism relying on adaptive functional plasticity (Micaux *et al.*, In Prep).
In conclusion, these findings reveal that repeated exposure to voluntary hypoxia, in the context of controlled exercise training in recreational sport, does not induce either neuroanatomical alteration of hippocampal subfields or significant memory deficits. This resilience appears to be underpinned by a functional brain reorganization involving hippocampal subfields that support the maintenance of episodic memory functions. This work positions freediving as a natural model to study the mechanisms of brain resilience to hypoxia, opening therapeutic perspectives for neurological pathologies occurring in such context.

Keywords: Freediving, Hypoxia, Brain Plasticity, Hippocampus, Episodic Memory, Neuroimaging, Anatomical Segmentation, Functional Connectivity

Résumé détaillé en français

1. Contexte et justification

L'hypoxie involontaire, définie comme une diminution de la disponibilité en oxygène au niveau tissulaire, constitue un facteur de risque majeur pour le cerveau humain. Elle est impliquée dans de nombreuses situations pathologiques ou environnementales, telles que l'hypoxie néonatale, l'accident vasculaire cérébral, l'apnée obstructive du sommeil ou encore les séjours prolongés en altitude. Dans ces contextes, elle entraîne des atteintes anatomiques et fonctionnelles significatives, en particulier au niveau de l'hippocampe. Cette structure du lobe temporal médian, composée de sous-champs interconnectés (gyrus denté -DG-, champs Ammonien CA1 à CA4 et subiculum), est cruciale pour la mémoire épisodique (Kandel *et al.*, 2012). Sa spécificité vasculaire et son métabolisme élevé la rendent particulièrement vulnérable aux variations d'oxygénation (Kann *et al.*, 2011; Spallazzi *et al.*, 2019). Des récentes études ont montré que l'hypoxie involontaire est associée à une atrophie hippocampique, à une désorganisation de la connectivité fonctionnelle au repos et à des déficits mnésiques notables (Bakker *et al.*, 2023; Olaithe *et al.*, 2018; Pfister *et al.*, 2023).
Un des processus essentiels à la mémoire épisodique et sous tendu par l'hippocampe est la séparation de pattern. Il s'agit de la capacité à encoder et distinguer des représentations mnésiques en réduisant l'interférence entre événements similaires. Ce mécanisme repose principalement sur le DG, qui transforme des entrées corticales similaires en traces neuronales distinctes, et sur CA3, qui amplifie cette différenciation (Ngo *et al.*, 2021; Yassa and Stark, 2011). La séparation de pattern est donc essentielle pour la mémoire épisodique, car elle permet de reconnaître qu'une expérience nouvelle, bien que ressemblant à une expérience passée, constitue un souvenir distinct. Sa sensibilité aux altérations hippocampiques en fait un indicateur privilégié pour évaluer les conséquences de l'hypoxie sur la cognition.

À l'inverse, la plongée en apnée, une forme d'hypoxie volontaire, se distingue par l'absence apparente d'effets délétères sur le cerveau. Les apnéistes, régulièrement soumis à des épisodes d'hypoxie intermittente volontaire et contrôlée lors de leur entraînement, ne présentent pas de troubles mnésiques majeurs (Allinger *et al.*, 2024). Cette observation soulève une question fondamentale : le cerveau humain, et en particulier l'hippocampe, serait-il capable de développer des mécanismes d'adaptation et de résilience face à l'hypoxie lorsque celle-ci est intermittente, volontaire et associée à un entraînement physique structuré ?

La plongée en apnée offre un modèle expérimental unique chez l'humain sain pour explorer cette hypothèse. Elle associe à la fois un entraînement physique régulier, dont les bénéfices sur la plasticité cérébrale sont bien documentés (Augusto-Oliveira *et al.*, 2023; Erickson *et al.*, 2011; Suwabe *et al.*, 2018), et des expositions répétées à une hypoxie contrôlée. Des données préliminaires indiquent des modifications de la connectivité fonctionnelle au repos, suggérant une priorisation des ressources nécessaires l'apnée (Annen *et al.*, 2021). Pourtant, jusqu'à présent, aucune étude multimodale longitudinale n'a examiné simultanément l'anatomie des sous-champs hippocampique, la connectivité fonctionnelle cérébrale et la mémoire épisodique dans cette population.

Cette thèse s'intègre dans le projet ANR HippoXia (coordonné par le Dr Marion Noulhiane), un projet collaboratif mené à la fois chez le rat et chez l'humain.

2. Objectifs et hypothèses

L'objectif principal de cette thèse était de caractériser, à travers une approche multimodale, les adaptations anatomiques, fonctionnelles et cognitives de l'hippocampe à l'hypoxie volontaire intermittente chez les apnéistes suivis sur une saison d'entraînement. Trois axes ont guidé ce travail, avec chacun une hypothèse :

1. **Axe neuroanatomique** : évaluer les volumes des sous-champs hippocampiques afin de déterminer si l'hypoxie volontaire induit des modifications détectables par IRM anatomique après une saison d'entrainement.
   Hypothèse : les volumes des sous-champs hippocampiques resteraient stables après plusieurs mois d'entraînement malgré l'exposition répétée à l'hypoxie volontaire

2. **Axe cognitif** : tester l'évolution de la mémoire épisodique dans cette population au cours d'une saison d'entraînement, en particulier la capacité de séparation de patterns, fonction hippocampique clé.
   Hypothèse : la mémoire épisodique serait préservée et comparable à celle d'un groupe témoin de sportifs

3. **Axe neurofonctionnel** : examiner les effets aigus (pendant une apnée) et chroniques (après l'entraînement) de l'apnée sur la connectivité fonctionnelle de l'hippocampe au repos et son éventuel lien avec les performances mnésiques.
   Hypothèse : une réorganisation spécifique de la connectivité hippocampique se mettrait en place, permettant une redistribution efficace des ressources neurales et soutenant la préservation de la performance cognitive

3. Méthodes

La cohorte de cette étude est composée de 17 apnéistes et 20 témoins sportifs masculins pratiquant des activités aérobiques, appariés pour l'âge, le niveau d'études et la charge hebdomadaire d'activité physique. Les apnéistes ont été suivis pendant une saison complète d'entraînement homogène (7 mois), avec deux temps d'évaluation (t_0 et t_1), incluant imagerie cérébrale et tests cognitifs. Les témoins ont maintenu leur entraînement habituel sans exposition volontaire à l'hypoxie.

- **IRM anatomique** : des acquisitions IRM 3T (séquences T1 et T2) ont permis la segmentation automatique des sous-champs hippocampiques grâce à l'outil Hippocampal Segmentation Factory (HSF©) (Poiret *et al.*, 2023).

- **Évaluation cognitive** : la tâche HippoPS, spécifiquement conçue pour mesurer la séparation de pattern de manière écologique, a été utilisée pour évaluer la mémoire épisodique. Dans la phase d'encodage, les participants visionnaient une série de vidéos associant un lieu et un geste uniques. Après un délai de 15 minutes, la phase de reconnaissance différée commençait : pour chaque vidéo, les participants devaient

indiquer si elle correspondait exactement à une scène déjà vue (« i. item identique »), si elle ressemblait à une scène vue mais avec une légère variation du lieu ou du geste (« ii. item similaire »), ou si elle était totalement nouvelle (« iii. item nouveau ») (Zhao and Noulhiane, In Prep).

- **IRM fonctionnelle au repos (rs-fMRI)** : L'activité fonctionnelle au repos a été acquise avec une séquence T2* multi-bande, durant laquelle les apnéistes ont été scannés en normoxie et en apnée, à deux reprises avant et après entraînement (t_0 et t_1). L'analyse a combiné des approches ROI-to-ROI, explorant les connexions avec l'ensemble du cerveau, et une approche seed-to-voxel ciblant spécifiquement l'hippocampe et ses interactions avec des réseaux définis a priori (frontal, fronto-pariétal, occipital et DMN). Le prétraitement a suivi le pipeline standard de CONN Toolbox. Les analyses statistiques ont appliqué un seuil de significativité de $p < 0,05$ avec correction pour comparaisons multiples.

4. Résultats principaux

Les volumes des sous-champs hippocampiques étaient comparables entre les groupes à t_0 et sont restés stables à t_1. Aucune atrophie ni altération volumétrique n'a été détectée malgré l'exposition répétée à l'hypoxie (Micaux *et al.*, 2025).
Les performances à la tâche HippoPS n'ont montré aucune différence significative entre apnéistes et témoins, ni avant ni après l'entraînement. Dans les deux groupes, le profil mnésique observé était typique : meilleures performances pour les items identiques, et une plus grande difficulté pour les items similaires. Les apnéistes n'ont donc présenté ni déficit, ni avantage significatif par rapport aux témoins. De plus, ils ont suivi la même courbe d'apprentissage après l'entraînement (Micaux *et al.*, 2025).

Les analyses de connectivité fonctionnelle ont révélé chez les apnéistes après entraînement une accentuation de l'hypoconnectivité hippocampe–cortex sensorimoteur et hippocampe-DMN et un renforcement des liens avec des régions cérébelleuses et visuelles. L'entraînement des apnéistes entraîne également des modifications à large échelle de la connectivité fonctionnelle au sein des réseaux sensorimoteurs, de saillance, attentionnels, fronto-pariétaux et visuels, reflétant une redistribution adaptative des ressources neuronales en condition d'hypoxie. De façon remarquable, la connectivité fonctionnelle hippocampo–cérébelleuse après entraînement était positivement corrélée aux performances mnésiques (Micaux *et al.*, In Prep).

5. Interprétation et discussion

Ces résultats montrent que l'hypoxie volontaire intermittente, contrairement à l'hypoxie pathologique ou environnementale, ne conduit pas à une atrophie hippocampique ni à un déficit mnésique mesurable. Au contraire, elle s'accompagne d'une réorganisation cérébrale fonctionnelle sélective, permettant le maintien des capacités mnésiques.

Cette adaptation rejoint le concept de réserve cognitive (Barulli and Stern, 2013; Verkhratsky and Zorec, 2024), selon lequel le cerveau peut mobiliser plusieurs mécanismes pour préserver ses fonctions. Dans notre cas, l'efficacité se traduit par une redistribution sélective des ressources (diminution des liens avec les régions sensori-motrices, augmentation de la connectivité avec le cervelet et les régions visuelles). La compensation correspond au recrutement de voies alternatives lorsque les circuits classiques deviennent insuffisants. Le maintien reflète la préservation de l'intégrité des réseaux malgré le stress métabolique répété, et la plasticité s'exprime à travers le maintien anatomique des sous-champs et la réorganisation dynamique des connexions hippocampiques.

Sur cette base, nous proposons le HippoXia-Induced Adaptability Model (HiAM), qui intègre plusieurs dimensions d'adaptation. Les facteurs neurocognitifs regroupent la stabilité anatomique, la redistribution fonctionnelle et la préservation mnésique. Les facteurs neurobiologiques incluent des mécanismes cellulaires et métaboliques (neurogenèse, angiogenèse, régulation énergétique). Enfin, les facteurs physiques concernent les ajustements physiologiques et l'effet de l'entraînement sportif. Ensemble, ces trois niveaux soutiennent l'idée que l'hippocampe est capable d'adapter son fonctionnement pour résister au stress hypoxique. Ce modèle heuristique ouvre également de nombreuses perspectives pour des recherches futures, en permettant de tester et affiner chacune de ces dimensions dans des contextes expérimentaux et cliniques variés. Les prolongements de ce travail incluent dans un futur immédiat l'analyse de la perfusion cérébrale (ASL) et de la spectroscopie hippocampique (MRS), afin de mieux caractériser les mécanismes neurovasculaires et métaboliques sous-tendant l'adaptation observée face à des contraintes métaboliques répétées.

Ainsi, l'hippocampe apparaît comme un véritable « hub » adaptatif : loin de subir uniquement des effets délétères, il manifeste une plasticité permettant de préserver la mémoire et une sensibilité qui en fait un marqueur privilégié des réponses cérébrales au stress hypoxique.

6. Conclusion et perspectives

La présente thèse apporte pour la première fois une démonstration que l'hypoxie volontaire intermittente, associée à un entraînement sportif, n'est pas que délétère, et peut induire une plasticité bénéfique. Ces résultats positionnent l'apnée comme un modèle naturel de résilience cérébrale à l'hypoxie. Ils ouvrent des perspectives thérapeutiques dans des contextes de déclin cognitif pathologiques où l'hippocampe est particulièrement vulnérable, comme l'apnée du sommeil, l'ischémie ou certaines épilepsies temporales. Ils suggèrent également que des protocoles combinant hypoxie contrôlée et activité physique pourraient être explorés comme pistes d'intervention visant à renforcer la plasticité cérébrale chez les populations âgées ou à risque.

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List of main abbreviations

AChA: Anterior Choroidal Artery

AMS: Acute Mountain Sickness

ANLS: Astrocyte-Neuron Lactate Shuttle

ANR: Agence Nationale de la Recherche

AO: Airway Obstruction

ASL: Arterial Spin Labeling

ATP: Adenosine Triphosphate

BOLD: Blood Oxygen Level Dependent

CA1 / CA2 / CA3: Cornu Ammonis 1, 2, 3

CEN: Central Executive Network

CMS: Chronic Mountain Sickness

CONN: Functional Connectivity Toolbox for MATLAB

COPD: Chronic Obstructive Pulmonary Disease

CPAP: Continuous Positive Airway Pressure

DAN: Dorsal Attention Network

DG: Dentate Gyrus

DMN: Default Mode Network

EC: Entorhinal Cortex

EM: Episodic Memory

EPI: Echo Planar Imaging

FD: Freediver

FDR: False Discovery Rate

fMRI: Functional Magnetic Resonance Imaging

FOV: Field Of View

FPN: Frontoparietal Network

HA: High Altitude

HiAM: HippoXia-Induced Adaptability Model

HIE: Hypoxic Ischemic Encephalopathy

HRF: Hemodynamic Response Function

HSF: Hippocampal Segmentation Factory©

Hx: Hypoxia

IHT: Intermittent Hypoxic Training

MNI: Montreal Neurological Institute (atlas)

MRS: Magnetic Resonance Spectroscopy

MTL: Medial Temporal Lobe

NC: Normal Controls

OSA: Obstructive Sleep Apnea

PCA: Posterior Cerebral Artery

PS: Pattern Separation

ROIs: Regions Of Interest

RPE: Rate of Perceived Exertion

rs-fMRI: Resting-State Functional Magnetic Resonance Imaging

RSNs: Resting-State Networks

SMA: Supplementary Motor Area

SN: Salience Network

SUB: Subiculum

TE: Echo Time

TR: Repetition Time

VAN: Ventral Attention Network

Neurons starving, lost
Memory’s essence fades dark -
Oxygen returns

J.O.

General introduction

How can freedivers sustain such extraordinary performances, holding their breath for several minutes without apparent cognitive decline? This phenomenon is remarkable, given that in almost every other context hypoxia is associated with impaired memory and hippocampal vulnerability. Consequently, freediving provides a unique opportunity to investigate whether and how the human hippocampus can adapt to hypoxic conditions.

The ANR HippoXia project ("Apnea: a relevant model to test hippocampal adaptability to hypoxia?", ANR-21-CE37-0022, PI. Marion Noulhiane) was designed to address this question through a translational and multimodal approach. It combines two complementary axes: (i) neuroimaging and cognitive investigations in humans, and (ii) neuroimaging, molecular and cellular analyses in rodents. The project is carried out in close collaboration between NeuroSpin (human studies, led by Dr. Marion Noulhiane) and NeuroPSI (animal studies, led by Dr. Marion Noulhiane & Dr. Valérie Doyère).

Within this framework, the present thesis focuses on the human neuroimaging and cognition axis. Freedivers were chosen as a natural model of voluntary intermittent hypoxia, characterized by the combination of repeated apnea episodes and exercise training. This approach complements the animal studies investigating underlying cellular processes. By providing in-vivo evidence in humans, this thesis aims to bridge anatomical and functional neuroimaging with episodic memory performance, thus offering a global and translational perspective on hippocampal adaptability.

The main objectives of this thesis are:

1. To investigate anatomical adaptations of the hippocampal subfields in freedivers.
2. To investigate functional adaptations of hippocampal connectivity in freedivers.
3. To test whether these potential adaptations support the preservation of episodic memory after voluntary intermittent hypoxia, the core cognitive function of the hippocampus.

This thesis is organized as follows: Chapter 1 reviews the current literature and theoretical background. Chapter 2 details the methodological approach. Chapter 3 presents the results, divided into anatomical and functional investigations, each linked to episodic memory outcomes. Finally, Chapter 4 discusses the implications of these findings in the broader context of hippocampal resilience and adaptation to hypoxia.

Chapter 1: Introduction

1. Anatomofunctional organization of the healthy hippocampus and its role in episodic memory

1.1. Anatomical organization of the hippocampus

1.1.1. Hippocampal anatomy and cytoarchitecture

The hippocampal formation, located in the medial temporal lobe (MTL), consists of several anatomically and functionally interconnected regions. It includes the hippocampus proper (Cornu Ammonis fields: CA1–CA4), the dentate gyrus (DG), and the subiculum, along with adjacent cortical areas such as the entorhinal, parahippocampal, and perirhinal cortices (Kandel *et al.*, 2012). The hippocampus is bilaterally present in the brain and connected across hemispheres via the hippocampal commissure of the fornix (Figure 1).

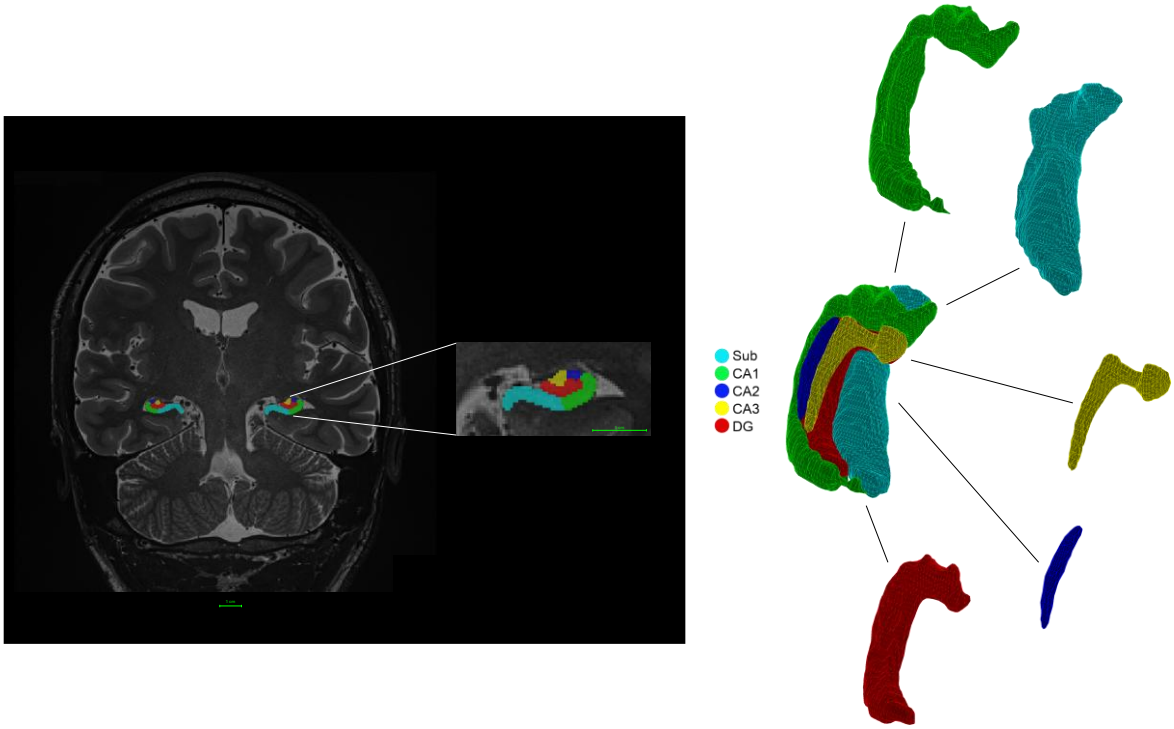


Figure 1: Hippocampal subfields segmented using Hippocampal Segmentation Factory, HSF© (Poiret et al., 2024). (A) T2 image of hippocampal subfields in the coronal plane and magnified view. (B) Segmentation of each subfield. Image from a control of the HippoXia cohort. DG: Dentate Gyrus, Sub: Subiculum.

Each hippocampal subfield is characterized by a distinct cytoarchitecture and supports specific roles in cognition and pathology (Duvernoy, 1998; La Joie *et al.*, 2013). The CA fields form a curved, laminar structure that encircles the DG. CA1 extends from the subiculum,

followed by CA2, CA3, and CA4. CA4 is embedded within the DG, forming a tightly integrated structure. Due to limited resolution of standard in vivo MRI, the boundary between CA4 and DG is often indistinguishable, leading to their merging in many neuroimaging analyses (Pluta *et al.*, 2012). The subiculum is located downstream of CA1 and functions as a principal output region of the hippocampus. It projects to both cortical and subcortical regions, including the entorhinal cortex. The entorhinal cortex, in turn, serves as the main entry point for information from the neocortex to the hippocampus, primarily through the perforant pathway (Kandel *et al.*, 2012) (Figure 2).

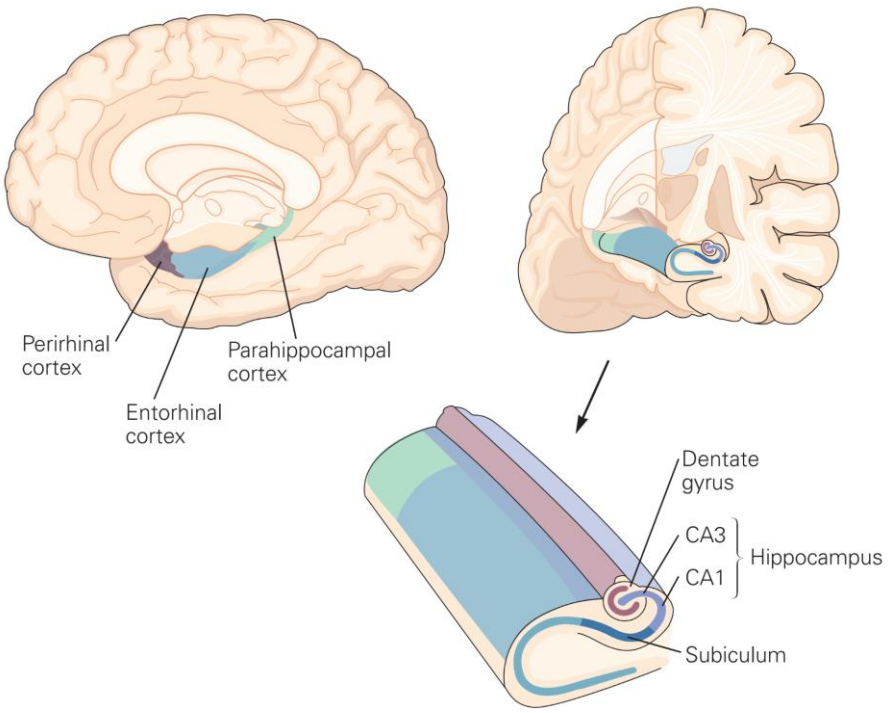


Figure 2: The key components of the medial temporal lobe, essential for memory processes. Adapted from Kandel et al. (2012).

1.1.2. Hippocampal subfields segmentation

Accurately measuring HS volume is essential to understand how intense physiological stressors might lead to anatomical adaptations. Yet, segmenting these small structures remains a major challenge due to their limited visibility on 3T MRI and the lack of consensus across segmentation protocols (Poiret *et al.*, 2023), as subfield boundaries often present poor tissue contrast. This is particularly true for regions like CA2, CA3 and CA4 which exhibit similar signal intensities in standard MRI sequences (La Joie *et al.*, 2013). These issues are intensified by other sources of uncertainty, such as inter-individual anatomical variability, motion artifacts, and inconsistencies between scanners. Segmentation accuracy can be limited, especially in the hippocampal head and tail where anatomical ambiguity is highest (Yushkevich *et al.*, 2015). Higher magnetic field strengths can however provide a partial solution to these challenges. Ultra-high-field 7T MRI offers significantly improved contrast and delineation of hippocampal subfields, revealing microanatomical variations that remain undetectable at 3T (Zsido *et al.*, 2023).

Manual segmentation has long been regarded as the gold standard, but it is laborious, subjective, and prone to variability across users and protocols. The lack of standardized anatomical definitions across subfield protocols also challenges reproducibility. For example, different studies merge subfields in inconsistent ways: CA2, CA3, and CA4 may be combined; CA3 and CA4 may be grouped with the DG; or CA4 may be merged with DG alone. In several protocols, the hippocampal head or tail is even excluded due to segmentation difficulty (Bender *et al.*, 2018; Winterburn *et al.*, 2013).

As these inconsistencies make comparison between studies unreliable, automated pipelines have emerged to reduce human bias. FreeSurfer is the most widely used solution, offering full-brain and hippocampal subfield segmentation. Yet, its performance on HS is limited by anatomical inaccuracies, particularly at the anterior and posterior ends (Mueller *et al.*, 2018). Moreover, it generates extensive unwanted outputs and requires long processing times (up to 10 hours per subject) making it impractical for focused studies. Additionally, studies have shown that its segmentations can deviate from anatomical ground truth, especially in subfields regions. Other tools like ASHS, HIPS, and HippUnfold have shown improved anatomical fidelity but present their own issues. For instance, ASHS tends to misclassify or omit slices at the edges of the hippocampus (Bender *et al.*, 2018). Overall, these segmentation tools are limited by their dependence on manually defined rules or hybrid methods, which restrict their ability to generalize across diverse imaging protocols and anatomical variability (Mueller *et al.*, 2018). These inconsistencies are further aggravated by the absence of universally accepted anatomical atlases. Even high-resolution atlases developed at 3T show variation in subfield boundaries across research groups, complicating reproducibility across studies (Winterburn *et al.*, 2013).

Recent progress in deep learning has made end-to-end models increasingly attractive for image segmentation. These approaches offer several key advantages over traditional pipelines: they are faster, more robust to anatomical variability, and show better generalization across different imaging conditions (Wang *et al.*, 2024). In hippocampal segmentation specifically, deep learning models known as convolutional neural networks (CNNs) have demonstrated superior performance in terms of both accuracy and test-retest reliability on public datasets (Sghirripa *et al.*, 2025). The time required to generate segmentations is also substantially reduced. While traditional pipelines may require several hours, deep learning models can complete segmentation in under one minute per subject. Moreover, their end-to-end architecture allows them to learn directly from the data, reducing their dependence on hand-crafted rules.

Despite these advantages, most deep learning models for HS segmentation are currently trained on limited datasets, which restrains their reproducibility and generalizability. Only few combine robust architecture, heterogeneous training data, and validated performance across image contrasts, field strengths, age groups, and clinical conditions (Sghirripa *et al.*, 2025; Wang *et al.*, 2024).

To address these limitations, recent architectures such as attention-gated 3D Capsule Networks have been proposed. These models enhance segmentation robustness in anatomically and clinically variable populations, extending the capabilities of convolutional approaches (Poiret *et al.*, 2023). Comparative studies evaluated up to ten segmentation methods, including FreeSurfer, FastSurfer, HippUnfold, and HSF. These benchmarks reveal that deep learning models are generally more precise and faster, but still face challenges in clinical settings, particularly due to over-segmentation in the hippocampal head (Sghirripa *et al.*, 2025).

In this context, we chose to use HSF (Hippocampal Segmentation Factory©), a recently developed deep learning-based tool specifically designed for fast, robust, and anatomically precise segmentation of HS across the entire lifespan (Poiret *et al.*, 2023). HSF outperforms existing solutions in terms of accuracy and reliability, closely matching manual segmentations while being much faster and more scalable. Importantly, HSF is one of the few tools validated on both T1- and T2-weighted MRI data. In our project, T2w images were acquired precisely to optimize subfield contrast, and HSF has demonstrated superior performance on this modality. Its ability to segment hippocampal subfields is particularly relevant given that regional effects of hypoxia (e.g., in the DG or CA1) may be spatially localized. This makes HSF the most appropriate choice to detect subtle changes related to training in the hippocampus of adult freedivers.
HSF is built on end-to-end deep learning architecture trained on a highly heterogeneous dataset, which includes variability across scanners, imaging protocols, and anatomical presentations. This design enhances its ability to generalize across a wide range of hippocampal morphologies, including those shaped by age-related changes and pathological alterations. Its high reproducibility and validation across both T1- and T2-weighted MRI enable reliable group-level analyses even in the presence of subtle anatomical differences. HSF was specifically designed to perform accurately across the full adult lifespan and across diverse anatomical phenotypes, making it well suited for our cohort (ages 29 to 55) and for detecting localized hippocampal changes linked to intermittent hypoxia in freedivers.

1.2. Functional organization of the hippocampus and episodic memory

1.2.1. The functional hippocampal network and surrounding cortices

The hippocampus plays an essential role in episodic memory and spatial navigation. It integrates multimodal sensory inputs (visual, auditory, olfactory, spatial, and temporal) through reciprocal connections with associative cortical areas. This integration enables the encoding of contextualized experiences into coherent memory representations.

The hippocampal circuitry is primarily organized around two main pathways: the trisynaptic and monosynaptic circuits. The trisynaptic pathway originates in the entorhinal cortex, which projects via the perforant path to the DG and to CA3. The DG, composed of granule cells, provides sparse coding that is crucial for effective pattern separation. From the DG, mossy

fibers carry information to CA3 pyramidal cells, which then project to CA1 through Schaffer collaterals. CA1 in turn sends output to the subiculum and entorhinal cortex. In parallel, the monosynaptic pathway links the entorhinal cortex directly to CA1, bypassing the DG and CA3 (Kandel *et al.*, 2012) (
Figure 3).

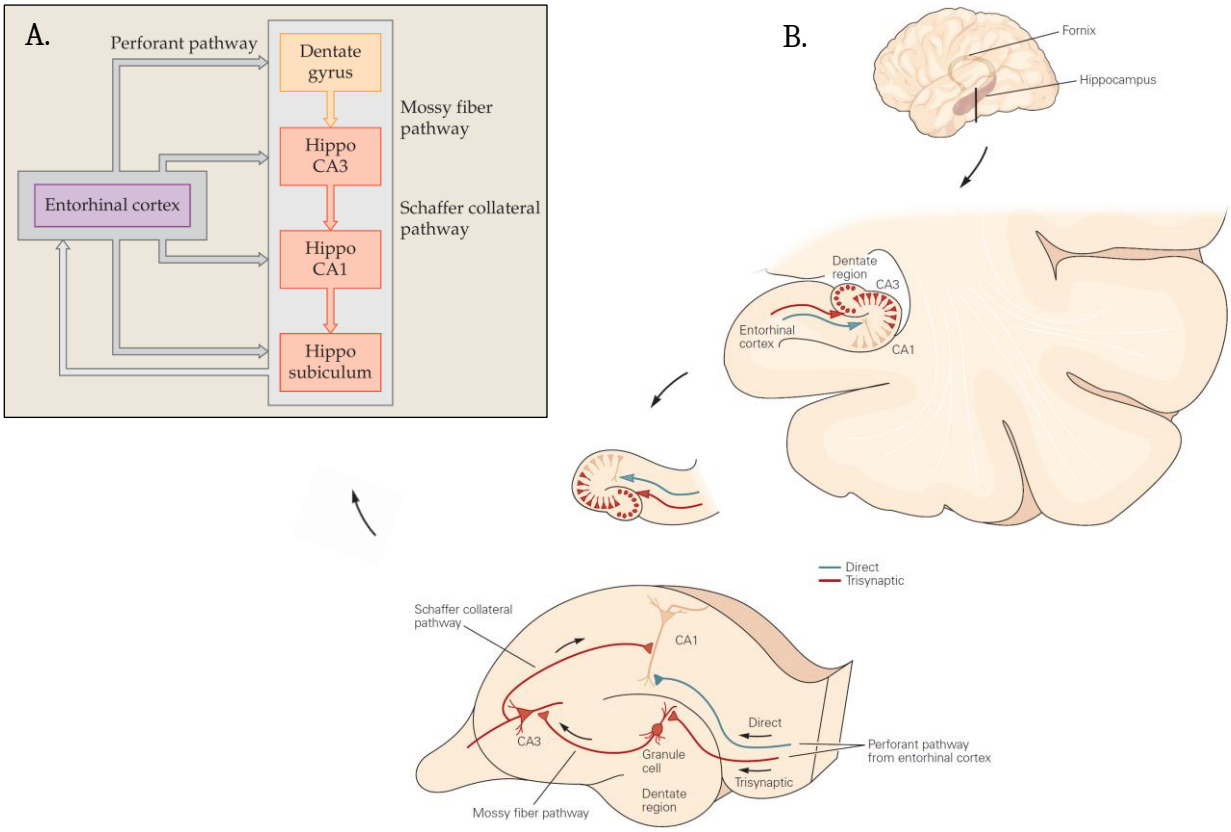


Figure 3: Hippocampal circuit involved in pattern separation. A. Connections within subregions of the hippocampus. B. Inputs from the entorhinal cortex reach CA1 pyramidal neurons via a direct pathway and an indirect trisynaptic pathway through the DG and CA3. Adapted from Kandel et al. (2012) and Purves (2008).

This organization supports core hippocampal computations involved in episodic memory, and notably pattern separation and pattern completion. Pattern separation, largely performed by the DG and CA3, enables the creation of distinct neural representations from overlapping inputs. Pattern completion, mainly supported by recurrent collaterals in CA3, allows for the reactivation of complete memory traces from partial or degraded inputs (Ngo *et al.*, 2021). Feedback projections from CA2–CA3 to the DG may further refine encoding.

CA1 plays an integrative role by receiving converging signals from both CA3 and the entorhinal cortex. It acts as a comparator, evaluating the match between new inputs and stored representations. This function is essential for detecting novelty and contributes to memory consolidation and retrieval (Yassa and Stark, 2011). The subiculum, considered functionally semi-independent, contributes to both spatial and mnemonic processing and plays a major

role in segregating and integrating hippocampal outputs (de Melo *et al.*, 2023). Additionally, it also appears to contribute to pattern separation, as detailed below (Bouyeure *et al.*, 2021).

The hippocampus is part of a broader brain network, and maintains reciprocal connections with MTL structures, including the entorhinal, perirhinal, and parahippocampal cortices. These cortices support parallel processing streams for information related to objects and spatial context (Kandel *et al.*, 2012). The entorhinal cortex serves as a hub linking the hippocampus with the neocortex, supporting the gradual transfer of memories toward long-term storage, consistent with Standard Consolidation Theory (Blum Moyse and Berry, 2024). The hippocampus therefore encodes fine-grained sensory and spatial details, while interactions with the medial prefrontal cortex support generalization and abstraction for flexible retrieval (Zheng *et al.*, 2025).
Additionally, the hippocampus is functionally connected to subcortical structures, including the amygdala, nucleus accumbens, thalamus, and mammillary bodies. These regions provide modulatory input related to emotional salience, motivation, and behavioral relevance, influencing the encoding and retrieval of emotionally significant or behaviorally relevant memories (Grodd *et al.*, 2020; Kaushal *et al.*, 2024; Palomero-Gallagher and Amunts, 2022).

The hippocampus contributes to memory consolidation and retrieval through mechanisms such as synaptic plasticity and spontaneous reactivation during rest or sleep (Deuker *et al.*, 2013; Goto, 2022). It is also essential for transforming short-term experiences into long-term memory traces and for generating internal cognitive maps of spatial environments.
The adult hippocampus is also one of the few brain regions capable of generating new neurons. This neurogenesis occurs in the subgranular zone of the DG, where progenitor cells continuously produce new neurons. Only a small fraction of these neurons reaches functional maturity, ensuring that hippocampal volume remains constant while still allowing for the anatomical plasticity necessary for learning and memory. Neurogenesis is regulated by both intrinsic and extrinsic factors. Intrinsic factors include genetic and epigenetic regulation (e.g., DNA methylation) and extrinsic modulators include neurotransmitters, hormones, growth factors, drugs, stress, environmental enrichment, and exercise training (Aimone *et al.*, 2014). These effects are particularly significant during the 1-to-4-week maturation window, a period during which new neurons are highly excitable and heavily involved in learning (Aasebø *et al.*, 2011).
At the cellular level, the functional specialization of hippocampal subfields is supported by synaptic plasticity, including long-term potentiation (LTP), synaptogenesis, and synaptic remodeling (Kandel *et al.*, 2012). This plasticity, combined with dense local connectivity and selective long-range projections, enables the hippocampus to balance specificity and generalization during memory formation and retrieval.

1.2.2. Episodic memory

Episodic memory is a core component of human memory, referring to the capacity to recall personal-specific experiences within their original context. Unlike semantic memory (general facts) or procedural memory (skills), episodic memory enables the re-experiencing of past events with rich spatial, temporal, emotional, and perceptual details. It allows individuals to

mentally travel back in time and is linked to autonoetic consciousness, a form of self-awareness described by Endel Tulving, that supports first-person recollection (Tulving, 1985). Episodic memory binds together disparate elements, such as sensory impressions, emotional states, and personal thoughts, into a cohesive representation of a unique event. The hippocampus is central to this binding process, and it interacts with several other brain regions to support episodic memory functions. These include the medial prefrontal cortex (encoding and retrieval), the posterior parietal cortex (attentional control during retrieval), and the broader MLT network (Kandel *et al.*, 2012).
In healthy adults, episodic memory supports main cognitive functions, including future thinking, decision-making, social cognition, and the construction of personal identity. This memory system is dynamic: each retrieval act can strengthen, distort, or modify the memory trace. Factors such as attention, emotion, and motivation during encoding strongly affect how vividly and accurately the memory is retrieved later. As memories age, they become progressively stabilized via hippocampal–neocortical interactions, a process known as systems consolidation. Over time, retrieval may rely more on cortical structures, although rich contextual or detailed memories may still require hippocampal involvement (Lavenex and Amaral, 2000; Winocur *et al.*, 2010).

At the mechanistic level, the hippocampus supports two main computations essential for episodic memory: pattern separation and pattern completion (Ngo *et al.*, 2021; Yassa and Stark, 2011).
Pattern completion is mainly supported by CA3's recurrent collateral network, enabling it to reconstruct full memory traces from partial or degraded cues. The CA3 pyramidal cells project onto themselves, and the activity of a small group can spread to re-activate the whole memory pattern. This process is crucial for retrieving memories when the available information is incomplete, as it helps maintain stable and reliable representations.
In contrast, pattern separation involves the generation of distinct neural representations for similar inputs, reducing interference between overlapping experiences. It is primarily mediated by the DG and CA3. In the DG, granule cells employ sparse coding to decorrelate similar inputs arriving from the entorhinal cortex via the perforant path. The resulting signals are transmitted to CA3 pyramidal cells via mossy fibers. This transformation ensures that the output representations are more distinct than the inputs (Figure 4).

Importantly, the efficacy of pattern separation depends on neurogenesis. Newly born neurons in the DG are believed to be particularly efficient in encoding novel inputs in familiar environments due to their increased excitability and plasticity (Kempermann, 2022).

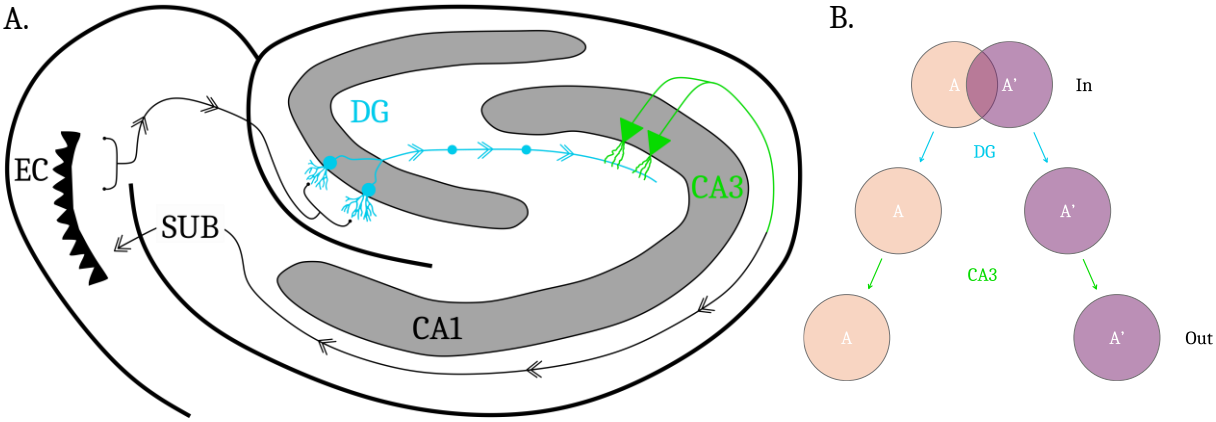


Figure 4: Circuits of pattern separation. A. Diagram of hippocampal cross-section showing regions involved in pattern separation: mainly performed by the DG (blue) and amplified by CA3 (green); B. Schematic representation of pattern separation: the process by which similar, overlapping inputs (e.g., A and A') are transformed into more distinct representations. DG: Dentate gyrus, SUB: subiculum, EC: Entorhinal cortex. Adapted from Dillon et al. (2017).

Pattern separation performance can be assessed using behavioral tasks that involve targets (identical stimuli), lures (similar stimuli), and foils (new stimuli). During encoding, the hippocampus must generate distinct traces for similar inputs. Consolidation is reflected in the ability to correctly differentiate these stimuli after a delay. Retrieval is evaluated based on correct recognition and discrimination. If a retrieval cue is degraded or ambiguous, pattern completion by CA3 may also be employed. These tasks provide a direct assessment of hippocampal functional integrity, allowing researchers to test encoding, consolidation, and retrieval processes with high sensitivity.

1.3. Functional connectivity of the hippocampus

1.3.1. General principle of resting-state fMRI

Functional magnetic resonance imaging (fMRI) relies on the coupling between neural activity, cerebral blood flow, and oxygen metabolism. When a brain region becomes active, local blood flow increases, leading to a relative increase in oxyhemoglobin (hemoglobin bound to oxygen, HbO_2) and a corresponding decrease in deoxyhemoglobin (hemoglobin not bound to oxygen, Hb). Because deoxyhemoglobin is paramagnetic, changes in its concentration alter the magnetic properties of tissue and produce small but measurable variations in the signal, known as the blood oxygenation level-dependent (BOLD) effect (Buxton, 2009). fMRI typically uses T2*-weighted echo-planar imaging sequences to capture these changes, providing an indirect measure of neuronal activity. The hemodynamic response unfolds over seconds, limiting temporal resolution, but spatial resolution at the millimeter scale enables mapping of brain function with high anatomical specificity. As such, fMRI has become a central tool for investigating both the organization of the healthy brain and its alterations in disease (Buxton, 2009).

Resting-state fMRI (rs-fMRI) uses T2*-weighted imaging to measure spontaneous BOLD signal fluctuations at rest without external tasks or distractions. These low-frequency variations result from ongoing neural processes and provide a good idea of the baseline

cognitive brain function. Data quality is shaped by acquisition parameters, with the repetition time (TR) determining temporal resolution and voxel size defining spatial resolution (Logothetis, 2008).

During acquisition, participants are instructed to rest quietly with eyes open or closed, without engaging in any specific task, typically for 5–10 minutes. In this resting state, the brain is active and performs important background processes such as memory consolidation and integration of past experiences. Low-frequency BOLD signal oscillations (0.01–0.1 Hz) reflect the brain's intrinsic functional architecture and are used to assess functional connectivity (Fox and Raichle, 2007) (Figure 5).

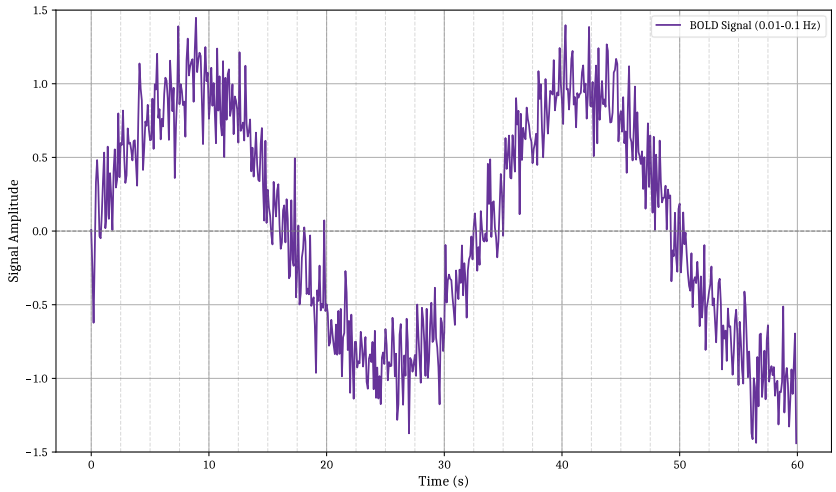


Figure 5: Example of resting-state BOLD signal from a control participant in the HippoXia cohort. The signal displays low-frequency spontaneous fluctuations (0.01–0.1 Hz), typical of rs-fMRI. These slow oscillations reflect changes in the Hb ratio, linked to underlying neural activity, and form the basis for functional connectivity analysis. The acquisition TR (2500 ms) of the T2-weighted EPI sequence is indicated by horizontal dashed lines every 2.5 seconds.*

rs-fMRI has gained importance due to its non-invasive, passive nature, and broad applicability across age groups and clinical populations. Because it doesn't require cognitive engagement or stimulus presentation, data acquisition is straightforward and less susceptible to performance variability. This simplicity is particularly advantageous for studying individuals unable to perform complex tasks, such as young children or patients with neurological or psychiatric conditions. This underscores the clinical potential of rs-fMRI for identifying neural signatures associated with conditions like obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), or stroke, and for guiding early intervention and treatment monitoring.

These resting-state networks (RSNs) have robust inter-individual consistency, but some fluctuations in connectivity may reflect current mental states or local neuronal dynamics (Deco *et al.*, 2011).

Although rs-fMRI data acquisition is relatively simple, isolating neural signals from noise remains a technical challenge. A large portion of the BOLD signal variance comes from non-neural sources, such as movement, respiration, and heartbeats. As a result, rigorous preprocessing is essential to ensure signal quality and interpretability of connectivity

measures. This includes motion correction (to align volumes across time), spatial smoothing (averaging voxel intensities with neighbors to increase signal-to-noise ratio), temporal filtering (e.g., band-pass filtering), and nuisance regression to remove non-neural signals (e.g., from white matter or physiological noise). Finally, normalization aligns individual brains to a common template (e.g., MNI atlas). No universal pipeline exists, and preprocessing must be adapted to the specific scanner parameters, study population, and objectives.

Functional connectivity is defined as the temporal correlation between BOLD signals in different brain regions, reflecting their functional interaction (Zuo and Xing, 2014). ROI-based approaches are commonly used to quantify, particularly the seed-based correlation method, introduced by (Biswal *et al.*, 1995). In this approach, a signal from a predefined seed region is correlated with signals from all other voxels in the brain, identifying regions that show synchronized activity. This enables the characterization of large-scale functional networks and has become a standard technique due to its simplicity and interpretability.

1.3.2. Resting-state networks

rs-fMRI has notably advanced our understanding of brain networks at rest. The default mode network (DMN) is one of the best characterized RSNs. It is consistently more active during internally focused mental activity, such as daydreaming, mind-wandering or self-referential thinking, and deactivates during goal-directed tasks. It supports autobiographical memory, social cognition, and future planning (Greicius *et al.*, 2003; Menon, 2023). The salience network (SN), by contrast, detects and filters salient stimuli from internal or external sources, facilitating dynamic switching between other networks. The central executive network (CEN) supports higher-order cognitive functions including decision-making and working memory (Smith *et al.*, 2019). The attention system is subdivided into the dorsal attention network (DAN) and the ventral attention network (VAN), which together manage attentional resources. The DAN is involved in goal-directed attention, whereas the VAN reorients attention to unexpected but relevant stimuli. These systems contribute to attention flexibility and awareness in different situations (Bernard *et al.*, 2020; Machner *et al.*, 2022). Additionally, sensory-motor networks are involved in basic sensory processing and motor control. These networks are particularly important for processing external sensory inputs (such as vision and touch) and executing movements (Edwards *et al.*, 2019). Figure 6 illustrates the principal RSNs typically identified with rs-fMRI.

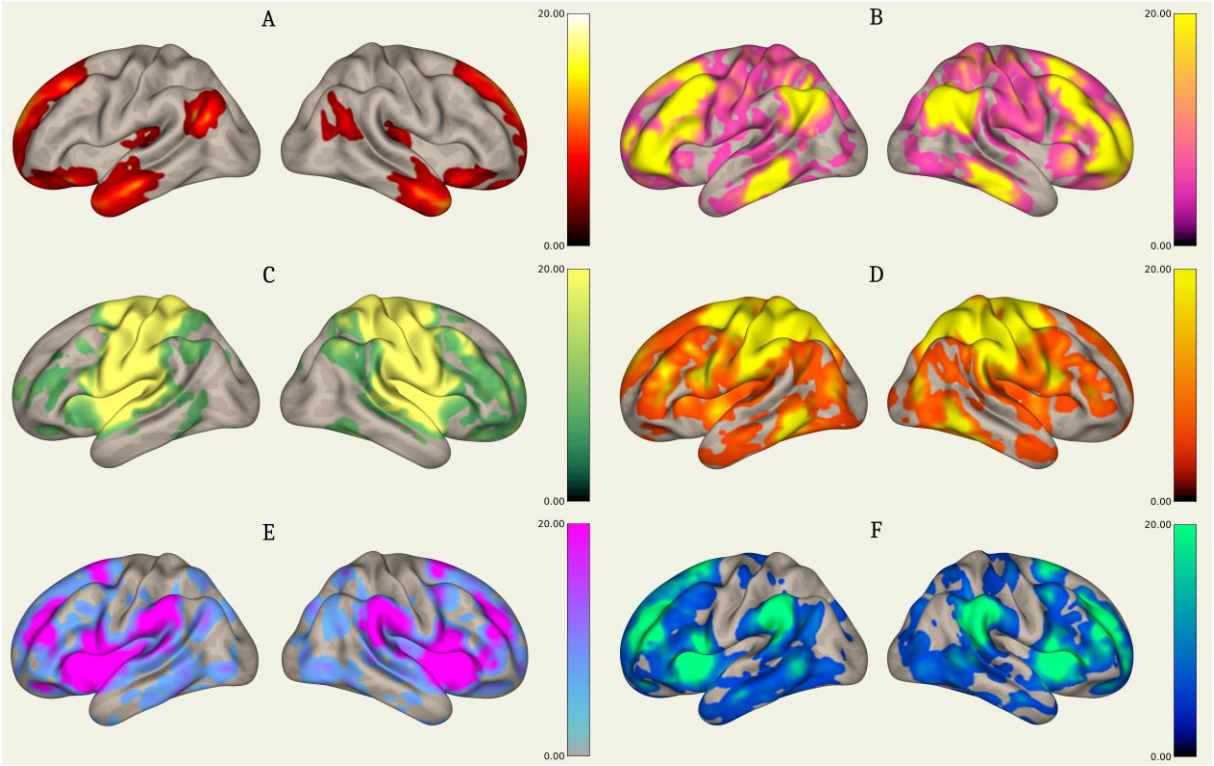


Figure 6: Surface plots of RSNs obtained with controls of the HippoXia cohort. A: Default mode network, B: Central executive network, C: Sensory-motor networks, D: Dorsal attention network, E: Salience network, F: Ventral attention network.

In addition to these large-scale systems, rs-fMRI also enables a more targeted exploration of specific regions such as the hippocampus, offering insights into its connectivity patterns and their modulation under different conditions by physiological or pathological factors (Dautricourt *et al.*, 2021; Heller-Wight *et al.*, 2023; Oren *et al.*, 2019).

1.3.3. rs-fMRI in the hippocampus and pattern separation

rs-fMRI has provided valuable insights into the connectivity of the hippocampus with brain networks. The hippocampus is consistently integrated within the DMN, particularly through its coupling with the posterior cingulate cortex and the medial prefrontal cortex, supporting its role in episodic memory and internally oriented cognition (Barnett *et al.*, 2021; Greicius *et al.*, 2004). Resting-state studies also highlight hippocampal connectivity with the somatomotor network, indicating that its functional coupling extends across multiple large-scale cortical systems (Ezama *et al.*, 2021). Importantly, hippocampal connectivity is highly plastic, and clinical studies demonstrate that pathological or environmental conditions can rapidly alter these networks. For instance, patients with OSA show disrupted hippocampal connectivity, partially restored after continuous positive airway pressure treatment (CPAP) (Huang *et al.*, 2023). Similarly, early Alzheimer's disease is characterized by hippocampal disconnection from DMN hubs (Dautricourt *et al.*, 2021; Wang *et al.*, 2006). These observations indicate that rs-fMRI can capture both stable functional networks and their dynamic alterations, which may precede or accompany cognitive decline.

Hippocampal connectivity is closely related to episodic memory performance. In healthy

development, adolescent children show correlation between hippocampal-cortical connectivity and improved memory abilities (Warren *et al.*, 2021). Conversely, in aging, elevated hippocampal connectivity with cortical regions has been linked to paradoxically poorer performance, suggesting inefficient compensatory mechanisms (Salami *et al.*, 2014). Longitudinal evidence further shows that changes in hippocampal connectivity following cognitive effort predict later memory decline, highlighting network adaptability as a marker of cognitive resilience (Oren *et al.*, 2019). In addition, disruption of hippocampal coupling with DMN regions, particularly the posterior cingulate cortex, has been consistently associated with episodic memory deficits in neurodegenerative disorders (Dautricourt *et al.*, 2021; Greicius *et al.*, 2004). These alterations can appear before clear clinical symptoms, supporting their value as early biomarkers of memory dysfunction. In this context, hippocampal connectivity fluctuations not only capture current cognitive status but also provide predictive information about future memory trajectories.

Pattern separation relies on hippocampal computations supported by distributed networks. Evidence suggests that connectivity between entorhinal cortex and hippocampus is crucial for mnemonic discrimination, with reduced circuit integrity predicting impaired performance in older adults (Adams *et al.*, 2022). On a larger scale, different cortico-hippocampal networks make distinct contributions to memory processing. A recent review highlights that prefrontal and parietal cortices interact with hippocampal circuits to optimize pattern separation, suggesting that discrimination emerges from distributed network cooperation rather than isolated hippocampal function (Amer and Davachi, 2023). Functional coupling between the hippocampus and DMN regions also predicts individual differences in mnemonic discrimination ability (Wahlheim *et al.*, 2022), and alterations in these networks are associated with impaired pattern separation in several conditions. For example, hippocampal disconnection in aging or neurodegeneration correlates with reduced discrimination performance (Adams *et al.*, 2022; Dautricourt *et al.*, 2021). These observations support the hypothesis that pattern separation is highly sensitive to changes at the network level, which is detectable at rest.

Together, these findings indicate that hippocampal resting-state connectivity is a robust marker of episodic memory function and, more specifically, of pattern separation ability. Given that involuntary hypoxia has been shown to alter hippocampal networks (Micaux, Troudi Habibi, *et al.*, 2025), we can hypothesize that voluntary hypoxia, as experienced in freediving, may also modulate hippocampal connectivity patterns. Such modulation could influence mnemonic discrimination capacities. Investigating the joint contribution of rs-fMRI measures and behavioral assessments of pattern separation provides a relevant framework for understanding hippocampal adaptation to voluntary hypoxia, offering new insights into the neural mechanisms of hippocampal vulnerability and potential resilience.

2. Anatomofunctional organization of the hippocampus under hypoxia and its impact on episodic memory

2.1. Involuntary hypoxia: environmental and pathological

2.1.1. Definition and types of hypoxia

Oxygen homeostasis is essential to maintain aerobic metabolism, as tissues continuously depend on an adequate supply of oxygen through respiratory and circulatory systems. Disruptions in oxygen delivery, transport, or utilization compromise this balance and generate hypoxic stress. At the cellular level, adaptive mechanisms such as the activation of hypoxia-inducible factors (HIFs) promote angiogenesis, glucose metabolism, and cell survival (Semenza, 2012). Yet, when oxygen deprivation becomes severe or prolonged, these responses may fail, resulting in dysfunction and tissue injury.

In medical and physiological contexts, hypoxia designates insufficient oxygen availability at the tissue level, whereas anoxia refers to its extreme form, complete oxygen absence. It is also distinct from hypoxemia, a state of reduced arterial oxygen partial pressure (PaO_2). Hypoxemia is a frequent cause of hypoxia, but the two are not equivalent, as hypoxia can occur without hypoxemia (e.g., ischemia, carbon monoxide poisoning, mitochondrial dysfunction), and mild hypoxemia can be compensated without inducing tissue hypoxia. Hypoxia is commonly classified into four main categories based on mechanism: hypoxic (low arterial O_2 pressure), anemic (reduced blood capacity to carry 0_2), circulatory (reduced tissue perfusion), and histotoxic (impaired cellular use of O_2). In this thesis, the focus will be on three descriptive dimensions: temporal pattern (acute vs. chronic), intentionality (voluntary vs. involuntary), and exposure mode (intermittent vs. continuous). This framework will guide the analysis of how distinct hypoxic profiles affect hippocampal integrity.

Acute vs. chronic hypoxia

The first classification dimension concerns the duration and onset of oxygen deprivation. Acute hypoxia refers to a sudden and transient reduction in oxygen supply, lasting several minutes. It is commonly observed in medical emergencies such as cardiac arrest, respiratory failure, or stroke. Experimental models often use induced cardiac arrest in rodents to simulate acute global hypoxic events (Weihs *et al.*, 2020). In clinical settings, resuscitated patients following out-of-hospital cardiac arrest provide valuable data on the short-term impact of severe oxygen deprivation on brain structures (Stamenova *et al.*, 2018).

In contrast, chronic hypoxia refers to prolonged exposure to reduced oxygen levels, lasting from several weeks to years. It is typically observed in individuals living at high altitude, or in patients with COPD (Wang *et al.*, 2017). Animal models using long-term exposure to hypobaric hypoxia, often in altitude simulation chambers, replicate chronic environmental conditions (Salyha and Oliynyk, 2023; Santocildes *et al.*, 2021).

Intermittent vs. continuous hypoxia

The second classification dimension refers to the temporal pattern of oxygen deprivation. Intermittent hypoxia consists of repeated cycles of hypoxic exposure alternating with normoxia. This profile is typical of OSA and some high-altitude activities involving repeated exposure (e.g., alpinism). In OSA, for instance, patients undergo dozens of nightly episodes of desaturation and reoxygenation (Feng *et al.*, 2012; Owen *et al.*, 2019). Similarly, athletes using intermittent hypoxic training (IHT) protocols may experience controlled cycles of oxygen deprivation and restoration (Rybnikova *et al.*, 2022). Notably, the effects of intermittent hypoxia are dose-dependent: brief controlled exposures may induce adaptive plasticity, whereas prolonged pathological cycles can cause hippocampal damage (Navarrete-Opazo and Mitchell, 2014).

By contrast, continuous hypoxia refers to sustained oxygen deprivation over short (e.g., cardiac arrest) or extended periods (e.g., COPD, high altitude residence) without interruption (Shushanyan *et al.*, 2023; Weihs *et al.*, 2020; Zhang *et al.*, 2022). In experimental settings, animals are subjected to constant hypobaric hypoxia for weeks to model this type of exposure (Zhang *et al.*, 2023).

Although all forms of hypoxia reduce oxygen availability, their temporal characteristics lead to distinct anatomical effects. Distinguishing acute, chronic, intermittent, and continuous patterns is essential to understand how hypoxia impacts the hippocampus.

Voluntary vs. involuntary hypoxia

The third classification dimension considers whether the hypoxic exposure is voluntary, i.e., deliberate, or involuntary, i.e., caused by environmental or pathological conditions.

Voluntary hypoxia is specific to behavioral or training contexts, and requires active control over exposure parameters (duration, intensity, recovery). One prominent example is freediving, where athletes intentionally hold their breath for extended periods, subjecting themselves to repetitive, acute hypoxic episodes (Annen *et al.*, 2021). Similarly, IHT is used in both athletic and medical settings to induce adaptive responses aimed at improving performance or metabolic function (Boulares *et al.*, 2024). These exposures are usually brief, well-controlled, and part of a training or therapeutic protocol. In contrast, involuntary hypoxia occurs without the individual's control and is generally associated with pathological or environmental conditions. It includes events such as respiratory failure, OSA, or chronic exposure to high altitude. This distinction is not merely conceptual but has direct physiological implications. Voluntary hypoxia is often preceded by preparatory strategies (e.g., hyperventilation in freedivers), allowing partial anticipation and mitigation of oxygen stress. In contrast, involuntary hypoxia is frequently unpredictable, prolonged, and uncontrolled, consequently increasing the risk of anatomical damage due to a lack of compensatory adaptation.

In practice, hypoxic conditions rarely falls into a single category and often represent combinations of the dimensions as described above (Figure 7): cardiac arrest is one of the many examples of acute, involuntary, continuous hypoxia. OSA represents a chronic, involuntary, intermittent form of hypoxia. High-altitude exposure is involuntary and may

either be chronic and continuous (e.g., permanent residents) or acute and intermittent (e.g., alpinists). Interestingly, freediving involves acute, voluntary, intermittent exposure; a category with limited representation. Understanding these composite profiles is essential when analyzing both experimental models and clinical populations, as the pattern, duration, and intentionality of hypoxia jointly determine the risk and nature of hippocampal vulnerability.

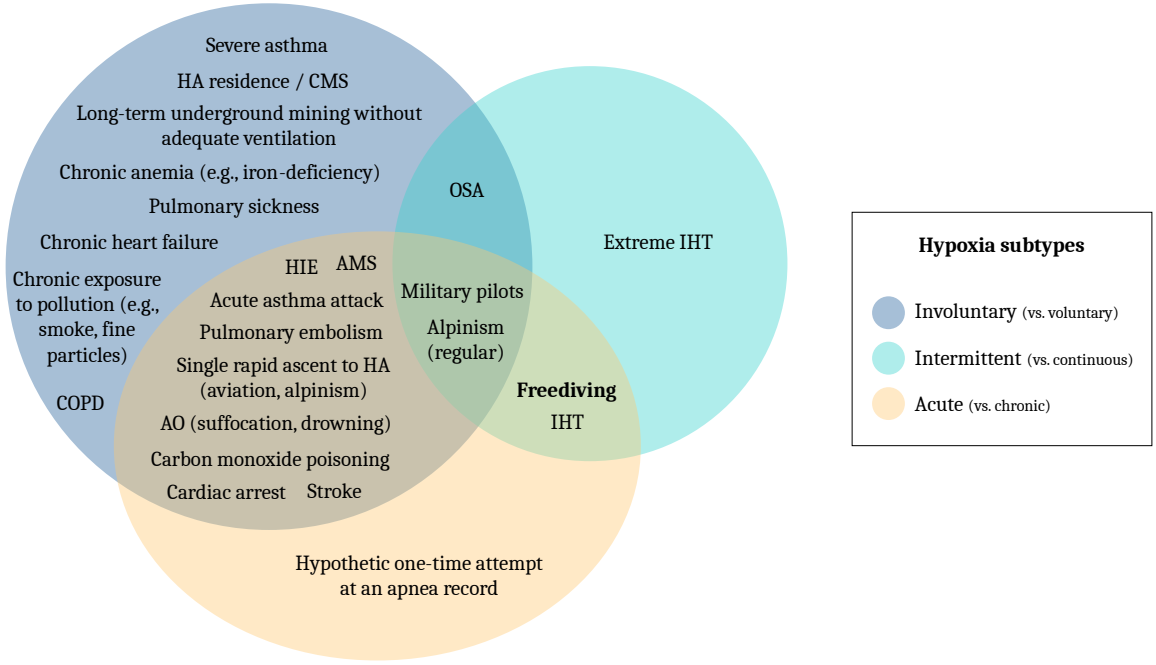


Figure 7: Schematic representation of hypoxia subtypes and illustrative examples. The intersections illustrate that hypoxia rarely falls into a single category, and underline both the diversity of hypoxic conditions and the fact that most hypoxia cases are involuntary, either acute or chronic, and continuous, while voluntary exposures (e.g., IHT, freediving) remain the exception. Common to all subtypes is that hypoxia represents a challenge with variable intensity and duration, where the overlap zones highlight situations combining external constraint, sudden onset, and/or repetition. AO: Airway Obstruction; AMS: Acute Mountain Sickness; CMS: Chronic Mountain Sickness; COPD: Chronic Obstructive Pulmonary Disease; HA: High Altitude; HIE: Hypoxic Ischemic Encephalopathy; IHT: Intermittent Hypoxic Training; OSA: Obstructive Sleep Apnea.

2.1.2. Impact of involuntary hypoxia on hippocampal anatomy and episodic memory

General mechanisms underlying hippocampal vulnerability to hypoxia

The hippocampus is particularly susceptible to oxygen deprivation due to converging vascular, metabolic, and synaptic factors.

The hippocampus receives dual arterial input from the posterior cerebral artery (PCA) and the anterior choroidal artery (AChA), with frequent anastomoses (i.e., direct connection between the two arteries). A mixed pattern is common: the AChA typically supplies the head, and the PCA supplies the body and tail. This border-zone arrangement lowers tolerance to hypoperfusion. Baseline oxygenation and neurovascular coupling are also lower than in the neocortex, limiting O_2 reserve even more. Noninvasive assessments of hippocampal venous

oxygenation can provide physiological markers that complement anatomical measures (Li *et al.*, 2024; Shaw *et al.*, 2021; Spallazzi *et al.*, 2019).
At the metabolic level, synaptic activity essential to memory encoding is very demanding in cellular energy (Adenosine TriPhosphate, ATP), leaving a small security margin (Kann *et al.*, 2011). Hippocampal neurons predominantly rely on mitochondrial oxidative phosphorylation and have limited glycolytic reserve. Consequently, an abrupt drop in O_2 rapidly diminishes ATP levels. The astrocyte–neuron lactate shuttle may buffer mild hypoxia but is insufficient under severe hypoxia (Magistretti and Allaman, 2018).
At the synaptic level, dense glutamatergic connectivity, especially in CA1, becomes a problem when hypoxia impairs glutamate clearance, causing calcium overload and neuronal death (Randall and Thayer, 1992). Intermittent hypoxia also promotes oxidative stress in hippocampal neurons, impairing learning and memory (Lu *et al.*, 2025). Dendritic spines constitute a convergence point for oxidative stress and glutamatergic signaling, linking physiological stress to subsequent memory impairments. Notably, controlled, moderate intermittent hypoxia may enhance hippocampal resilience (Cui *et al.*, 2024). With this in mind, we will here focus on macroscopic alterations at the hippocampal subfields level.

Impact of involuntary hypoxia on hippocampal anatomy

Acute hypoxia results in rapid and global hippocampal damage, often centered on the CA1 subregion. Post-mortem studies after brief cardiac arrest consistently report neuronal death and cellular loss especially in CA1, highlighting the extreme vulnerability of this area to transient oxygen deprivation (Fujioka *et al.*, 2000; Weihs *et al.*, 2020). MRI findings in survivors of cardiac arrest support these observations, revealing persistant hippocampal atrophy despite relatively preserved global brain volumes (Stamenova *et al.*, 2018). In neonates with hypoxic-ischemic encephalopathy (HIE), anatomical MRI studies also reveal persistent volume reduction in the hippocampus, even following therapeutic hypothermia (Annink *et al.*, 2021; Pfister *et al.*, 2023), suggesting irreversible anatomical damage. Carbon monoxide-induced hypoxia in rodents leads to measurable hippocampal atrophy as well, especially in the DG, which is accompanied by reduced cellular density (Liu *et al.*, 2016). Interestingly, partial recovery has been documented in animal models weeks after acute hypoxic injury: CA1 repopulation was observed 20 weeks post-cardiac arrest (Weihs *et al.*, 2020), suggesting some anatomical plasticity in the hippocampus.
In contrast, chronic hypoxia leads to more uniform, progressive anatomical alterations, often extending to the whole hippocampus. In patients with COPD, bilateral hippocampal atrophy has been documented, often accompanied by reductions in cortical gray matter (Li and Fei, 2013; Wang *et al.*, 2017). Similarly, prolonged high-altitude exposure is associated with decreased hippocampal volume and signs of vascular and perfusion deficits (Chen *et al.*, 2023; Lu *et al.*, 2025). These effects appear to reflect cumulative hypoxic events rather than sudden injury. As a result, chronic exposure alters multiple subfields, as shown by Lu *et al.* (2025), who report changes in the DG, CA1, and CA3 regions. Animal studies under sustained hypobaric conditions show significant anatomical degeneration as well (Kanaan *et al.*, 2006; Shushanyan *et al.*, 2023; Zhang *et al.*, 2023).

Overall, acute hypoxia induces rapid, prominent and often irreversible anatomical changes, predominantly affecting CA1, whereas chronic hypoxia produces slower, progressive, and widespread hippocampal damage involving DG, CA1, and CA3, even under milder hypoxic conditions (Hencz *et al.*, 2023).

Intermittent hypoxia, as typically seen in OSA, provokes repeated cycles of desaturation and reoxygenation. This pattern is particularly disruptive for plastic regions of the hippocampus, such as the DG. Post-mortem studies reported reduced cellular layer thickness in DG tissues from OSA patients (Owen *et al.*, 2019). In both pediatric and adult populations, neuroimaging consistently reveals damage in the DG as well (Cha *et al.*, 2017; Feng *et al.*, 2012). Anatomical atrophy in these cases correlates with the severity of nocturnal desaturation and cognitive impairment. Experimental models of intermittent hypoxia in rodents also show that chronic intermittent exposure leads to disruption of hippocampal architecture and volume reduction, particularly in the DG (Khuu *et al.*, 2019). Notably, the DG emerges here as a particularly sensitive subfield under intermittent stress, supporting the hypothesis that intermittent hypoxia preferentially targets plastic subfields.
In contrast, continuous hypoxia, such as in COPD or prolonged high-altitude exposure, leads to overall anatomical degradation, predominant in CA1, similar to acute hypoxia. Accordingly, imaging studies highlight global hippocampal atrophy (Li and Fei, 2013; Muñoz-López *et al.*, 2017), with specific focal alterations in CA1 (Weihs *et al.*, 2020).
In summary, intermittent hypoxia rapidly disrupts synaptic structure and neurogenesis in the DG, potentially leading to early cognitive dysfunction. Recent evidence also suggests sex-specific vulnerability, with male rodents exhibiting DG alterations under intermittent hypoxic stress, unlike females (Takenouchi *et al.*, 2025). Continuous hypoxia, on the other hand, produces more gradual yet global volume loss, consistent with a progressive anatomical degradation via hypoperfusion.

Across all forms of involuntary hypoxia, the hippocampus emerges as a consistently vulnerable target (Figure 8). Yet, the severity, trajectory, and subfield specificity of damage vary depending on the type, duration, and temporal pattern of exposure. Acute hypoxia leads to rapid, focal damage, predominantly in CA1; chronic hypoxia induces uniform atrophy affecting multiple subfields; intermittent hypoxia, if severe, preferentially affects plastic regions like the DG and continuous hypoxia results in overall progressive degeneration, especially in CA1, as seen in acute hypoxia. These findings are consistent across human and animal data, as well as imaging and histological techniques.
Although theoretical classifications are useful, real-world exposures often overlap, producing unique—and sometimes exacerbated—patterns of hippocampal alteration that deviate from predictions based on isolated exposure types. In particular, we observed that individuals exposed to more than one hypoxic condition, whether sequentially or simultaneously, exhibit hippocampal atrophy patterns that diverge from those expected under single-category frameworks. For example, OSA is typically classified as intermittent hypoxia, but its chronicity (daily exposure over several years) makes it more accurately characterized as chronic intermittent hypoxia. Imaging studies in OSA consistently show bilateral hippocampal

atrophy, with a particularly marked reduction in DG volume (Cha *et al.*, 2017; Feng *et al.*, 2012). In addition, pre-existing chronic hypoxia can sensitize the hippocampus to further acute damage.
This suggests that hybrid hypoxic profiles lead to unique combinations of focal and diffuse hippocampal atrophy, often involving multiple subfields and reflecting interacting damage mechanisms. These patterns cannot be fully explained by studying isolated hypoxia types in experimental models, underscoring the need for studies that consider realistic exposure profiles.
This complexity raises the question of whether certain populations may develop adaptive hippocampal responses to repeated hypoxic stress. For example, freedivers who experience acute (but controlled) voluntary intermittent hypoxia, have been reported to show preserved cognitive performance (Ridgway and McFarland, 2006), possibly reflecting compensatory mechanisms. Understanding such non-pathological adaptations could ultimately inform strategies to mitigate hippocampal atrophy in patients suffering from involuntary hypoxia. However, developing such targeted interventions requires a deeper understanding of how specific patterns of hypoxic exposure shape the hippocampus over time, a key aim of this thesis. Additionally, these anatomical changes, observable in both clinical and experimental models, form the basis for hypoxia-induced episodic memory deficits, which will be addressed in the next section.

Impact of involuntary hypoxia on episodic memory

Episodic memory depends on the anatomical integrity of the hippocampus and its connected networks, making it especially vulnerable to hypoxic insults. As shown in the previous section, involuntary hypoxia alters hippocampal anatomy depending on the type, severity, and pattern of oxygen deprivation, and these anatomical changes have measurable consequences on memory performance. Across clinical and experimental studies, involuntary hypoxia, whether acute, chronic, intermittent, or continuous, is consistently associated with episodic memory deficits. Yet, the onset, severity, and reversibility of these impairments vary with the type and duration of hypoxia, as well as the developmental stage at exposure.

Acute hypoxia leads to sudden, often irreversible impairments in memory. For instance, Nation *et al.* (2017) showed that pilot training at high altitude impaired quickly episodic memory performance in military aircrew. We observe similar deficits in other types of memory in adults: even brief hypoxic events such as cardiac arrest can cause lasting damage. Stamenova *et al.* (2018) reported persistent verbal memory deficits months after resuscitation, in parallel with hippocampal atrophy on MRI. In neonates with HIE, the cognitive impact becomes apparent later in development but is often more profound, as shown by Holder *et al.* (2025) who documented working memory deficits in school-aged children with a history of HIE. Anatomical imaging by Annink *et al.* (2021) also revealed significant hippocampal volume reductions associated with episodic memory deficits, despite early therapeutic intervention. These findings indicate that early-life acute hypoxia can permanently disrupt memory. In animal studies, (Liu *et al.*, 2016) showed that mimicking carbon monoxide poisoning in rodents causes delayed memory impairments, accompanied by reduced

hippocampal neurogenesis. Although partial functional recovery was observed after hyperbaric oxygen therapy, anatomical damage persisted. Zhang *et al.* (2023) further confirmed that short-term hypobaric hypoxia causes alterations that impair learning and memory retrieval.
By contrast, chronic hypoxia produces more gradual and cumulative effects on memory, often progressing silently before manifesting as clinical deficits. In adults with COPD, cognitive decline has been linked to hippocampal atrophy, with the severity of the disease correlating with cognitive performance (Li and Fei, 2013). These findings suggest that chronic hypoxia impairs memory function even before clear respiratory symptoms emerge. Similar patterns have been reported in populations living at high altitude. Li and Wang (2022) and Chen *et al.* (2023) documented impaired spatial and working memory in long-term residents of high-altitude environments, with severity proportional to duration of exposure. Children with cyanotic congenital heart disease offer a developmental model of chronic hypoxia: Muñoz-López *et al.* (2017) found that these children exhibit severe deficits in episodic memory, alongside volume loss in the hippocampus. Notably, these impairments occurred in the absence of general cognitive delay, reinforcing the hippocampal specificity of the deficits.
Altogether, these results indicate that acute involuntary hypoxia produces abrupt episodic memory impairments, particularly when CA1 and DG are affected. While some recovery may be possible under specific conditions, most studies point to long-lasting memory loss, especially following early developmental exposure. Chronic involuntary hypoxia appears instead to produce progressive episodic memory dysfunction. Although initially subclinical, these deficits tend to become more severe over time, as hippocampal atrophy and network disruption accumulate. Relative to acute hypoxia, the trajectory is slower and may involve compensatory plasticity; however, with prolonged insult, the risk of irreversible damage increases and cognitive outcomes are similarly detrimental.

The temporal pattern of oxygen deprivation also shapes episodic memory, illustrated by intermittent hypoxia cases. In adults with OSA, several studies report reduced DG volume accompanied by impairments in visual, verbal and working memory (Cha *et al.*, 2017; Olaithe *et al.*, 2018). In addition, OSA has been linked to impaired pattern separation, reflecting deficits in episodic memory consolidation during sleep (Berisha *et al.*, 2024). These findings strengthen the evidence that the DG, as a highly plastic region, is particularly sensitive to intermittent hypoxic stress. With this in mind, OSA could become a potential target for early therapeutic intervention, especially in children or cognitively vulnerable individuals. In some cases, partial reversibility of memory deficits has already been reported, and CPAP treatment in OSA has led to modest cognitive improvements (Olaithe *et al.*, 2018).
In contrast, continuous hypoxia seems to result in more progressive memory impairment. Wang *et al.* (2017) reported that patients with stable COPD exhibit initially subclinical memory dysfunction, often preceding anatomical imaging findings. Animal studies confirm that sustained hypobaric hypoxia disrupts memory function associated with hippocampal anatomical degradation (Zhang *et al.*, 2023). Unlike intermittent patterns, continuous hypoxia has a global and cumulative impact on memory, often without clear opportunities for

reversal. However, experimental hyperbaric oxygen has been shown to mitigate memory decline in rodents exposed to acute continuous hypoxia (Liu *et al.*, 2017).
In summary, due to the vulnerability of the hippocampus to hypoxic stress, all forms of involuntary hypoxia studied across different contexts result in memory impairments, predominantly affecting working and episodic memory (Malle *et al.*, 2012).

Modulating factors: age, duration, reversibility

The extent and reversibility of these hippocampal damages depends on several modulating factors:

- Developmental timing: Early-life exposure (e.g., HIE or congenital heart disease) leads to profound and long-lasting memory deficits, due to disruption of maturing hippocampal networks (Holder *et al.*, 2025; Muñoz-López *et al.*, 2017).

- Exposure duration and severity: Chronic and severe hypoxia, whether continuous (e.g., COPD) or intermittent (e.g., OSA), is associated with broader memory impairment and more extensive anatomical degeneration (Li and Fei, 2013; Olaithe *et al.*, 2018).

- Pattern of hypoxia: Intermittent hypoxia impairs encoding processes early, while continuous hypoxia leads to delayed but more extensive memory loss due to cumulative anatomical changes (Liu *et al.*, 2016; Olaithe *et al.*, 2018).

- Therapeutic potential: Partial memory recovery is possible under certain conditions (e.g., early intervention, CPAP use, hyperbaric oxygen, therapeutic hypothermia), but this reversibility is often incomplete and declines with prolonged hypoxic exposure (Huang *et al.*, 2023; Liu *et al.*, 2016).

In summary, converging evidence indicates that involuntary hypoxia causes significant episodic memory impairment, following patterns that mirror the anatomical damage (Figure 8). However, the extent, distribution, and reversibility of these alterations vary according to the profile (acute vs. chronic) and pattern (intermittent vs. continuous) of exposure. These differences help explain the heterogeneity in anatomical and cognitive outcomes across hypoxia types. CA1 appears particularly vulnerable to acute continuous hypoxia, whereas the DG is more affected in chronic and intermittent exposures. The specific location, extent, and progression of hippocampal damage influence both clinical expression and potential for recovery. Moreover, it is possible that functional connectivity alterations (addressed in the following section) mediate these local damages.

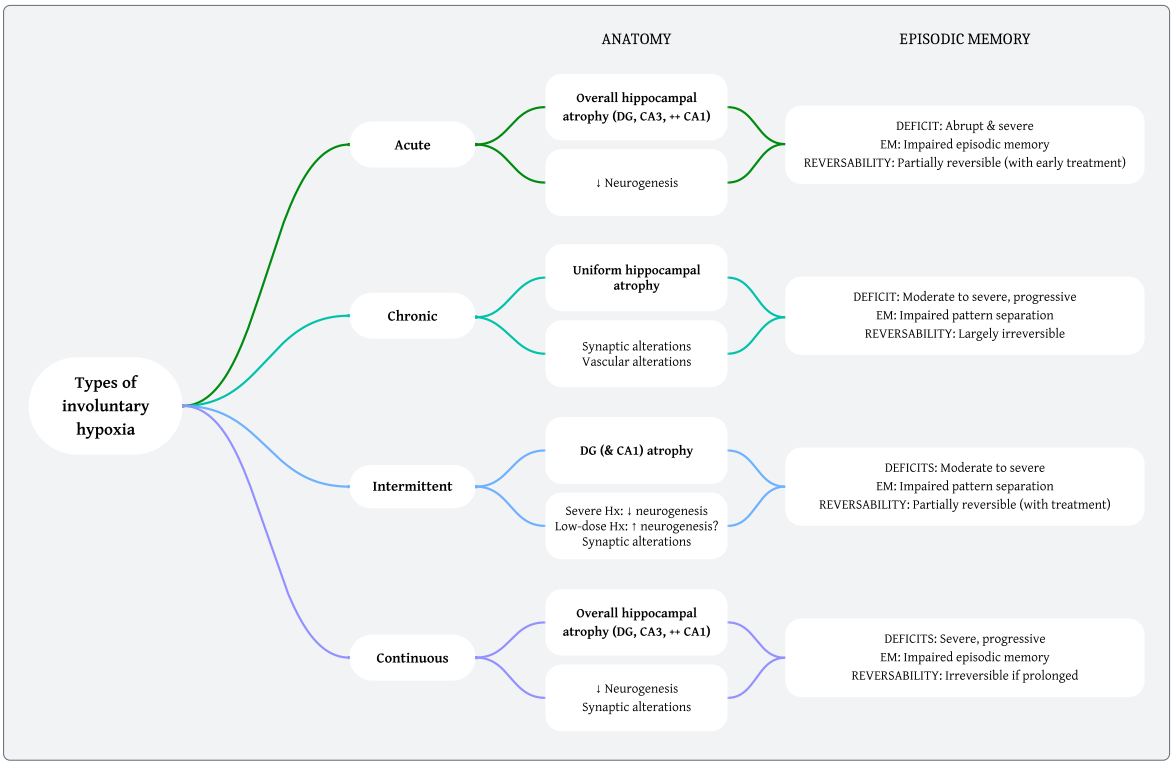


Figure 8: Hippocampal vulnerability: hypoxic patterns and episodic memory outcomes. Acute hypoxia leads to overall hippocampal atrophy (especially in CA1) and abrupt memory loss, particularly when occurring during early development. Chronic hypoxia produces uniform hippocampal damage and gradual episodic memory decline, often missed until irreversible. Intermittent hypoxia disrupts episodic memory early by targeting plastic subfields (DG), whereas continuous exposure causes overall hippocampal atrophy (especially in CA1, similar to acute hypoxia) and results in progressive but severe episodic memory deterioration. DG: Dentate Gyrus, EM: Episodic Memory, Hx, Hypoxia.

These findings emphasize the need for early detection and intervention to preserve memory function in populations at risk, and therapeutic strategies must be adapted to hypoxia type. For intermittent hypoxia in conditions like OSA, CPAP therapy directly targets respiratory instability, showing partial reversibility of memory deficits (Huang *et al.*, 2023; Olaithe *et al.*, 2018). In acute hypoxia, interventions like hyperbaric oxygen therapy may rescue neurogenesis and memory function if applied early (Liu *et al.*, 2016), though long-term cognitive benefits require further validation in controlled trials. In neonatal care, the persistence of memory deficits after acute hypoxia despite interventions like therapeutic hypothermia underscores the need to develop early cognitive rehabilitation programs for infants at risk (Holder *et al.*, 2025). It is important to highlight that for chronic continuous hypoxia (e.g., high altitude or advanced COPD), no treatment exists: prevention of cumulative damage through oxygenation support or environmental adaptation remains essential.

Despite the consistency of findings, several contradictions and limitations emerge when comparing studies, often due to methodological differences, heterogeneous definitions of hypoxia, and variation in assessment tools.
One major source of inconsistency is the lack of standardization in defining hypoxia across studies. For example, "intermittent hypoxia" may refer to minutes of desaturations during years in OSA, or to controlled alternations in oxygen concentration during a few weeks in

experimental protocols (Cha *et al.*, 2017; Kanaan *et al.*, 2006). In addition, the severity, frequency, and duration of hypoxia exposure are often poorly quantified or inconsistently reported: some OSA studies provide desaturation indices and apnea scores (apnea–hypopnea index), others rely on clinical diagnosis alone. This makes it challenging to establish dose-response relationships between hypoxia and hippocampal outcomes.
Another issue is the heterogeneity in cognitive testing. Some studies isolate episodic memory using validated learning and memory tasks (Berisha *et al.*, 2024; Naëgelé *et al.*, 2006), while others report global cognitive scores or subjective complaints (Huang *et al.*, 2023). The inconsistent use of assessments specific to one memory domain complicates comparison between studies and may mask selective impairments. In imaging studies, differences in MRI resolution, segmentation protocols, and hippocampal subfield description lead to variability in reported atrophy patterns. For instance, while some studies report bilateral global volume loss (Li and Fei, 2013), others identify subfield-specific changes, particularly in CA1 or DG (Cha *et al.*, 2017; Weihs *et al.*, 2020). Moreover, studies directly linking hippocampal subfield damage with memory subcomponents (e.g., pattern separation) remain limited.
Some discrepancies likely stem from factors specific to the population, including age, baseline cognitive reserve, and comorbid conditions. For example, older adults may experience accelerated memory decline under hypoxia, while children with perinatal HIE face developmental disruption of memory systems. These different baselines introduce variability in vulnerability and recovery potential. Studies on OSA face the additional challenge of confounding effects of poor sleep quality, fatigue, and mood disorders, which may independently affect memory (Olaithe *et al.*, 2018). Without proper controls, it is difficult to attribute memory deficits solely to hypoxia-induced hippocampal damage.
To date, most papers focus on one modality, limiting the ability to directly study the relationships between anatomy and function.
Importantly, while anatomical studies provide essential information about hippocampal damage, they do not capture the functional dynamics of hippocampal networks under hypoxic stress. This leads to the next section: how involuntary hypoxia alters the functional connectivity of the hippocampus. Such alterations may mediate cognitive impairments and represent both a marker of dysfunction and a potential target for intervention.

2.1.3. Impact of involuntary hypoxia on hippocampal functional connectivity and episodic memory

Hypoxia's Impact on Hippocampal Functional Connectivity: Insights from Resting-State fMRI Studies. Micaux, J., Troudi Habibi, A., Mauconduit, F., Noulhiane, M. (2025). *Brain Sciences*, *15*(6), 643. https://doi.org/10.3390/brainsci15060643

The preceding sections of this introduction have described the effects of involuntary hypoxia on hippocampal anatomy and episodic memory. This section integrates a published review that focuses on the impact of involuntary hypoxia (both environmental and pathological) on hippocampal functional connectivity. As seen previously, involuntary hypoxia is frequently associated with hippocampal atrophy and memory impairments. rs-fMRI enables

investigation of these effects at the network level, by quantifying how the hippocampus interacts with other large-scale brain systems under these conditions.

The review addresses three aims:
(1) identify the RSNs that support hippocampal functional connectivity at rest
(2) characterize how acute and chronic involuntary hypoxia alters these interactions
(3) compare common and distinct patterns across acute and chronic forms
The networks most consistently involved include the DMN, FPN, DAN and VAN, as well as sensorimotor and visual networks. Studies report both converging alterations (e.g., hippocampal–DMN decoupling) and differences between the different types of hypoxia.

In the context of this thesis, the review targets a specific gap: although anatomical and cognitive consequences of involuntary hypoxia are well documented, direct resting-state evidence on hippocampal functional connectivity remains limited.

brain sciences

MDPI

Review

Hypoxia's Impact on Hippocampal Functional Connectivity: Insights from Resting-State fMRI Studies

Julia Micaux [1,2,†], Abir Troudi Habibi [1,2,†], Franck Mauconduit [3] and Marion Noulhiane [1,2,*]

[1] University Paris-Saclay, CEA, Joliot Institute, NeuroSpin, Clinical and Translational Applied NeuroImaging Research Unit (UNIACT), 91191 Gif-sur-Yvette, France; julia.micaux@outlook.fr (J.M.); abir.habibi@cea.fr (A.T.H.)
[2] University of Paris Cité, Inserm, U1141 NeuroDiderot, InDev Team, 75019 Paris, France
[3] CEA, NeuroSpin, CNRS, University of Paris-Saclay, 91191 Gif-sur-Yvette, France; franck.mauconduit@cea.fr
* Correspondence: marion.noulhiane@cea.fr
† These authors contributed equally to this work.

Abstract: The hippocampus is one of the brain's most vulnerable structures to hypoxia, playing a crucial role in memory and spatial navigation. This sensitivity makes it a key region for understanding the effects of hypoxia on brain connectivity. This review examines the effects of both acute and chronic hypoxia on resting-state networks (RSNs) that contribute to hippocampal functional connectivity (FC). Hypoxia, characterized by a reduced oxygen supply to the brain, can result from environmental factors (such as high-altitude exposure) or hypoxia-induced pathological conditions (including obstructive sleep apnea and hypoxic–ischemic encephalopathy). The hippocampus's susceptibility to hypoxic damage significantly impairs brain connectivity. This review examines through rs-fMRI studies how hypoxia alters hippocampal FC, focusing on its effects on RSNs involved in hippocampal functions, and compares acute and chronic hypoxic states. We seek to determine whether distinct or shared patterns of FC changes exist between acute and chronic hypoxia, and how hypoxia indirectly changes hippocampal FC, given the challenges of studying it in isolation. By addressing these questions, this review aims to deepen our understanding of hypoxia-induced changes in hippocampal FC and provide insights into potential therapeutic strategies to mitigate its effects on cognitive functions.

Keywords: resting-state functional MRI; cerebral hypoxia; hippocampus; functional connectivity; resting-state networks

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1. Introduction

1.1. Background

A rapid decline in oxygen levels marks the transition from normoxia to hypoxia. Hypoxia can be classified into two main etiology types, acute and chronic, which can arise in both environmental and pathological contexts. Environmental hypoxia, such as high-altitude exposure or voluntary breath-holding in freediving, can either induce transient (acute) or sustained (chronic) oxygen deprivation. Similarly, hypoxia can cause pathological conditions in both acute and chronic forms, including obstructive sleep apnea and hypoxic–ischemic encephalopathy. While these forms differ in etiology, both environmental and pathological hypoxia can lead to significant cognitive and physiological consequences [1–3]. Acute hypoxia involves sudden oxygen deprivation, while chronic hypoxia is marked by prolonged exposure to reduced oxygen levels. Both forms can profoundly disrupt hippocampal structure and function, a brain structure involved in memory and spatial

navigation [4,5]. The hippocampus is susceptible to oxygen deprivation, making it highly vulnerable to hypoxic injury [6–10]. This vulnerability positions the hippocampus as a critical region for understanding how hypoxia affects neuronal integrity and brain connectivity. Structural MRI studies have shown that both acute and chronic hypoxia can lead to changes in hippocampal volume and neural network disruptions [7,11,12]. Also, disrupted hippocampal function is well documented, leading to cognitive impairments, including memory deficits and executive function decline [4]. These changes likely result from impaired neuronal communication, reduced neurogenesis, and decreased metabolic adaptation [13,14]. Given the hippocampus's pivotal role in cognitive function, understanding how hypoxia alters its FC is crucial for understanding long-term cognitive effects.

Resting-state functional MRI (rs-fMRI) is a non-invasive imaging technique used to investigate spontaneous brain activity in the absence of task performance. During rs-fMRI acquisition, the subject lies quietly (eyes open or closed) and the scanner captures low-frequency (<0.1 Hz) fluctuations in the blood-oxygen-level-dependent (BOLD) signal across the whole brain. These fluctuations reflect changes in the relative concentrations of oxyhemoglobin and deoxyhemoglobin, serving as an indirect marker of neuronal activity and neurovascular coupling [15–20].

Data are typically acquired using gradient-echo echo-planar imaging (EPI) sequences over 5–10 min, providing full-brain coverage with high sensitivity to neurovascular coupling [21]. By using the rs-fMRI technique, researchers can investigate and explore neural and vascular responses to oxygen deprivation, as it provides valuable insights into intrinsic brain connectivity. This method helps identify disruptions in networks, such as the hippocampus and its default mode network (DMN), which are particularly sensitive to hypoxic conditions [22–25]. Measures such as seed-based connectivity, independent component analysis (ICA), and amplitude of low-frequency fluctuations (ALFF) provide complementary insights into FC and regional spontaneous neural activity [26–28]. Advanced tools, including functional connectivity density (FCD) and dynamic causal modeling (DCM), further enhance our understanding of the brain's functional organization under hypoxic conditions [29–31].

However, direct assessments of hippocampal FC during hypoxia have been limited, with most studies focusing on RSN FC and reporting memory loss as a cognitive outcome. This review aims to fill this gap by specifically examining changes in hippocampal FC through RSN alterations under hypoxic conditions.

1.2. Scope of Review

This narrative review focuses on environmental hypoxia and hypoxia-induced pathologies, with an emphasis on understanding hippocampal FC changes during such hypoxic conditions. The review aims to achieve the following:

1. Identify the RSNs involved in the hippocampal networks during rest.
2. Explore how rs-fMRI reveals changes in hippocampal FC during hypoxia.
3. Compare the effects of acute and chronic hypoxia on brain FC, examining whether they produce distinct or shared patterns of network changes.

By addressing these questions, this review seeks to provide an integrative perspective on hippocampal adaptability to hypoxic conditions and inform the development of potential interventions to enhance cognitive resilience in individuals exposed to hypoxia. Our objective is not to exhaustively catalogue all published studies on the topic, but rather to synthesize key findings, identify common methodological approaches and limitations, and highlight emerging patterns that may inform future research.

2. Physiological Basis of Hypoxia in the Context of Resting-State fMRI

Hypoxia, defined as insufficient oxygen availability to meet metabolic demands, has profound effects on brain physiology and FC [32,33]. Oxygen is critical for ATP production via oxidative phosphorylation. When oxygen levels drop, either suddenly (acute hypoxia) or over prolonged periods (chronic hypoxia), the brain undergoes a cascade of compensatory and pathological processes that can alter neuronal activity and disrupt BOLD signal dynamics [34].

Acute hypoxia triggers rapid oxygen deprivation (e.g., high-altitude or apnea) and elicits immediate systemic responses such as hyperventilation and increased cardiac output. In the brain, it induces oxidative stress and mitochondrial dysfunction, particularly in regions like the hippocampus and prefrontal cortex [35,36]. These changes impair synaptic function and may transiently disrupt resting-state networks, which are sensitive to metabolic alterations. Although some oxidative markers normalize within 24 h, apoptotic pathways may remain active, potentially affecting rs-fMRI readouts beyond the hypoxic exposure window [33,35,37,38].

Chronic hypoxia, characterized by prolonged oxygen deprivation over weeks to years, is commonly associated with conditions such as high-altitude exposure or obstructive sleep apnea, which leads to sustained metabolic stress [34,39]. Adaptations like erythropoiesis and vascular remodeling help maintain oxygen delivery but are often accompanied by white matter changes, hippocampal atrophy, and altered FC patterns in rs-fMRI [40,41]. The structural and functional alterations are also implicated in the cognitive decline observed in chronic hypoxia and may predispose individuals to neurodegenerative diseases such as Alzheimer's [42]. Moreover, chronic hypoxia impacts hormonal responses, particularly in the context of exercise. For example, chronic resistance training under normobaric hypoxia has been shown to suppress the growth hormone response to exercise in older adults [43]. These findings highlight the complex interplay between chronic hypoxia, systemic physiological responses, and its long-term impact on brain health and cognitive function. Understanding these mechanisms is essential for developing interventions to mitigate the detrimental effects of chronic hypoxia.

The transition from normoxia to hypoxia and then to reoxygenation (e.g., during intermittent hypoxia or following apnea) initiates dynamic oxidative and metabolic changes that modulate the BOLD signal. As illustrated conceptually in Figure 1, the acute reoxygenation phase is often accompanied by a surge in reactive oxygen species (ROS), which may transiently disrupt local neuronal signaling and induce short-range functional disconnection or altered network synchrony detectable by rs-fMRI [25,37]. If oxidative stress persists, it may evolve into a chronic state. This may progressively affect baseline neuronal activity and contribute to disruptions in long-range connectivity [35]. These alterations may reflect broader shifts in brain network organization associated with sustained metabolic stress and neurovascular adaptations.

By understanding how oxygen availability shapes brain physiology, rs-fMRI can serve as a valuable tool for capturing both transient and lasting effects of hypoxia on neural networks.

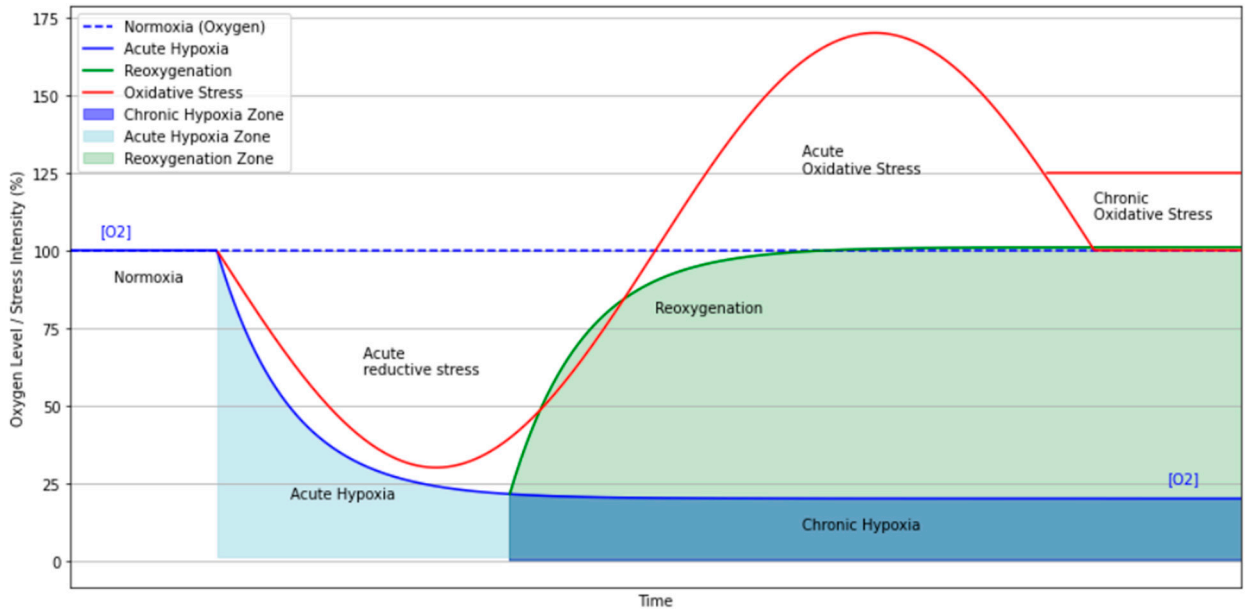


Figure 1. A schematic representation of the physiological phases associated with acute and chronic hypoxia. The transition from normoxia to acute hypoxia triggers a rapid drop in oxygen availability ("acute hypoxia zone"), followed by a reoxygenation phase during which oxidative stress peaks due to a surge in reactive oxygen species (ROS). This phase may transiently alter resting-state network activity through metabolic and neurovascular disruption. If hypoxia persists or if reoxygenation remains incomplete, a state of chronic hypoxia may develop, leading to sustained oxidative stress, neuroinflammation, and structural brain changes. These chronic alterations can disrupt long-range connectivity and modulate baseline BOLD signal fluctuations, as often observed in rs-fMRI studies of patients with chronic hypoxic exposure.

3. Hippocampal Functional Networks at Rest

Rs-fMRI reveals intrinsic brain organization through resting-state networks (RSNs), which reflect patterns of spontaneous, coordinated activity across different brain regions [25,44]. The hippocampus, a key hub for memory, spatial navigation, and future thinking, is functionally integrated into multiple RSNs, several of which are particularly relevant for understanding how hypoxia may impact brain function.

The DMN, first identified by Greicius et al. [45], is closely linked to the hippocampus, is active during self-referential and memory-related processes, and is especially sensitive to metabolic and vascular changes, making it a primary target of hypoxia-related dysfunction [46–50]. The fronto-parietal network (FPN), involved in executive control, attention, and cognitive flexibility, modulates hippocampal activity during memory encoding and retrieval, facilitating the dynamic balance between internal and goal-directed cognition [51].

The salience network supports the detection of emotionally or contextually significant stimuli, as its interactions with the hippocampus help prioritize memories based on relevance and emotional salience [52–54].

The central executive network (CEN) engages in higher-order cognitive functions, such as working memory, decision-making, and problem-solving. It enables cognitive control and is activated during tasks requiring sustained attention or complex reasoning. The hippocampus interacts with the CEN to ensure smooth transitions between memory processes, cognitive control, and emotional regulation [55,56].

Attention-related networks, the dorsal (DAN) and ventral VAN attention networks, coordinate goal-directed and stimulus-driven attention, respectively [57,58]. The hippocampus contributes contextual and spatial information essential for sustaining attention and guiding behavior [59–62]. Sensory–motor networks (SMNs), while primarily responsible for

sensory processing and motor control, also interact with hippocampal subregions such as the dentate gyrus and CA3 during spatial navigation and sensorimotor integration [49,63].

Lastly, the visual network, encompassing primary and extra-striate visual areas, engages with the hippocampus during visuo-spatial tasks, supporting memory-guided perception and navigation [50,52,64].

Together, these interactions highlight the hippocampus's central role in a broad range of functional networks, as presented in Figure 2. As such, any hypoxia-induced disruption in these RSNs, whether acute or chronic, is likely to alter hippocampal FC. This hypothesis will be further explored in the following sections.

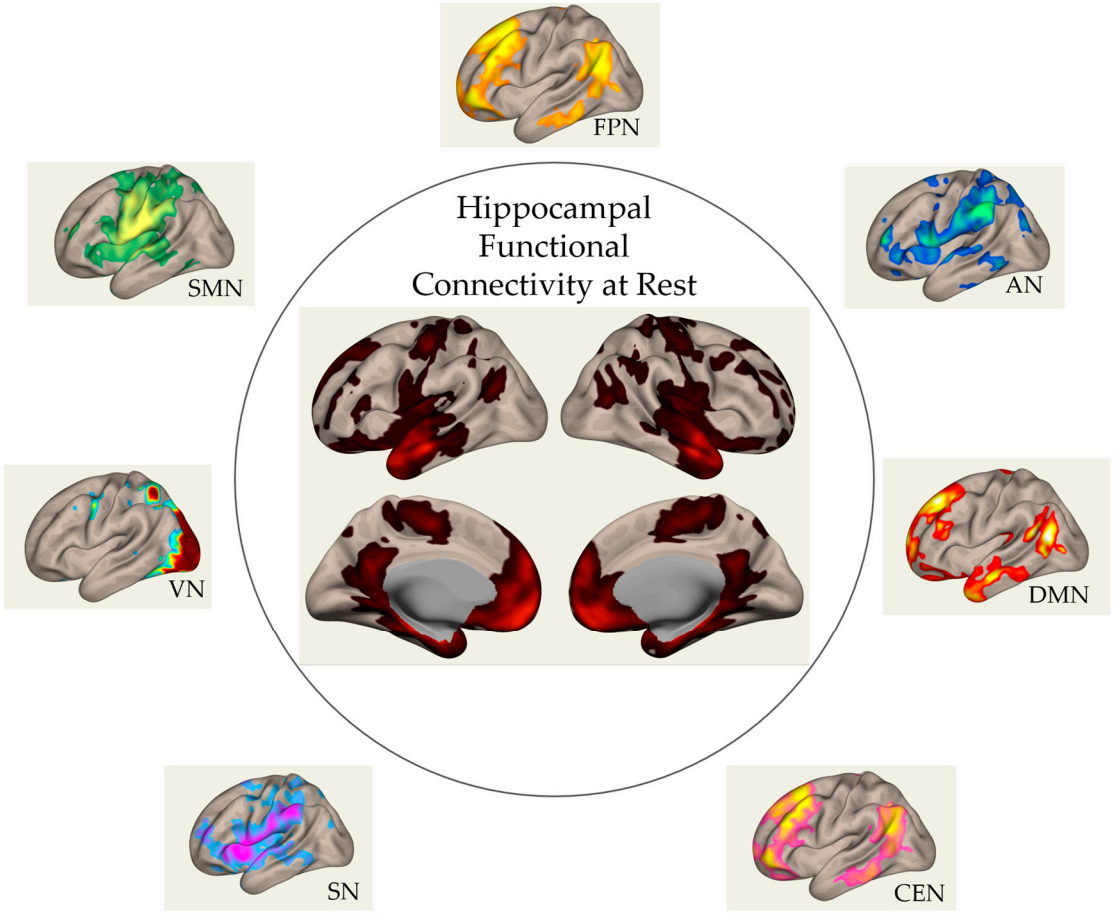


Figure 2. Surface plots of the FC of the hippocampal network at rest with other RSNs identified using a seed-based connectivity analysis on a sample of 20 healthy adult males from the HipoXia Project (ANR-21-CE37-0022 HippoXia, Ethic Approval Number: 2022-A01030-43). DMN: default mode network; SMN: sensory–motor network; SN: salience network; CEN: central executive network; VN: visual network; AN: attention network; FPN: fronto-parietal network.

4. Rs-fMRI in Acute Hypoxia

4.1. Cerebral Adaptations to Hypoxic Environments

Hypoxic environments, particularly those causing acute hypoxia, significantly challenge brain function by limiting oxygen supply to neuronal tissues. Such conditions can arise in high-altitude environments, during intense physical activity, breath-holding, aviation, carbon monoxide poisoning, or in confined spaces with low oxygen levels.

Short-term exposure leads to functional changes in the hippocampus due to its high sensitivity to oxygen levels. Functional recordings showed a significant increase in the frequency of slow oscillations (2.1–2.2 Hz) under hypoxic conditions. Additionally, the firing frequency of interneurons in the hilus and CA3 region decreased, while the activity

of pyramidal cells in the CA1 and CA3 regions increased. Notably, hypoxia also disrupted the regularity of neuronal firing patterns in these regions. The findings indicate that mild, short-term hypoxia can induce significant alterations in hippocampal network activity, which may affect information processing [12].

At high altitude, the body engages compensatory mechanisms such as increased ventilation, elevated heart rate, and augmented erythropoiesis [65]. Yet these physiological responses are often insufficient to safeguard optimal hippocampal function.

Recent studies using rs-fMRI have demonstrated that acute high-altitude exposure leads to decreased FC between the hippocampus and critical cortical regions, including the prefrontal cortex and the DMN. This reduced FC correlates with deficits in sustained attention and memory retrieval, highlighting the hippocampus as a central hub impaired during hypoxic stress [66].

Additionally, simulated high-altitude hypoxia has shown decreased FC between important networks linked to the hippocampus, such as the FPN and visual network, as well as the DAN and VAN, leading to perceptual deficits across sensory modalities, notably auditory and visual processing [22]. These connectivity disruptions manifest as longer reaction times, reduced response accuracy, impaired memory, and overall cognitive slowing, particularly in prefrontal and parietal cortices [66,67].

Interestingly, controlled breathing techniques have emerged as potential modulators of these effects by improving cerebral oxygenation and supporting hippocampal activity under acute hypoxia [68]. In aviation, pilots are exposed to rapid altitude ascents, which have been associated with hippocampal volume alterations and shifts in DMN connectivity, possibly reflecting adaptive changes [69,70]. However, exposure to aircraft noise has been linked to hippocampal dysfunction and related cognitive impairments, especially in working memory and emotional regulation, with changes observed in connectivity involving the amygdala, thalamus, and frontal gyrus [71–73].

In contrast, hyperoxia conditions have been shown to enhance connectivity within the DMN and AN, reinforcing the hippocampus's sensitivity to oxygen level fluctuations [5,74].

Despite the detrimental effects of acute hypoxia, the brain demonstrates a remarkable capacity for adaptation. With repeated exposure or acclimatization, cognitive functions such as attention and executive control may be preserved or even improved [75]. This is attributed to neuroplastic mechanisms, where the brain compensates for reduced connectivity by enhancing activity in alternative regions and responses in specific regions [76–78]. Yet, although such compensatory strategies help mitigate some effects, they cannot fully restore hippocampal-dependent processes like flexible memory encoding and retrieval [79].

Lastly, interventions such as intermittent hypoxic training and cognitive stimulation were shown to promote neuroplasticity, enhance hippocampal resilience, and activate neuroprotective pathways, offering promising strategies to counteract the cognitive challenges associated with hypoxia [77]. Figure 3 illustrates hippocampal FC changes under environmental acute hypoxia.

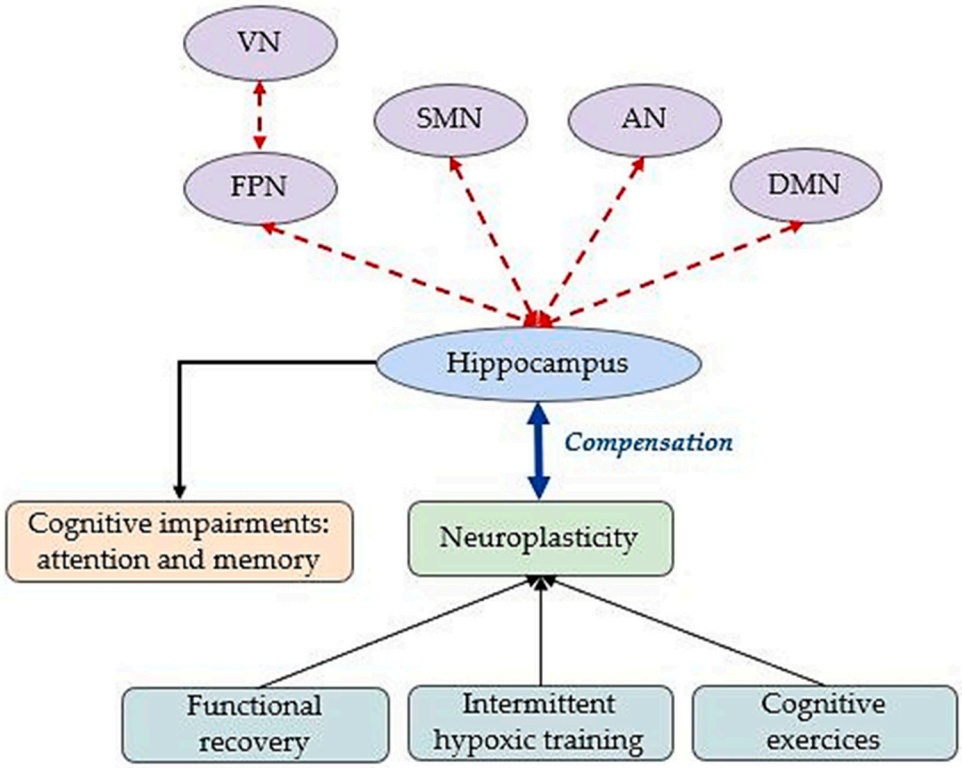


Figure 3. Cerebral adaptations to environmental acute hypoxia. The red dashed edges illustrate altered FC. DMN: default mode network; SMN: sensory–motor network; VN: visual network; AN: attention network; FPN: fronto-parietal network.

4.2. Cerebral Adaptations to Hypoxia-Induced Pathological Conditions

Acute hypoxia, as seen in conditions like hypoxic–ischemic encephalopathy (HIE) and acute mountain sickness (AMS), induces significant cerebral changes, particularly affecting the hippocampus. Despite compensatory neurophysiological mechanisms, these adaptations often fail to fully maintain homeostasis under low-oxygen conditions, contributing to persistent altitude-related health issues such as AMS [80].

In AMS, rapid ascent to HA leads to brain-centered symptoms, with rs-fMRI having identified the SMN as a key predictor of AMS severity and its cognitive [81]. Importantly, hypoxia-related disturbances prominently affect the hippocampus, a region susceptible to oxygen deprivation, resulting in disruptions across connected networks such as the DMN and FPN. These network alterations impair attentional performance under hypobaric hypoxia, exacerbated by additional environmental stressors such as low temperatures, dehydration, and sleep deprivation [82].

Similarly, in the HIE, a leading cause of long-term neurodevelopmental deficits, the hippocampus is particularly vulnerable to hypoxic injury. Severe HIE cases show decreased local network efficiency and altered connectivity, notably involving the left rolandic operculum and superior temporal gyrus [83]. FC reductions within sensory–motor and cognitive networks have been reported in moderate to severe HIE [84], while compensatory increases between motor areas and frontal, temporal, and parietal cortices suggest attempts at functional reorganization [85].

The hippocampus, through its integrative role between memory and sensorimotor processes, appears central in these adaptive mechanisms. Its compromised function not only underlies cognitive impairments but also predicts long-term neurodevelopmental outcomes. Indeed, network degradation, particularly affecting hippocampal connections, correlates with poorer motor and developmental scores [86].

Despite structural vulnerabilities, evidence of neuroplasticity offers promising perspectives: cooled children with HIE without severe disabilities exhibit functional recovery, hinting at the hippocampus's capacity for adaptive reorganization [87]. Similarly, animal models confirm spontaneous hippocampal plasticity supporting motor recovery following neonatal hypoxic injury [88].

Moreover, studies focusing on full-term infants with varying severity of HIE show preserved small-world network organization, but severe cases present reduced local efficiency and fewer hub regions, notably involving hippocampal structures, which could serve as early biomarkers for targeted interventions [83].

As shown in Figure 4, the hippocampus emerges as a central node mediating neuroplastic responses and predicting cognitive and motor outcomes, making it a critical target for therapeutic strategies such as intermittent hypoxic training, neuroprotective interventions, and rehabilitation aimed at enhancing functional recovery.

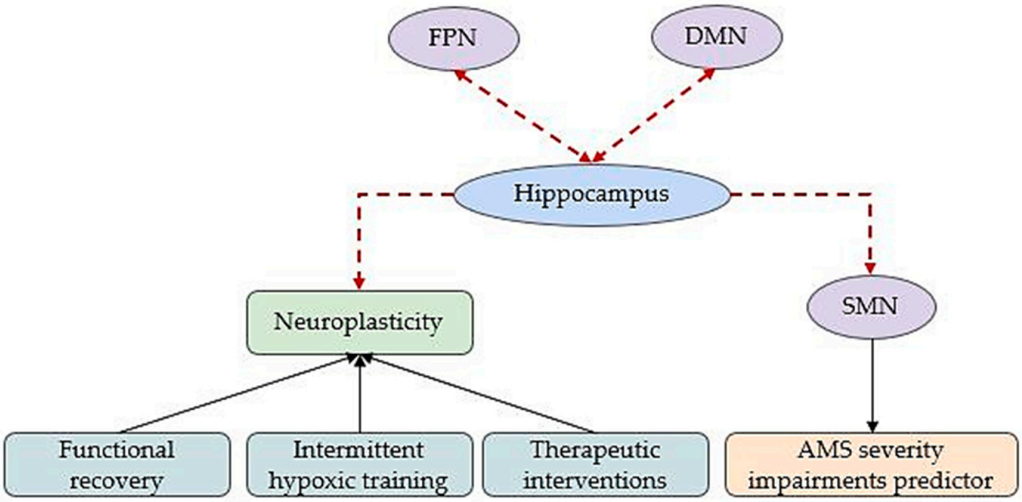


Figure 4. Cerebral adaptations to acute hypoxia-induced pathologies. Dashed edges illustrate altered FC. DMN: default mode network; SMN: sensory–motor network; FPN: fronto-parietal network; AMS: acute mountain sickness.

5. Rs-fMRI in Chronic Hypoxia

5.1. Cerebral Adaptations to Chronic Hypoxic Environments

Prolonged exposure to high-altitude environments, where oxygen levels are significantly reduced, has profound effects on cognitive functions, particularly affecting the hippocampus. Chronic hypoxia leads to reduced FC between the hippocampus and other brain regions involved in memory processes [89], contributing to lasting cognitive deficits, especially in memory formation and spatial navigation [90].

Adaptations to high-altitude environments are evident in populations like Tibetans, who show structural changes in the hippocampus, including the bilateral CA3, right CA4, and dentate gyrus. These adaptations are potentially linked to genetic factors influencing hemoglobin and hematocrit levels, which support oxygen transport [91]. In contrast, Han Chinese individuals living at high altitudes showed smaller hippocampal volumes compared to those living at sea level, though the differences were not always statistically significant [92]. The effect of high-altitude exposure on cognitive abilities varies based on altitude and duration of exposure, with psychomotor skills and long-term memory showing the most pronounced decline, while perceptual processes, inhibitory control, and problem-solving abilities often remain unaffected [93,94].

Additionally, high-altitude exposure impairs verbal working memory and brain functionality [95], with decreased FC post exposure strongly correlated with declines in memory

and reaction time. These FC changes reflect alterations in the topological properties of brain functional networks, particularly in regions involved in attention, perception, memory, and motor modulation, ultimately impairing cognitive performance. In particular, volume changes in the left hippocampus and right caudate were positively associated with improvements in delayed verbal memory performance [96,97]. As the hippocampus plays a critical role in recollection, damage to this medial temporal structure leads to selective deficits in this function. Specifically, the left hippocampus is more involved than the right in cognitive processes such as temporal sequence memory [98], associative memory for match–mismatch tasks [99], and event memory [100].

Chronic hypoxia further disrupts neuronal activity and FC in the visual network, leading to increased activity in areas such as the right calcarine gyrus and supplementary motor cortex, while reducing connectivity between the lingual gyrus and postcentral gyrus, indicating SMN disruption [101], which could be a crucial predictor for ACM [81]. Executive function is similarly impaired, with decreased accuracy and slower response times in cognitive tests linked to reduced gray matter density in the olfactory cortex, insula, and temporal lobes [102]. Despite these adaptive brain activity changes in response to low oxygen, long-term exposure may have detrimental effects, with FC alterations correlating with cognitive impairments in the FPN and SMN [103]. Patients with CMS and soldiers exposed to high altitudes also exhibit significant brain structure and functional changes, with CMS patients showing memory decline and soldiers demonstrating increased FC as a compensatory mechanism [104,105]. These findings suggest that chronic hypoxia induces brain reorganization and neural compensation [89,106–108]. Animal models further support these effects, with rats exposed to prolonged hypobaric hypoxia showing impaired cognitive performance [109], structural abnormalities, neural apoptosis, and mitochondrial damage in the hippocampus and frontal cortex [110]. Furthermore, cognitive deficits have been observed in mice exposed to a simulated high altitude, particularly in learning and memory tasks [111].

Overall, chronic exposure to high-altitude environments significantly alters hippocampal functional integrity and structure, as illustrated in Figure 5, leading to cognitive impairments. These insights emphasize the need for strategies to mitigate the long-term effects of hypoxia on brain health [112].

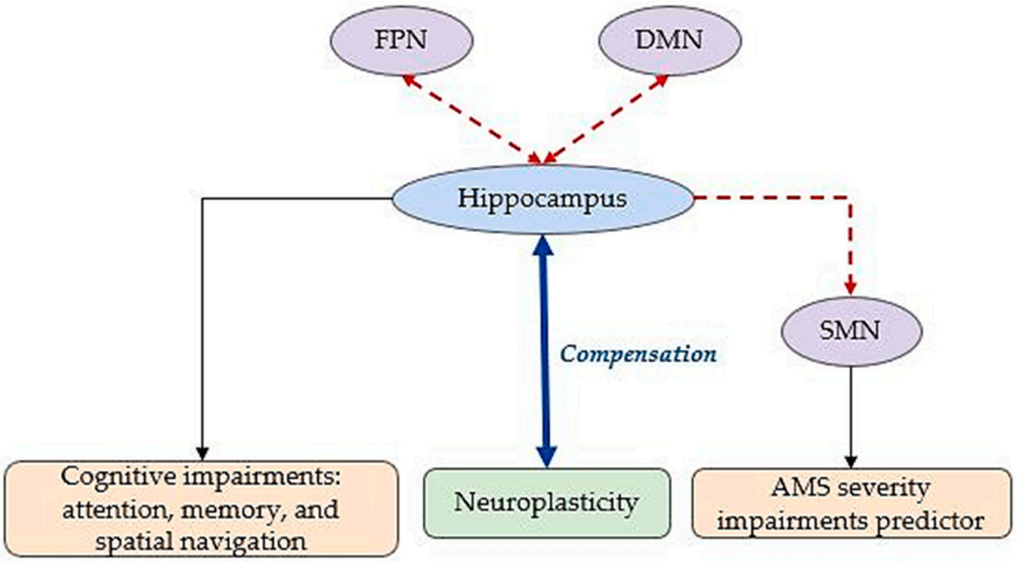


Figure 5. Cerebral adaptations to environmental chronic hypoxia. The red dashed edges illustrate altered FC. DMN: default mode network; SMN: sensory–motor network; FPN: fronto-parietal network.

5.2. Cerebral Adaptations to Hypoxia Induced by Pathological Conditions

Obstructive sleep apnea (OSA) is characterized by repeated breathing interruptions during sleep, leading to fragmented sleep and intermittent hypoxia, which has been associated with cognitive deficits, particularly in attention, memory, and executive function [113]. Studies suggest that OSA can affect crucial brain structures such as the hippocampus and frontal cortex, which are integral for cognitive performance [114].

FC in the DMN has been significantly associated with hypoxemia measures, such as the apnea–hypopnea index (AHI) and oxygen desaturation index (ODI) [115], suggesting that disrupted connectivity in brain regions, especially in the hippocampus, correlates with poorer cognitive outcomes. Patients with OSA exhibit altered brain connectivity, particularly involving the hippocampus. These changes have been linked to intermittent nocturnal hypoxia and sleep fragmentation, both of which are hallmark features of OSA. While some studies suggest a compensatory mechanism in certain populations, such as Tibetans with OSA [116], the cumulative impact of repeated hypoxic episodes and disrupted sleep architecture may impair hippocampal function through complementary pathways, including neuroinflammation, oxidative stress, and reduced neurogenesis [117].

Further research has shown functional differences under high-altitude conditions in the hippocampus, reporting that hypoxia and disrupted sleep could contribute to neuronal loss in the hippocampus [118]. Further animal studies have shown that prolonged sleep deprivation significantly suppresses cell proliferation in the dentate gyrus of the hippocampus, with no evidence of recovery after a short period of sleep. Both sleep-deprived rats and those given a brief recovery sleep showed a marked reduction in new cell production compared to controls, with the effect being more pronounced in the posterior hippocampus. These findings suggest that extended sleep loss has a lasting negative impact on hippocampal neurogenesis that is not quickly reversed [119].

Dynamic FC (dFC) studies have also highlighted changes in FC related to sleep indicators and cognitive performance, with altered FC in networks such as the DMN, DAN, VAN, and SN contributing to neuropsychological deficits [120–122].

Abnormal dynamic regional spontaneous brain activity has been observed in patients with OSA, especially in the frontal gyrus, cingulate gyrus, and precuneus [121].

OSA patients with MCI showed altered FC in various brain regions such as the temporal gyrus, the frontal gyrus, and the bilateral posterior cingulate/calcarine/cerebellar anterior lobe [122]. Given that these regions, especially the frontal gyrus, are functionally connected with the hippocampus, it is plausible that FC changes in OSA could indirectly impact hippocampal connectivity. However, this hypothesis has not yet been directly confirmed by the available studies.

Additionally, topological analysis in severe, untreated OSA patients revealed disrupted small-world network properties, with decreased global efficiency and increased local efficiency, further suggesting a potential mechanism for cognitive impairment in OSA [123]. Spontaneous brain activity analysis has shown that OSA patients exhibit lower FC in regions associated with the DMN, while showing higher FC in regions such as the cerebellum, cingulate gyrus, and lentiform nucleus, with these changes correlating negatively with sleep stages [124]. In older adults with OSA, increased FC between hippocampal regions, such as the para-hippocampal cortex, correlates with severe nocturnal hypoxemia and poorer working memory performance [125]. Similar cognitive impairments are seen in children with OSA, where changes in brain activity and FC measures highlight the impact of hypoxia on hippocampal function [126].

Chronic environmental hypoxia, as seen in chronic mountain sickness (CMS), similarly affects brain function [80], with individuals suffering from CMS exhibiting abnormal brain activity across multiple regions, particularly the para-hippocampal gyrus [127]. This

suggests that prolonged exposure to chronic hypoxia enhances neuronal activity and enlarges hippocampal volume, which in turn disrupts the normal physiological regulation of hyperventilation, ultimately exacerbating the hypoxic condition as reported by other studies [128–130].

Given the heterogeneity of the available findings and the limited number of studies specifically investigating the effects of chronic hypoxia on the hippocampus, we summarized in Figure 6 the main cerebral changes reported in chronic hypoxia-induced pathologies. These changes involve altered FC between the SMN, FPN, and DMN with the hippocampus, which may contribute both to cognitive impairments and to disrupted neuroplasticity necessary for functional recovery.

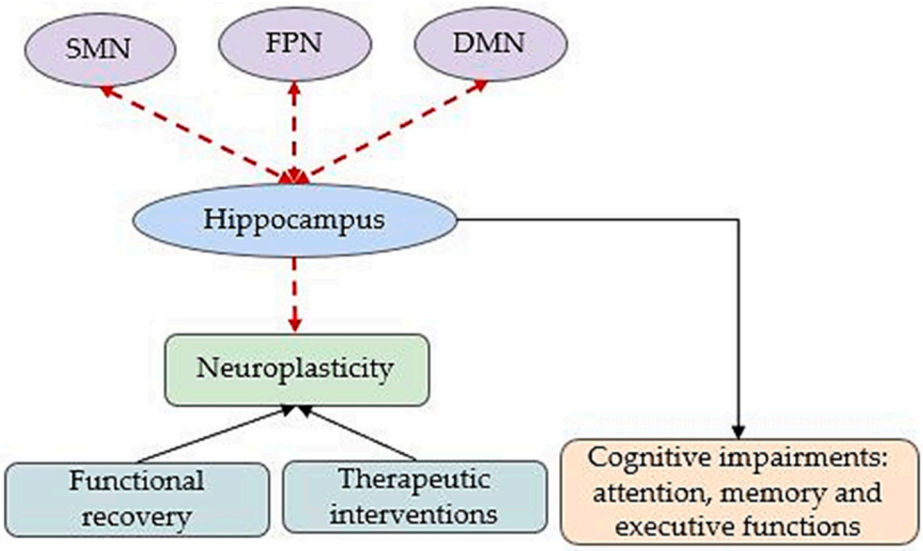


Figure 6. Cerebral adaptations to pathological conditions induced by chronic hypoxia. The red dashed edges illustrate altered FC. DMN: default mode network; SMN: sensory–motor networks; FPN: fronto-parietal network.

6. Acute and Chronic Hypoxia Patterns

As summarized in Table 1, acute and chronic environmental hypoxia both impact brain FC, particularly in networks involving the hippocampus, which plays a crucial role in memory and cognitive control. In both conditions, studies consistently report reduced hippocampal FC with regions such as the prefrontal cortex and the DMN, which correlates with impairments in memory retrieval and executive functions [66,71].

Table 1. Summary of key findings on effects of acute and chronic hypoxia on hippocampal functional connectivity.

Hypoxia's Type	Key Findings	Affected Networks
Acute Hypoxia (e.g., High Altitude, Aviation)	Decreased FC between the hippocampus and prefrontal cortex/DMN: impaired attention and memory. Disrupted FC in DAN, VAN, and FPN: longer reaction times. Controlled breathing improves cerebral oxygenation. Aviation-related hypoxia alters hippocampal volume and DMN connectivity.	DMN, FPN, DAN, VAN, Visual, Prefrontal
Pathological Acute Hypoxia (e.g., HIE, AMS)	FC impairments in DMN, SMN, and FPN, with SMN as a key predictor of AMS severity. HIE shows decreased local efficiency and hippocampal connectivity. Compensatory increases in FC among motor, frontal, and parietal areas: neuroplasticity observed in recovery cases.	DMN, SMN, FPN, Motor, Temporal

Table 1. *Cont.*

Hypoxia's Type	Key Findings	Affected Networks
Chronic Environmental Hypoxia (e.g., High Altitude)	Reduced hippocampal FC with memory networks: cognitive decline in memory and spatial navigation. FC disruptions in visual network and SMN: adaptation varies across populations. Animal models show hippocampal damage and mitochondrial impairment.	DMN, FPN, SMN, Visual, Memory Networks
Chronic Pathological Hypoxia (e.g., OSA, CMS)	Altered FC in DMN, DAN, VAN, and SN; hippocampal dysfunction linked to intermittent hypoxia and sleep fragmentation: cognitive impairments in attention, memory, and executive functions. Topological disruptions in network efficiency. Para-hippocampal activity changes in CMS; observed effects in adults, children, and animal models.	DMN, VAN, DAN, SN, Frontal, Para-Hippocampal Gyrus

However, the patterns of disruption and adaptation differ between acute and chronic hypoxia. Acute hypoxia elicits immediate physiological responses (e.g., increased ventilation and heart rate) aimed at enhancing oxygen delivery. The responses often fall short, leading to short-term cognitive deficits and transient FC alterations [78]. Conversely, chronic environmental hypoxia induces long-term structural and functional brain changes, including persistent reductions in hippocampal FC. These adaptations involve complex genetic and environmental mechanisms, such as increased hemoglobin, which may partially compensate for oxygen deprivation, but do not fully prevent long-term cognitive decline [77,101].

Similarly, acute and chronic pathological hypoxia both affect brain FC with similar network targets but distinct trajectories. Acute pathological hypoxia leads to immediate, severe disruptions in brain activity, resulting in rapid cognitive impairment. Yet there is potential for recovery through neuroplasticity, particularly with therapeutic interventions [85,87]. Chronic pathological hypoxia results in long-term, intermittent, and cumulative FC disruptions, particularly in the hippocampus and attentional networks. While some compensatory increases in FC have been observed, they are often insufficient to fully mitigate the sustained cognitive impairments [89,110].

In summary, both acute and chronic pathological hypoxia impair cognitive function and brain connectivity, especially in the hippocampus. Acute hypoxia tends to cause immediate but potentially reversible effects, whereas chronic hypoxia produces more durable impairments with limited compensatory recovery.

7. Discussion

Despite growing interest in the impact of hypoxia on brain function, hippocampal FC under hypoxic conditions remains insufficiently characterized, even though the hippocampus is known to be highly vulnerable to oxygen deprivation [8,131]. This narrative review aims to shed light on the functional changes within the hippocampal network by examining FC changes in RSNs associated with the hippocampus, focusing on both environmental and pathological hypoxia. We highlighted (1) RSNs associated with the hippocampal network during rest, (2) how rs-fMRI uncovers changes in hippocampal connectivity under hypoxic conditions, and (3) the effects of acute and chronic hypoxia on brain connectivity, analyzing whether these conditions yield distinct or overlapping patterns of network changes.

At rest, the hippocampus is primarily embedded with the DMN, but it also interacts with networks involved in memory, executive function, and attention. Several rs-fMRI studies have shown that acute hypoxia, marked by a sudden drop in oxygen availability, leads to transient disruptions in FC between the hippocampus and cortical areas, notably in

the DMN and attention network, with accompanying cognitive impairments such as slower reaction times and memory deficits [22]. In contrast, chronic hypoxia, often due to sustained environmental or induced pathological conditions such as high-altitude exposure or OSA, induces more persistent and widespread FC alterations. These include long-term reductions in FC between the hippocampus and regions critical for memory and spatial processing, along with potential but often insufficient compensatory increases in FC elsewhere [132]. Overall, chronic hypoxia, in both environmental hypoxia and induced pathologies, may lead to adaptive neuroplastic changes, such as compensatory increases in connectivity in certain brain areas, although these compensatory mechanisms are often insufficient to prevent cognitive decline.

Despite these differences in temporal profiles between acute and chronic hypoxia, both forms consistently disrupt FC patterns, particularly involving hippocampal interactions with memory and executive-related brain networks. However, comparing findings across studies remains challenging due to significant methodological heterogeneity. Differences in hypoxia-induced protocols (e.g., simulated altitude, clinical OSA), subject populations (e.g., age, comorbidities), rs-fMRI acquisition parameters (e.g., scan length, TR), and analytic strategies (e.g., seed-based vs. data-driven approaches) can lead to inconsistent results and hinder metanalytic comparisons [133–135].

A promising methodological advance in recent years is the integration of rs-fMRI with arterial spin labeling (ASL) perfusion imaging, allowing for simultaneous investigation of both functional and physiological changes. Unlike rs-fMRI alone, which is sensitive to neurovascular fluctuations without direct metabolic quantification, ASL provides quantitative measures of cerebral blood flow (CBF) and, in more advanced implementations, oxygen extraction and metabolism. Combined ASL-rs-fMRI approaches have been used to fit biophysical models estimating the cerebral metabolic rate of oxygen consumption ($CMRO_2$), thereby offering a more complete picture of tissue oxygenation and neurovascular coupling under hypoxic stress [136–138].

One notable technique includes dual-echo ASL acquisitions, which allows researchers to obtain both perfusion and BOLD data without prolonging scan duration. These data can be fitted to flow metabolism matching models to estimate voxel-wise $CMRO_2$ [139]. Additionally, early attempts at single-sequence acquisitions, such as the EPI-ASL-PAIR sequence, have demonstrated feasibility for integrating ASL and BOLD contrasts in a resting-state context within a short 5 min scan per slice [140]. However, most $CMRO_2$ quantification methods were originally developed for task-based studies and are yet to be validated robustly in the resting-state paradigm [141].

Despite their promise, these multimodal techniques introduce additional complexity, require careful calibration, and often demand specialized MRI hardware. To date, there is no widely accepted standard for integrating ASL and rs-fMRI within a single, harmonized acquisition and analysis pipeline [142]. While both ASL and rs-fMRI rely on BOLD contrast mechanisms, they probe different components of the hemodynamic response: ASL primarily captures CBF and perfusion dynamics, while rs-fMRI reflects low-frequency oscillations related to neural synchrony. Their partial complementarity offers a compelling rationale for joint acquisition, but interpretation requires careful modeling of neurovascular coupling [143].

To fully realize the clinical potential of these advanced imaging techniques in hypoxia research, several critical steps are needed: (1) standardization of multimodal imaging protocols; (2) extending $CMRO_2$ quantification to resting-state paradigms (current methods for voxel-wise $CMRO_2$ estimation need to be adapted and validated for resting-state data, especially under spontaneous physiological fluctuations induced by hypoxia); (3) integra-

tion with cognitive and behavioral metrics; and finally (4) validation in prospective clinical models for monitoring hypoxia-related neurological disorders.

8. Conclusions

In conclusion, this review highlights the critical yet underexplored area of hippocampal FC changes under hypoxic conditions, emphasizing both acute and chronic environmental and pathological hypoxia. The hippocampus, due to its high metabolic demand, emerges as a key structure vulnerable to oxygen deprivation, with acute hypoxia associated with transient but potentially reversible FC disruptions, and chronic hypoxia linked to enduring structural and functional impairments.

Beyond identifying these connectivity patterns, we underscore the added value of advanced multimodal approaches, particularly the integration of rs-fMRI with ASL perfusion imaging. These techniques offer complementary insights into both neural and vascular dimensions of brain function and hold promise for improving the specificity of hypoxia-related biomarkers.

Nonetheless, to translate these developments into clinically useful tools, several challenges remain. Chief among them is the lack of standardization across imaging protocols, analysis pipelines, and outcome metrics. We therefore advocate coordinated efforts to harmonize acquisition parameters, validate multimodal biomarkers in prospective cohorts, and link imaging findings to cognitive and behavioral outcomes. Addressing these methodological and translational gaps will be essential for advancing our understanding of hypoxia-induced hippocampal dysfunction and for informing targeted therapeutic interventions.

Author Contributions: A.T.H. and J.M. contributed equally to this work and share first authorship. A.T.H., J.M., and M.N. were involved in the conceptualization, methodology, and literature investigation. A.T.H. led the original draft preparation, review, editing, and preparation of the final version, while J.M. focused on critical review and editing. A.T.H. and J.M. contributed to the creation of visual materials for the manuscript. M.N. provided overall supervision, guidance, and critical feedback throughout the writing process. F.M. was responsible for the design of the MRI sequences of the HippoXia Project. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The research protocol adheres to ethical guidelines for research involving humans (Declaration of Helsinki) and was approved by the ethics committee (Ethical Approval Number: 2022-A01030-43, approval date: 1 September 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The datasets referenced in this article are not publicly available, as participants consented to their data being used solely under the supervision of the principal investigator. Requests to access the datasets should be directed to M.N.

Conflicts of Interest: Abir Troudi Habibi and Julia Micaux share first-author contributions. The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AHI	Apnea–Hypopnea Index
ALFF	Amplitude of Low-Frequency Fluctuations
AMS	Acute Mountain Sickness
ASL	Arterial Spin Labeling

ATP	Adenosine Triphosphate
BH	Breath Holding
BOLD	Blood-Oxygen-Level Dependent
CEN	Central Executive Network
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CMS	Chronic Mountain Sickness
DAN	Dorsal Attention Network
DCM	Dynamic Causal Modeling
dFC	Dynamic Functional Connectivity
DMN	Default Mode Network
EPI	Echo-Planar Imaging
fALFF	Fractional Amplitude of Low-Frequency Fluctuation
FC	Functional Connectivity
FCD	Functional Connectivity Density
FPN	Fronto-Parietal Network
HA	High Altitude
HIE	Hypoxic–Ischemic Encephalopathy
ICA	Independent Component Analysis
MCI	Mild Cognitive Impairment
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PAIR	Presaturation with Inversion Recovery
ReHo	Regional Homogeneity
ROS	Reactive Oxygen Species
rs-fMRI	Resting-State Dunctional Magnetic Resonance Imaging
RSN	Resting-State Network
SMN	Sensory–Motor Network
SN	Salience Network
VAN	Ventral Attention Network
VN	Visual Network

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Conclusion

This review demonstrates that involuntary hypoxia consistently alters RSNs involved in hippocampal function, including the DMN, FPN, attention networks, SN, sensorimotor and visual systems. Both acute and chronic forms show overlapping effects, the most visible being reduced connectivity in the DMN.

The review also highlights the limited number of studies that directly assess hippocampal connectivity, as most focus on broader RSN alterations. This gap underscores the relevance of investigating hippocampal functional connectivity in detail, as undertaken in the present thesis. The synthesis of typical network involvement and current methodological limitations establishes the reference framework used for the subsequent analyses.

2.2. The effects of sport on the hippocampus: aerobic and anerobic exercise training

2.2.1. The effects of aerobic exercise training on the hippocampus

Anatomical brain changes and consequences on episodic memory

Regular exercise training induces multi-scale adaptations in the hippocampus, a brain region known for its plasticity across the lifespan. These adaptations primarily involve neurogenesis in the DG and angiogenesis throughout the hippocampus (Ben-Zeev *et al.*, 2022). Exercise training also promotes the integration of new neurons into existing circuits and increases vascular density, improving metabolic support. Although these processes rely on complex cellular and molecular cascades (including neurogenesis, angiogenesis, glial modulation, and synaptic remodeling), this chapter focuses solely on anatomical outcomes measurable with neuroimaging.

Multiple neuroimaging studies have shown that aerobic exercise training induces measurable anatomical changes in the human hippocampus. These include increased hippocampal volume and perfusion, particularly in subfields implicated in memory and plasticity (Firth *et al.*, 2018; Palmer *et al.*, 2023).

Erickson *et al.* (2011) demonstrated consistent increases in total hippocampal volume following aerobic training, reporting changes ranging from 1 to 2% after 6 to 12 months of moderate-intensity aerobic activity, particularly in previously sedentary individuals. These gains are notable, as they approximate the magnitude of annual hippocampal volume loss associated with normal aging. High-intensity interventions such as HIIT and resistance training may also contribute to hippocampal preservation (Moreno-Infantes *et al.*, 2024; Ribeiro *et al.*, 2025). Notably, Ribeiro *et al.* (2025) showed that resistance training over 12 months preserved hippocampal volume and improved adjacent white matter integrity in older adults with mild cognitive impairment.

These anatomical changes are regionally heterogeneous. Analyses at the subfield level using high-resolution segmentation methods suggest that the DG and CA1 are the most responsive to training (Farmand *et al.*, 2025). These areas are known to maintain anatomical plasticity in adulthood and appear to be selectively adaptable through aerobic activity. Walking

interventions have also been shown to increase hippocampal volume (Khalil, 2025), reinforcing the notion that even moderate-intensity aerobic activity can be beneficial.
However, anatomical gains are not always permanent. Alfini *et al.* (2016) showed that improvements in hippocampal perfusion among older trained individuals declined after training was stopped. This suggests that the anatomical benefits of exercise training depend on regularity and can be reversed.
Several moderating factors influence the extent of these anatomical adaptations. Age is a key variable: older adults tend to show more pronounced volumetric gains, possibly due to greater baseline atrophy. Physical condition at baseline also matters, with less active individuals showing larger relative changes. Sex differences have been reported but remain inconsistent across studies. Finally, training modality, intensity, and duration play a crucial role. Resistance and endurance exercises training are most effective, with dose-response relationships observed in both human and animal models (Augusto-Oliveira *et al.*, 2023).
Perfusion-sensitive imaging techniques such as arterial spin labeling (ASL) also reveal functional correlates of these anatomical effects. Chapman *et al.* (2013) and Palmer *et al.* (2023) reported increased hippocampal blood flow after several weeks of aerobic exercise, particularly in older adults and individuals with lower baseline perfusion. These perfusion increases may serve as early markers of vascular plasticity and support subsequent volume changes. It is also worth noting that regular exercise training appears to stimulate angiogenesis, particularly in aging and pathological conditions, supporting long-term hippocampal integrity (Mansoor *et al.*, 2025).
In summary, exercise training induces robust anatomical remodeling of the hippocampus, particularly within DG and CA1. These changes include volume increases, perfusion enhancements, and potential modifications in tissue density. While not uniform across individuals, they appear to follow identifiable patterns related to age, baseline condition, and exercise characteristics.

Anatomical adaptations in the hippocampus following exercise training have important implications for cognitive abilities (Zhang *et al.*, 2025). Erickson *et al.* (2011) demonstrated that one year of moderate aerobic training in older adults not only led to hippocampal volume gains but also improved spatial memory, with volumetric changes mediating the observed cognitive effects. Similarly, HIIT has been shown to improve episodic memory with effects lasting up to five years (Blackmore *et al.*, 2024). As suggested by Stillman *et al.* (2016), anatomical plasticity appears to act as the link between exercise training and neurocognitive function, especially in older adults.
These associations are particularly relevant in individuals at risk of cognitive decline. Exercise training may slow or partially reverse hippocampal atrophy, preserving memory function in populations vulnerable to neurodegeneration or vascular deterioration. Increased volume in the DG may support pattern separation and memory encoding, while CA1 remodeling may enhance retrieval processes. In fact, evidence from resistance training in older adults with mild cognitive impairment shows significant gains in episodic memory (Ribeiro *et al.*, 2025), possibly through improved encoding (Loprinzi *et al.*, 2020).

Aside from normal aging, exercise training has been proposed as beneficial in certain clinical contexts and as a means to reduce vulnerability to neurological diseases (Liang *et al.*, 2021). Overall, converging imaging, cognitive, and longitudinal evidence supports exercise training as a modulator of hippocampal architecture, and consequently of episodic memory. But beyond these anatomical and cognitive effects, recent evidence suggests that exercise training also reshapes brain functional connectivity, particularly within memory networks.

Functional brain changes and episodic memory

Exercise training induces significant and diverse modifications in brain functional connectivity, depending on the type, intensity, and chronicity of the exercise. These changes support cognitive improvements and reflect plastic adaptations within large-scale brain networks.

Several studies highlight changes in resting-state functional connectivity in response to exercise training. Endurance athletes exhibit enhanced connectivity between the FPN and the frontal cortex, involved in executive function. In parallel, they show reduced connectivity between the DMN and regions associated with somatosensory functions, motor control and visual abilities, suggesting a shift towards task-specific engagement (Raichlen *et al.*, 2016). Similarly, Tai Chi training enhances functional connectivity in key hubs of the DMN (precuneus and posterior cingulate cortex), while reducing functional connectivity in the inferior temporal cortex. These modifications are positively correlated with cognitive flexibility gains, indicating a reconfiguration of intrinsic brain networks toward more integrated and efficient cognitive processing. Elite Tai Chi athletes also display decreased functional connectivity between the left prefrontal lobe and right sensorimotor area during movement execution, reflecting neural efficiency (Wang and Lu, 2022). Acute exercise sessions can also rapidly influence functional connectivity: ten minutes of light cycling increases functional connectivity between the DG/CA3 and cortical regions, linked to improved pattern separation performance (Suwabe *et al.*, 2018). Interestingly, exercise intensity modulates functional connectivity non-linearly. In an example of moderate-intensity aerobic exercise, functional connectivity within the DAN reached a peak while functional connectivity between the DMN and DAN was the lowest, correlating with a better attention post-exercise. In contrast, low or high intensity fails to elicit similar gains, highlighting possible optimal intensity range for cognitive benefit (Ko *et al.*, 2023). Sport-specific training also shapes functional connectivity. Skeleton athletes show increased functional connectivity in brain regions associated with cognitive and motor control (superior frontal gyrus, insula), reward learning (putamen), visual processing (precuneus), spatial cognition (inferior parietal), and emotional processing. This suggests a shift toward circuits supporting their specific expertise (Jin *et al.*, 2024).

In youth, higher daily exercise training is associated with decreased functional connectivity between the hippocampus and right superior frontal gyrus, and increased connectivity with the left superior temporal sulcus. These findings illustrate how exercise training may promote functional specialization and shape hippocampal networks during development (Heller-Wight *et al.*, 2023). HIIT also induces a significant increase in functional connectivity between the hippocampus and other networks and improved cognitive function in aged adults, which

persisted after 5 years (Blackmore *et al.*, 2024). Lastly, fitness is associated with greater motor cortex functional connectivity at rest. This may indicate improved automaticity and reduced cognitive load during motor planning in highly trained individuals (Li *et al.*, 2023).
Overall, exercise training reshapes functional connectivity across multiple brain networks in ways that reflects demands specific to each sport and promotes greater neural efficiency. These modifications enhance cognitive functions such as attention and executive control, and contribute to memory improvement by complementing the anatomical adaptations previously described, indicating that both functional connectivity changes and anatomical remodeling jointly underlie enhancement of episodic memory after exercise training.

2.2.2. The effects of anaerobic exercise training on the hippocampus

Previous sections described the deleterious effects of involuntary hypoxia on hippocampal anatomy, functional brain connectivity, and episodic memory. Hippocampal atrophy was shown to vary by subfield and hypoxia type, with CA1 and DG being particularly sensitive, while memory impairment followed patterns aligned with anatomical damage. In parallel, exercise training was associated with increased hippocampal volume (notably in CA1 and DG), improved perfusion, functional connectivity remodeling, and enhanced episodic memory, especially in older or sedentary adults. Some studies have also examined the interaction between exercise training and hypoxia: current evidence indicates that exercise training may either mitigate or amplify the effects of involuntary hypoxia, depending on dosage, exposure pattern, and individual characteristics (Chroboczek *et al.*, 2023; Jung *et al.*, 2020; Seo *et al.*, 2017). This dose-dependent duality is also reflected in emerging findings on a very different category of hypoxia: voluntary, controlled intermittent hypoxia, often used in therapeutic or experimental contexts.

Voluntary intermittent hypoxia protocols, such as short cycling of low-oxygen exposure, have shown beneficial effects on hippocampal plasticity and episodic memory, with duration and intensity still being crucial (Boulares *et al.*, 2024; Navarrete-Opazo and Mitchell, 2014).
These observations contrast the detrimental or mixed outcomes observed under involuntary hypoxia with preliminary but promising results emerging from studies on voluntary hypoxia protocols combined with exercise training. These protocols are applied deliberately and under controlled conditions, often with therapeutic or cognitive enhancement objectives. Although still limited in number, such studies suggest that voluntary hypoxia, when paired with exercise training, may engage distinct mechanisms and hold potential for modulating brain plasticity and memory function. This section reviews this emerging literature, which forms the foundation for the experimental work developed in this thesis.

Freediving as a model of acute voluntary intermittent hypoxia

Freediving is the practice of diving underwater on a single breath, without the use of breathing apparatus. It covers a range of disciplines, from static apnea (breath-holding without movement) to dynamic and deep dives, practiced competitively or recreationally (Pelizzari and Tovaglieri, 2004). This activity requires extensive preparation involving both physical conditioning (to enhance tolerance to hypoxia, increase lung capacity, and optimize oxygen

efficiency) and cognitive control (including training in relaxation, focus, and anxiety regulation) to minimize oxygen consumption and delay the urge to breathe. From a physiological perspective, freediving induces acute intermittent hypoxia, typically characterized by transient but significant reductions in oxygen saturation. These events trigger compensatory mechanisms such as the diving reflex, including reflex bradycardia and peripheral vasoconstriction, and result in specific modifications of cerebral blood flow (Bouten *et al.*, 2020).
Due to its deliberate and repetitive exposure to low oxygen conditions in healthy individuals, freediving offers a natural and controlled model of hypoxic tolerance. Freediving combines two key components: (1) voluntary acute intermittent hypoxia, and (2) regular exercise and respiratory training (Figure 9). This dual characteristic may uniquely engage adaptive processes involving brain plasticity, neurovascular regulation, and cognitive modulation.

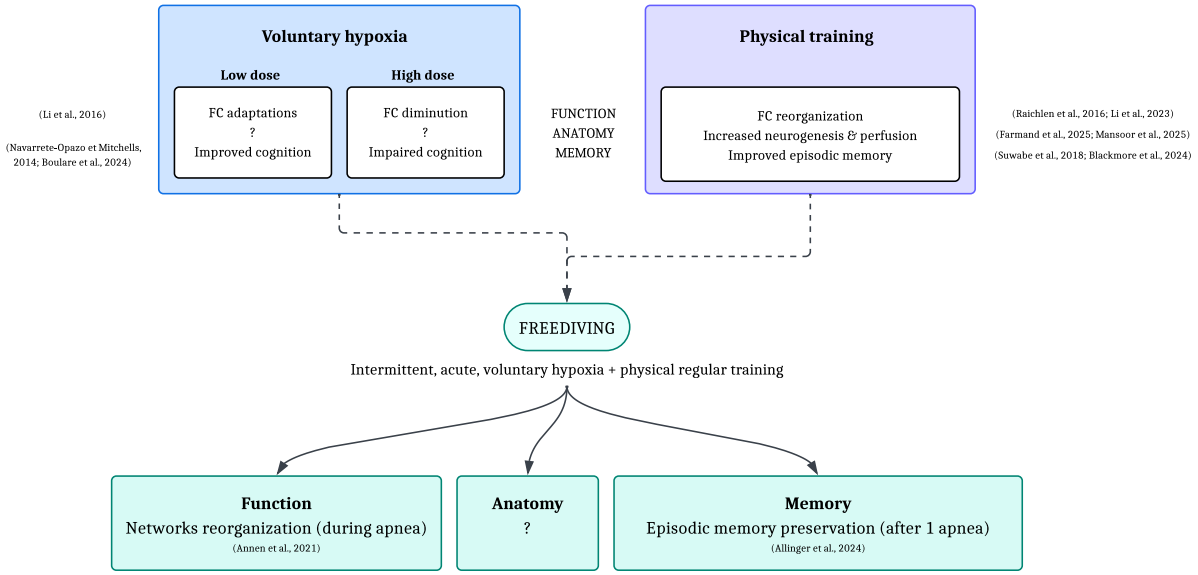


Figure 9: Schematic representation of the potential combined effects of intermittent, acute, voluntary hypoxia (left) and exercise training (right) in freediving on brain function, anatomy, and episodic memory. Freediving may induce specific functional adaptations (Annen et al., 2021) and therefore episodic memory preservation (Allinger et al., 2024), with still unknown anatomical effects. FC: Functional Connectivity, DG: Dentate Gyrus.

Specific studies on freediving and their results

A study by Annen *et al.* (2021) investigated the neurofunctional effects of voluntary apnea in a world-class freediving athlete. Using fMRI during a dry apnea lasting approximately 6.5 minutes, the study captured real-time brain responses to acute hypoxia, revealing significant modifications in brain connectivity. On fMRI, increased functional connectivity was observed during apnea in subcortical regions (bilateral thalamus, caudate, right amygdala) and in cortical territories involving the DMN and executive control networks. In parallel, decreased connectivity was mainly found in sensory-motor regions and additional temporal, parietal, insular and occipital cortices. The observed connectivity shifts may reflect an optimization of brain function, potentially enhancing resistance to low-oxygen environments. This idea is supported by (Allinger *et al.*, 2024), who demonstrated that elite divers maintain intact episodic memory despite repeated hypoxic challenges.

To our knowledge, however, no study has directly assessed the hippocampus, leaving a major gap in understanding the full cognitive and anatomical consequences of such exposures. Nevertheless, the work of Annen *et al.* (2021) provides compelling evidence of neuroplasticity under voluntary hypoxia in trained individuals.

Other forms of voluntary hypoxia: comparative findings

Other models of voluntary hypoxia have been investigated, including apnea during synchronized swimming. In a study by Jones and Cooper (2018), near-infrared spectroscopy was used to assess oxygenation patterns in elite synchronized swimmers. Results showed that cerebral oxygenation was preserved more effectively than muscular oxygenation during apnea, showing that the brain is prioritized and protected. Yet, no direct evaluations of connectivity or memory were conducted.

In contrast, Maeshima *et al.* (2017) examined cognitive performance in older synchronized swimmers. They reported superior scores on delayed recall tasks compared to control groups, implying a potential benefit of long-term apnea training on episodic memory. Still, this study lacked neuroimaging data, and no anatomical or functional information on the hippocampus was provided. Together, these studies suggest a subtle but detectable cognitive advantage, though mechanistic insights remain limited.

IHT protocols have also been used to explore the impact of voluntary hypoxia on brain function. In a study by Li *et al.* (2016), participants exposed to hypoxia showed decreased connectivity during acute sessions but a slower cognitive decline over time following IHT. This suggests functional adaptation and increased hypoxic tolerance, although no hippocampal or memory data were reported. Rybnikova *et al.* (2022) reviewed evidence from animal and human studies and concluded similarly that IHT enhances neuronal plasticity and resilience. However, the review did not detail hippocampal anatomy or episodic memory changes. Similarly, Boulares *et al.* (2024) conducted a systematic review highlighting general cognitive improvements following IHT, especially in older adults and patients with mild cognitive impairment. While possible neuroprotective effects on the hippocampus were mentioned, evidence on hippocampal volume, connectivity, or direct memory outcomes remained limited or inconclusive.

Importantly, several studies emphasize the dose-dependent nature of hypoxic effects. Navarrete-Opazo and Mitchell (2014) demonstrated in rodents that low-dose acute intermittent hypoxia enhanced hippocampal neurogenesis, spatial learning, and neuroprotection. In contrast, excessive or chronic intermittent hypoxia resulted in hippocampal damage and cognitive decline. This inverted U dose–response relationship underlines the necessity of precise protocol calibration to control beneficial effects without causing harm. Boulares *et al.* (2024) echoed this view, noting that positive cognitive outcomes occurred only under tightly controlled, short-term exposures. In contrast, pathological forms like OSA remained clearly deleterious, particularly for hippocampal integrity and memory.

Taken together, these findings suggest that voluntary hypoxia, when applied intermittently and at moderate intensity, may enhance brain resilience and cognitive performance.

Nevertheless, these effects are highly sensitive to dose, frequency, duration, and contextual factors such as exercise training type and baseline health status.

In conclusion, as noted in the previous chapter, most studies to date have focused on involuntary hypoxia and its adverse consequences. In contrast, preliminary data on voluntary hypoxia protocols, particularly when combined with exercise training, show promising signs of cognitive and functional enhancement. Unlike uncontrolled exposures, these protocols are deliberate, structured, and often designed with therapeutic or cognitive optimization in mind. Although still limited, current evidence suggests that voluntary hypoxia may engage distinct brain mechanisms and offer a unique window into adaptive neuroplasticity.
Yet, an important gap persists: no existing study has simultaneously assessed hippocampal anatomy, hippocampal connectivity, and episodic memory performance in the context of voluntary hypoxia. The effects of such exposures appear functionally beneficial under specific conditions (as seen in IHT), but are inconsistently documented across studies. Protocol variability, including differences in duration, cycle number per day, and whether exposure occurs on consecutive days or intermittently, may contribute to these divergences (Navarrete-Opazo and Mitchell, 2014). The exact neural mechanisms underlying voluntary hypoxia-induced adaptations remain therefore speculative.
Given the hippocampus's essential role in episodic memory and its vulnerability to oxygen deprivation, it is essential to characterize how voluntary hypoxia impacts this structure specifically. Freedivers represent an ideal population for such investigations, as they demonstrate remarkable tolerance to hypoxia after repeated exposures. Understanding the neural adaptations in this population may inform preventive or therapeutic strategies for pathological hypoxia and age-related cognitive decline.
This thesis addresses these gaps by systematically evaluating the effects of voluntary hypoxia on hippocampal anatomy, functional connectivity, and episodic memory performance in freedivers. It aims to shed light on the brain's adaptive potential under non-pathological, controlled hypoxic conditions and contribute to a more nuanced understanding of hippocampal neuroplasticity.

3. Aim and hypotheses

3.1. General objectives

This thesis addresses a central question: can the human hippocampus adapt to repeated episodes of voluntary intermittent hypoxia, as seen in trained freedivers? To address this question, we investigated hippocampal adaptability in healthy individuals, using a cohort of freedivers. Specifically, we aimed to determine whether repeated intermittent hypoxic episodes induce anatomical and functional hippocampal changes, and whether such changes underlie preserved episodic memory performance.

This work focuses on three complementary axes (Figure 10):

(1) Neuroanatomical axis: assessing whether hippocampal subfields anatomy differs between freedivers and controls using anatomical MRI

(2) Episodic memory axis: evaluating whether episodic memory is preserved in freedivers compared to controls using a pattern separation task

(3) Functional connectivity axis: identifying resting-state functional connectivity, particularly within hippocampal networks, in freedivers compared to controls using rs-fMRI

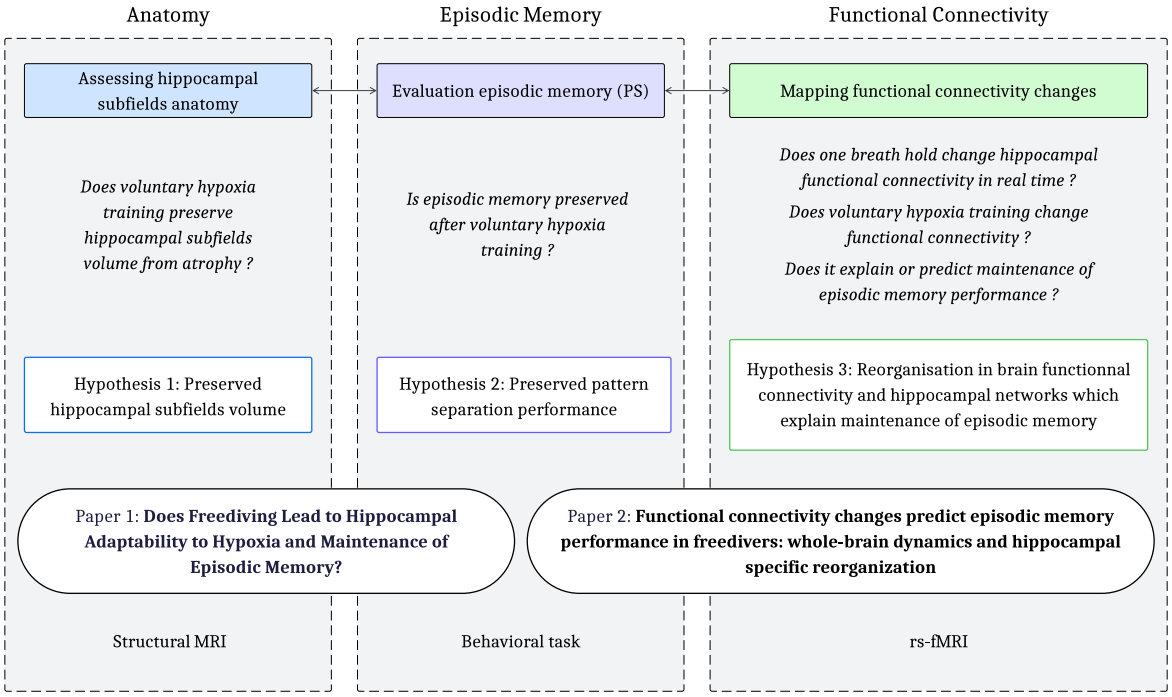


Figure 10: Architecture of the Ph.D. dissertation aimed at characterizing anatomical, cognitive and functional adaptations of the hippocampus to repeated voluntary hypoxia. The work is organized into three main axes: (1) hippocampal subfields anatomy, (2) episodic memory performance, and (3) brain functional reorganization at rest. Each axis is supported by an experimental contribution based on anatomical MRI, rs-fMRI, or cognitive assessment. PS: Pattern Separation.

3.2. Structure of the dissertation

The remaining chapters of this thesis are organized as follows:

Chapter 2 presents the methods used throughout the project. It describes the two study populations (freedivers and controls), the cognitive assessments employed to evaluate both global cognitive and episodic memory functions, and the acquisition protocol for both anatomical and functional MRI. This chapter also outlines the analytical pipelines used for hippocampal segmentation and rs-fMRI analysis.

Chapter 3 presents the experimental contributions, organized around the three previously defined axes. The objective was to advance an interdisciplinary understanding of how hypoxia affects the hippocampus in the context of freediving by integrating perspectives from neuroanatomy, episodic memory, and functional connectivity, as well as their interrelations:

Axis 1 – Neuroanatomy

Aim 1: We first aimed to determine whether freedivers exposed to repeated voluntary hypoxia exhibit differences in hippocampal anatomy compared to controls. We hypothesized that, unlike the atrophy typically observed in involuntary hypoxia, the hippocampal volume in freedivers would be preserved, suggesting the presence of neuroprotective or adaptive mechanisms.

Paper 2: ***Does Freediving Lead to Hippocampal Adaptability to Hypoxia and Maintenance of Episodic Memory?*** Micaux, J., Poiret, C., Zhao, J., Hajj, A. E., Tillenon, M., Habibi, A. T., Mauconduit, F., Boumezbeur, F., Chiron, C., Noulhiane, M. (2025). *Journal of Integrative Neuroscience*, *24*(7), 36672. https://doi.org/10.31083/JIN36672

This study focused on hippocampal anatomy and episodic memory performance, combining anatomical MRI analysis of hippocampal subfields with a behavioral assessment of episodic memory using a pattern separation task (HippoPS) in freedivers, before and after training. This is the first study to jointly evaluate anatomical hippocampal integrity and episodic memory in a healthy population subjected to voluntary hypoxia. It provides a foundation for understanding non-pathological brain adaptation to extreme environments.

Axis 2 – Episodic memory

Aim 2: The second objective was to explore whether episodic memory (and particularly pattern separation ability) is maintained in freedivers. We expected memory performance in freedivers to be comparable to or exceed that of controls, indicating cognitive resilience despite the physiological stress induced by voluntary hypoxia (paper 2). In addition, we hypothesized that preserved episodic memory performance would rely on the maintenance of hippocampal subfield volumes together with a reorganization of hippocampal functional connectivity (paper 2 & 3).

Axis 3 – Neurofunctional

Aim 3: Lastly, we investigated whether voluntary hypoxia affects whole-brain and hippocampal functional connectivity. We hypothesized that it would induce a specific

reorganization involving the hippocampus visible using rs-fMRI, reflecting network plasticity.

Paper 3: ***Functional Connectivity Changes Predict Episodic Memory Performance in Freedivers: Whole-Brain Dynamics and Hippocampal Specific Reorganization.*** Micaux, J., Habibi, A. T., Mauconduit, F., Noulhiane, M. *In Submission for Human Brain Mapping.*

This study focused on understanding functional reorganization under voluntary hypoxia. rs-fMRI was used to compare brain connectivity during normal breathing and controlled apnea in freedivers, before and after training. This is the first neuroimaging study to examine real-time functional connectivity changes during voluntary apnea in humans, and delayed effects of voluntary hypoxic training over time. It highlights how the hippocampus reorganizes in response to controlled hypoxic stress, opening new perspectives on brain adaptability.

Chapter 4 provides the general discussion. It integrates findings from all three axes, situates them within the existing literature, discusses methodological limitations, proposes future research directions, and introduces the HiAM model, a conceptual framework of hippocampal adaptability to intermittent voluntary hypoxia.

Chapter 2: Methods

This chapter summarizes the experimental protocols, participant characteristics, cognitive testing procedures, MRI acquisition parameters, and analysis pipelines used in this present thesis. All procedures were approved by the local ethics committee and implemented consistently across all participants. For full methodological details, including protocol, preprocessing parameters, and statistical models, see articles in Chapter 3 Micaux *et al.*, In Prep).

1. Population

This study was conducted in accordance with ethical standards for human research and approved by the local ethics committee (CPP 2022-A01030-43). Informed written consent was obtained from all participants. Between 2022 and 2024, a total of 37 healthy male subjects were enrolled from aquatic sports centers and clubs in the Île-de-France region (including Paris, Yvelines, and Hauts-de-Seine). The sample included two groups: 17 trained freedivers (FD) and 20 control athlete subjects (NC), aged between 27 and 55 years. All participants had a behavioral assessment at two time points: before and after training for FD, with the equivalent interval for NC. MRI data was acquired twice for FD (pre- and post-training) and once for NC.

1.1. Freedivers

The FD group consisted of 17 men regularly practicing recreational freediving. All were members of an official freediving club, which ensured that training was consistent, structured, and supervised throughout the study. FD had a mean age of 47.9 years (SD = 4.8) and an average of 16.9 years of formal education (SD = 1.7) (Figure 11). During the study, these participants followed a 7-month training protocol designed to elicit repeated voluntary exposure to moderate hypoxia through apnea practice. Training intensity was standardized across individuals and approximately five hours per week. A mobile application and website were developed to allow participants to monitor their progress, maintain communication with the rest of the team, encourage a sense of community and to support their motivation during the longitudinal study. The platform also provided a space to address participants' questions. Each diver completed MRI and cognitive evaluations both at baseline (t_0) and after the training period (t_1). Eligibility criteria required the absence of neurological, psychiatric, respiratory, or cardiovascular conditions and no current treatment affecting brain function. All testing procedures and scanning sessions were conducted under identical conditions.

1.2. Controls

The NC group was composed of 20 healthy male volunteers, matched to the FD group in terms of age (mean = 44.8, SD = 9) and education (mean = 16.5 years, SD = 2.4) (Figure 11). NC engaged in aerobic exercise (e.g., running, cycling) on a regular basis, with a comparable

weekly training volume (~5 hours), but had no history of apnea practice. Behavioral assessments were administered twice, at time points matched to the FD group. Anatomical and functional MRI were acquired at the first session (t_0) only. All participants in the NC group met the same inclusion criteria and underwent the same procedures and ethical protocol as the FD group.

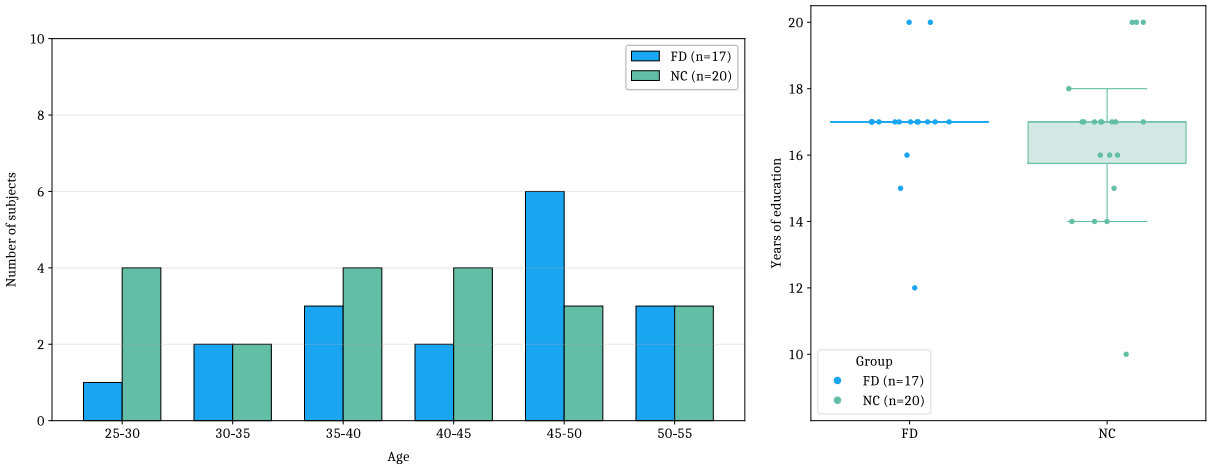


Figure 11: Age distribution (left panel) and education level of participants (right panel, no significant difference). Freedivers (FD, blue); Control group (NC, green).

2. Behavioral assessments

To evaluate general cognitive function and episodic memory ability, participants completed a standardized battery of behavioral tests. Except for the memory task, these were administered once for all subjects. Assessments included non-verbal reasoning (Raven's progressive matrices task), verbal fluency, short-term memory (memory span), and a pattern separation task specifically targeting episodic memory (HippoPS). The same procedures and task versions were used across both groups and time points. Testing took place in a quiet environment, and instructions were given in French by the same person.

2.1. Global intelligence

2.1.1. Nonverbal reasoning: Raven's progressive matrices task

Non-verbal abstract reasoning was measured using Raven's standard progressive matrices. This task assesses fluid intelligence by requiring participants to identify the missing element in a series of visual patterns with increasing complexity. Performance was quantified based on the number of correct responses within a fixed time limit.

2.1.2. Verbal fluency: phonemic and semantic verbal fluency task

Lexical access and executive function were assessed using a verbal fluency task. Participants were asked to generate as many words as possible belonging to a given category (semantic fluency) and starting with a specific letter (phonemic fluency), each within 1-minute time intervals. The final score was the total number of valid words produced across conditions.

2.1.3. Memory span: digit span task

Short-term memory capacity was evaluated through forward and backward digit span tasks. Sequences of digits were read aloud, and participants were required to repeat them in the same (forward) or reverse (backward) order. The longest correctly repeated sequence defined the span score (in one, two, or three attempts). The score was calculated as follows:

$$memory\ span\ -\ \frac{number\ of\ trials - 1}{3}.$$

2.2. Episodic memory: HippoPS task

Episodic memory performance was assessed using the HippoPS task, an ecological and validated paradigm specifically designed to investigate hippocampal pattern separation. This task has been used in multiple independent cohorts, including healthy adults, older individuals, and patients with temporal lobe epilepsy (Azevedo, 2025; Zhao and Noulhiane, In Prep).

HippoPS consists of two phases: encoding and delayed recognition. During the encoding phase, participants viewed 28 short videos, each presenting a distinct static image of a spatial location paired with a simple gesture. Each item was displayed once, in randomized order. Following a 15-minute delay, the recognition phase was administered. Participants were shown static images extracted from the original videos and asked to classify each as: (i) identical (same gesture and location), (ii) similar (same gesture or same location, but not both), or (iii) new (completely novel combination). Three accuracy scores were computed, one for each response category. These scores served as individual memory indices to measure episodic memory capacity, and were also included in correlations with hippocampal functional connectivity data.

3. MRI acquisitions

All neuroimaging data was acquired at NeuroSpin (CEA Saclay, France) using the 3 Tesla Siemens Magnetom Prisma MRI scanner. Anatomical and functional sequences were collected following a standardized acquisition protocol (Figure 12).

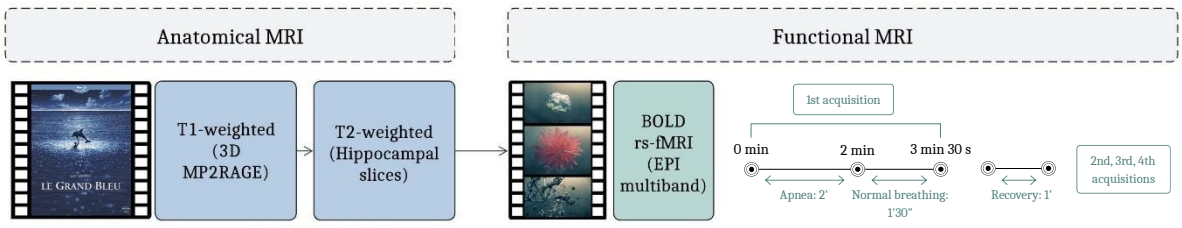


Figure 12: Schematic overview of the MRI acquisition protocol. Anatomical MRI included T1- and T2-weighted images. Functional connectivity was assessed across 4 rs-fMRI runs, each lasting 3 minutes and 30 seconds and structured into: an apnea phase (2 minutes), a normal breathing phase (1 minute 30 seconds), and a recovery period (1 minute).

3.1. Anatomical MRI

Anatomical imaging included a 3D T1-weighted sequence for whole-brain morphometry and a coronal T2-weighted sequence optimized for the hippocampus. T2-weighted acquisition

parameters were: TR = 9600 ms, TE = 83 ms, voxel size = 0.5 × 0.5 × 1.0 mm^3, FOV = 192 mm, number of slices = 60, duration = 6 min 46 s. These sequences were used to assess hippocampal anatomy and for co-registration with functional data. Anatomical images were acquired for all participants at baseline (t_0). In the FD group, T1 and T2 scans were repeated after training (t_1).

3.2. Functional MRI

Resting-state functional images were acquired using a multiband echo-planar imaging (EPI) sequence sensitive to BOLD contrast. Acquisition parameters were: TR = 2500 ms, TE = 26 ms, flip angle = 71°, voxel size = 1.7 × 1.7 × 1.8 mm^3, number of slices = 68, multiband factor = 2, FOV = 192 mm, volumes per run = 80. Each run lasted 3 minutes and 30 seconds. To correct for geometric distortions, two additional spin-echo EPI scans with opposite phase-encoding directions (anterior-posterior and posterior-anterior) were also acquired (TR = 3510 ms, TE = 55.4 ms, and same resolution as above).

Four rs-fMRI runs were collected per session. In the FD group, each run included a 2-minute apnea block followed by 90 seconds of normal breathing. Between runs, a 1-minute rest period was added. Participants were instructed to remain still and watch short, silent movies adapted from Vanderwal *et al.* (2015), which included countdown messages indicating apnea start and end. This naturalistic movie paradigm has been validated to improve compliance, reduce motion artifacts, and give high-quality data even during apnea. Vanderwal *et al.* (2015) have shown that unlike other movies, it mirrors RSNs and especially DMN activity seen at rest. Different movie clips were used for each run to maintain attention. In the NC group, the four rs-fMRI runs were acquired following the same protocol as in the FD group, but without apnea. Acquisitions parameters are summarized in Table 1.

Table 1: MRI acquisition parameters

MRI modality	Sequence	TR (ms)	TE (ms)	Voxel size (mm)	Slices	Multiband	Duration
Anatomical MRI	T1-weighted (3D MP2RAGE)	5000	2.98	1.0 x 1.0 x 1.0	176	No	8’ 22”
	T2-weighted (Hippocampal slices)	9600	83.0	0.5 x 0.5 x 1.0	60	No	6’ 46”
Functional MRI	Spin-Echo Fieldmap x2 (AP-PA)	3510	55.4	1.7 x 1.7 x 1.8	68	No	0’ 29”
	BOLD fMRI (EPI multiband)	2500	26.0	1.7 x 1.7 x 1.8	68	Yes (factor 2)	3’ 30” / run

Anatomical imaging included T1-weighted and T2-weighted scans focused on the hippocampus. Functional acquisitions comprised BOLD fMRI using a multiband EPI sequence and dual spin-echo fieldmap sequences (AP–PA) for distortion correction. The table reports the sequence type, repetition time (TR), echo time (TE), voxel resolution, number of slices, multiband status, and total acquisition duration for each protocol.

4.Statistical analysis

Statistical analysis evaluated behavioral outcomes, hippocampal subfields volume, and functional connectivity at rest. All tests were two-sided, and significance was set at $p < 0.05$. Analysis was performed using *R* (4.4.2), *Python* (version 3.10), and *MATLAB* (CONN Toolbox version 20.b), with specific packages detailed in the respective publications (Micaux *et al.*, In Prep; Micaux *et al.*, 2025).

4.1. Behavioral data

Cognitive performance in global intelligence tasks (Raven's progressive matrices task, phonemic and semantic verbal fluency task, and digit span task) was compared between groups using the non-parametric Mann–Whitney test due to non-normal data distributions.
Episodic memory scores from the HippoPS task were analyzed using a two-way repeated-measures ANOVA. The model included three factors: Group (FD vs NC), Item type (Identical, Similar, New), and Session (t_0 vs t_1, within the FD group). Between-group comparisons (FD vs NC) and within-group effects (FDt_0 vs FDt_1) were examined separately.

4.2. Anatomical MRI

Anatomical MRI data was processed using HSF© (4.0.0) to automatically segment hippocampal subfields, including DG, CA1, CA2, CA3, and subiculum, using T2-weighted MRI scans (Poiret *et al.*, 2023). Volumes for each subfield, as well as the entire hippocampus, were quantified at two timepoints. Due to deviations from normal distribution, between-group comparisons at t_0 and t_1 employed Mann-Whitney tests, and within-FD changes between FDt_0 and FDt_1 used Wilcoxon signed-rank tests. Multiple comparisons across subfields were corrected using FDR correction.

4.3. Functional MRI

rs-fMRI data was preprocessed using CONN Toolbox (v. 20.b) on *MATLAB*. Each FD's run was split into "apnea" and "rest" segments based on their actual apnea duration. Functional connectivity analysis focused on the hippocampus and four additional regions of interest (ROIs): the frontal pole, frontoparietal network (FPN), DMN, and occipital pole (as a visual control). Two types of analysis were conducted: ROI-to-ROI (based on the Harvard-Oxford atlas), to examine global brain connectivity, and seed-to-voxel, to assess functional connectivity between each ROI and other brain regions. Given known hemispheric asymmetries in those networks, analysis was performed separately for each hemisphere. Group-level comparisons were carried out using predefined contrasts between conditions (e.g., apnea vs rest, before vs after training, and FD vs NC). Functional connectivity maps and connectivity matrices were derived for each comparison. In addition, seed-to-voxel correlations were computed between hippocampal functional connectivity and episodic memory scores obtained from the HippoPS task. All statistical analyses included an FDR correction for multiple comparisons.

Chapter 3: Results

This thesis investigated hippocampal integrity and brain connectivity at rest in freedivers, with the aim of linking these findings to episodic memory performance. Chapter 3 presents the results along these axes, first examining hippocampal anatomy and episodic memory, and then functional connectivity in relation to the same memory scores.

1. Global intelligence

We first evaluated global intelligence to ensure comparable general cognitive abilities between groups, before focusing on episodic memory. This assessment included fluid reasoning, working memory, and verbal fluency tasks. Establishing similar baseline profiles was necessary to confirm that any eventual differences in episodic memory scores in our population could not be attributed to disparities in overall cognitive function. Variations in general intelligence have been associated with differences in brain structure, including hippocampal volume, as well as with the organization of large-scale functional networks that support memory processes (Cox *et al.*, 2019; Dubois *et al.*, 2018; Hearne *et al.*, 2016).

However, we found no evidence of cognitive impairment in either group, and showed that no significant differences exist at baseline, indicating comparable global cognitive profiles (Figure 13). Therefore, subsequent findings can be interpreted as specific adaptations rather than consequences of pre-existing cognitive differences.

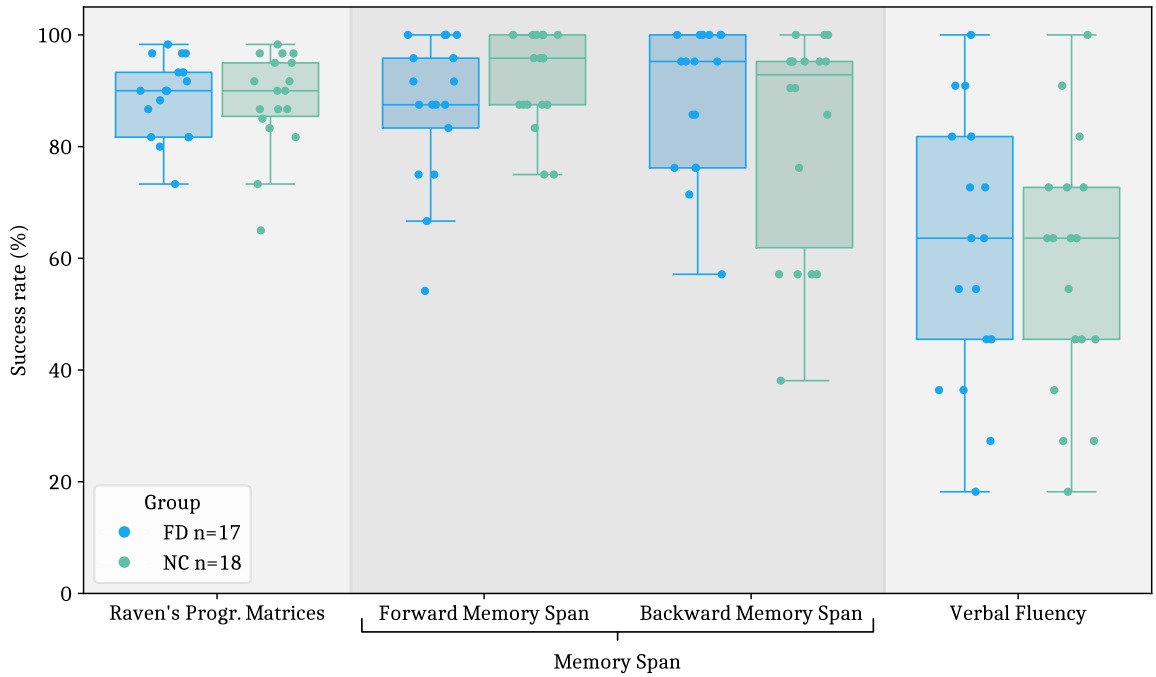


Figure 13: Cognitive performance in both groups. Success rates (in %) of FD and NC on the 3 cognitive tasks: Raven's Progressive Matrices (fluid intelligence), forward and backward memory span (working memory), and verbal fluency (language processing, executive control). No significant group differences were observed, indicating comparable general cognitive abilities between FD and NC. FD: Freediver, NC: Controls.

2. Hippocampal anatomy and episodic memory

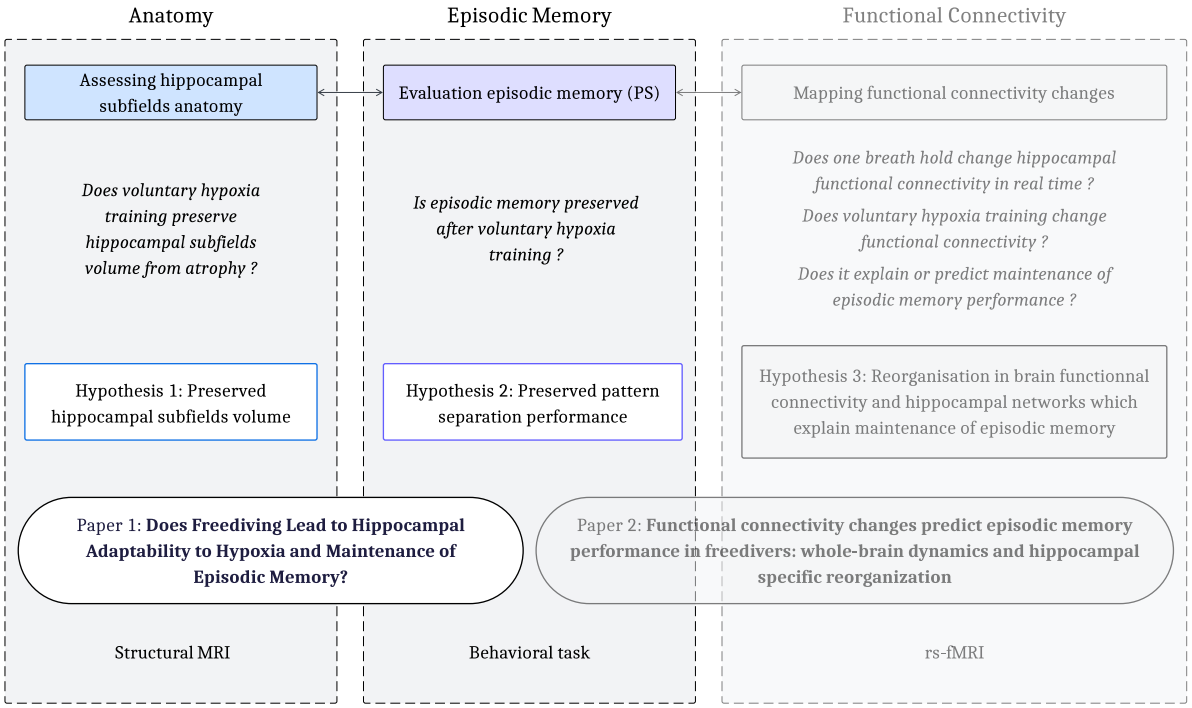


Figure 14: Architecture of the Ph.D. dissertation: hippocampal subfields anatomy and episodic memory performance. PS: Pattern Separation.

Does Freediving Lead to Hippocampal Adaptability to Hypoxia and Maintenance of Episodic Memory?

Micaux, J., Poiret, C., Zhao, J., Hajj, A. E., Tillenon, M., Habibi, A. T., Mauconduit, F., Boumezbeur, F., Chiron, C., Noulhiane, M. (2025). *Journal of Integrative Neuroscience*, *24*(7), 36672. https://doi.org/10.31083/JIN36672

Involuntary hypoxia, whether caused by pathological conditions such as OSA, COPD, or by environmental exposure at high altitude, consistently leads to anatomical damage to the hippocampus and measurable deficits in episodic memory (Olaithe *et al.*, 2018; Pfister *et al.*, 2023). The hippocampal subfields, and particularly the DG and CA1, are highly vulnerable to oxygen deprivation due to their high metabolic demand and complex vascularization (Lu *et al.*, 2025). Pattern separation, a key process of episodic memory primarily supported by the DG, prevents interference between overlapping experiences and relies on the integrity of hippocampal subfields. Additionally, DG is one of the few brain regions where adult neurogenesis occurs, supporting both memory encoding and anatomical plasticity. As a result, hippocampal subfields volumetry and pattern separation performance represent complementary markers of hippocampal integrity.
Remarkably, freedivers, who repeatedly expose themselves to acute, intermittent hypoxia during voluntary breath-holding, do not appear to have memory impairments. Only a few

studies have addressed this topic, but they reported preserved cognitive performance in experienced freedivers, even following maximal apnea (Allinger *et al.*, 2024; Ridgway and McFarland, 2006). Freediving combines voluntary hypoxic exposure with exercise training, and current literature suggests that exercise promotes neurogenesis, angiogenesis, and enhanced memory performance (Farmand *et al.*, 2025; Firth *et al.*, 2018). The combination of these two factors may produce a different outcome from involuntary hypoxia alone. These observations raise an important question: could voluntary hypoxia, under controlled and intermittent conditions, lead to anatomical and cognitive preservation, or even adaptive changes, instead of degeneration?

Despite this potential, previous work on freedivers is limited. The few studies are cross-sectional, involve small samples, or assess cognitive performance only once after a diving session. No longitudinal study has investigated the effects of a freediving season on hippocampal volume and pattern separation performance, using hippocampal subfield segmentation combined with a targeted episodic memory task.

To address this gap, this study determined whether repeated voluntary hypoxia during freediving training induces measurable anatomical changes in hippocampal subfields or affects episodic memory performance (Figure 14). Volumes were extracted from T2-weighted MRI using HSF©, and episodic memory was assessed with the HippoPS task, a validated ecological measure of pattern separation. We hypothesized that freedivers would maintain stable hippocampal volumes and pattern separation performance over time, in contrast with the degenerative patterns seen in involuntary hypoxia. This work provides the necessary baseline for the following chapter, which explores functional connectivity changes in the same cohort. The interpretation of this functional data depends on confirming that any potential network-level adaptations occur in the absence of clear anatomical damage or cognitive decline.

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Original Research

Does Freediving Lead to Hippocampal Adaptability to Hypoxia and Maintenance of Episodic Memory?

Julia Micaux[1,2], Clément Poiret[1,2], Jingwen Zhao[1,2], Aya El Hajj[3], Morgane Tillenon[4,5], Abir Troudi Habibi[1,2], Franck Mauconduit[6], Fawzi Boumezbeur[7], Catherine Chiron[1,2], Marion Noulhiane[1,2,*]

[1]Paris-Saclay University, CEA, Joliot Institute, NeuroSpin, UNIACT, F-91191 Gif-sur-Yvette, France
[2]Paris City University, Inserm, U1141 NeuroDiderot, InDev Team, F-75019 Paris, France
[3]Sport Sciences Department, Univ Rouen Normandie, CETAPS, F-76000 Rouen, France
[4]Paris Brain Institute, Centre d'Investigation Clinique; Assistance Publique Hôpitaux de Paris, Département des Maladies du Système Nerveux, Hôpital Pitié-Salpêtrière, F-75013 Paris, France
[5]Public Assistance Hospitals of Paris, Department of Neurology, Institute of Memory and Alzheimer's Disease, Pitié-Salpêtrière Hospital, F-75013 Paris, France
[6]CEA, NeuroSpin, CNRS, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France
[7]BAOBAB, NeuroSpin, CNRS, CEA-SACLAY, F-91191 Gif-sur-Yvette, France
*Correspondence: marion.noulhiane@cea.fr (Marion Noulhiane)
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Abstract

Background: Accidental hypoxia has detrimental effects on the brain, particularly on the hippocampal subfields (HS), which are highly sensitive to oxygen deprivation and play a crucial role in episodic memory. This raises the question: could freediving training induce anatomical changes in the HS and lead to significant memory deficits? This study aimed to investigate the impact of a season of freediving training on HS anatomy and episodic memory performance, as freedivers represent a unique natural model for studying the effects of repeated voluntary hypoxic exposure on brain function in healthy individuals. Extending previous research, this study assessed these effects over a prolonged training period. **Methods**: Seventeen male freedivers were evaluated before and after 7 months of training and compared with a control group of 20 non-freediver athletes. HS anatomical volumes were measured using MRI segmentation and episodic memory performance was evaluated using a pattern separation (PS) task. This task specifically targeted HS-related memory processes by distinguishing between three types of items: (i) identical, (ii) similar, and (iii) new. **Results**: No significant differences were observed between freedivers and controls in HS volumes or memory performance, either before or after the 7 month training period. A two-way repeated measures ANOVA revealed that freedivers exhibited the same memory pattern as the control group in the PS task. Specifically, both groups performed better with (i) identical items compared with (ii) similar items ($p < 0.001$) and were less accurate with (ii) similar items compared with (iii) new items ($p < 0.001$). This aligns with expectations, as distinguishing similar items from previously presented ones is more cognitively demanding than recognizing new items. **Conclusions**: These findings suggest that repeated voluntary hypoxic exposure during freediving training does not impair episodic memory function. Freedivers' memory performance remained comparable with that of the control group, with no detectable adverse effects on hippocampal anatomy.

Keywords: episodic memory; hippocampus; hypoxia; diving; cognition

1. Introduction

The hippocampal subfields (HS) within the medial temporal lobe are essential for episodic memory, a form of long-term memory that enables the recall of events in specific spatial and temporal contexts. These subfields, which include Cornu Ammonis (CA) 1, CA2, CA3, and CA4, the dentate gyrus (DG), and the subiculum [1], facilitate episodic memory formation [2] through processes such as pattern separation (PS), which reduces interference between similar events [3]. The DG plays a crucial role in PS, as it supports perceptual discrimination and encoding [4–6]. Within the DG network, cortical input spike trains are transformed, leading to less similar output spike trains in granule cells; a process further amplified by the CA3 network at the level of single pyramidal cells [7]. Together, these mechanisms allow the HS to balance the retrieval of past experiences while encoding new, yet similar, events.

Another essential function of the HS is its role in neurogenesis, particularly within the DG [8]. This process involves the generation of new neurons, alongside some interneurons and glial cells (e.g., oligodendrocytes or astrocytes). While most newly generated neurons undergo selective pruning, only a small fraction matures and integrates existing networks, thereby maintaining the DG volume. This neurogenic process is essential for encoding new information and supports hippocampal plasticity. Newborn

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granule cells contribute to PS [9], forming distinct memory traces for overlapping inputs and reducing interference during learning similar items over time, ultimately enhancing memory encoding and retrieval [3,10–12].

Involuntary hypoxia, regardless of its cause, significantly affects hippocampal anatomy and episodic memory. For instance, chronic hypoxia from prolonged residence at high altitudes induces structural and cellular changes within the HS, impairing learning and memory functions, and highlighting its vulnerability to prolonged hypoxia [13]. Similarly, chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD), which lead to progressive lung impairment and chronic hypoxia, are associated with substantial memory deficits. Individuals with COPD experience significant cognitive impairments, including episodic memory deficits, which correlate with hippocampal atrophy and reduced hippocampal volume [14,15]. Furthermore, obstructive sleep apnea syndrome (OSA), characterized by frequent breathing interruptions during sleep, leads to intermittent but prolonged hypoxia. OSA is specifically associated with episodic memory deficits [16] and is accompanied by cellular and neurophysiological changes in the hippocampus, contributing to broader cognitive and behavioral impairments [17]. Exposure to extreme altitudes (>6000 m) in high-altitude mountaineering has been also shown to result in significant episodic memory impairments, with hippocampal sensitivity to hypoxia contributing to long-term memory deficits lasting up to 12 months [18]. Climbers experiencing memory deficits after brief high-altitude stays further underscore the hippocampus's vulnerability to hypoxic environments [19].

These examples illustrate the detrimental effects of involuntary hypoxia on hippocampal function and memory performance, regardless of its cause. In contrast, the impact of voluntary hypoxia in sports remains unclear, with previous studies reporting conflicting results. Allinger *et al*. (2024) [20] found no adverse effects of hypoxia on memory in freedivers, even following a freediving session. This study assessed episodic memory using a PS task and found no evidence of deficits in individuals with approximately five years of freediving experience. Similarly, an earlier study reported no long-term memory impairments in elite breath-hold divers, using a series of standardized neuropsychological tests evaluating visual and verbal attention and recall tasks abilities [21].

Interestingly, Loprinzi *et al*. (2019) [22] reported unexpected advantages of mild acute hypoxia on episodic memory, primarily through the upregulation of brain-derived neurotrophic factor (BDNF). BDNF, a crucial factor in memory function, is regulated by hypoxia-inducible factor-1 during acute hypoxic exposure, enhancing synaptic plasticity and, consequently, memory function. This hypoxia-induced BDNF production not only facilitates episodic memory by strengthening synaptic connections but also improves PS by reducing memory interference. Acute hypoxia exposure may thus mitigate retroactive interference, where new information disrupts previously learned content. These cognitive benefits have been linked to mechanisms such as enhanced synaptic plasticity, neurotransmitter modulation, and improved cerebral blood flow, all contributing to optimizing memory and learning processes.

Additionally, the beneficial effects of aerobic physical exercise on memory (e.g., endurance), particularly PS, are well established [23]. Physical exercise enhances the survival rate of newly generated neurons in the DG [24], which are crucial for PS. Notably, endurance sports primarily rely on aerobic capacity, except during intense and prolonged efforts that engage anaerobic energy systems, whereas apnea training focuses on enhancing the body's adaptability to anaerobic conditions. The combined effects of exercise and hypoxia on memory and cognition reveal a complex interaction between the two factors. Ando *et al*. (2020) [25] found that cognitive performance seems to be significantly influenced by the interplay between exercise's beneficial effects and hypoxia's detrimental effects. The severity of hypoxia emerges as a critical determinant: moderate hypoxia during moderate exercise may enhance cognitive performance, whereas severe hypoxia often impairs tasks requiring memory and attention. These findings highlight the importance of balancing exercise intensity, hypoxia severity, and exposure duration to optimize cognitive outcomes.

Recently, Damgaard *et al*. (2023) [26] reported potential neuroprotective benefits of moderate hypoxia in brain disorders, with most human studies indicating cognitive improvements. Low-dose hypoxia combined with exercise was associated with enhanced cognitive performance and neuroplasticity, emphasizing the therapeutic potential of this combination. However, higher doses of hypoxia were linked to adverse effects, underscoring the need to carefully calibrate hypoxic exposure to maximize benefits while minimizing risks. Despite the detrimental effects of accidental hypoxia, previous studies on memory performance in freedivers, who voluntarily subject themselves to intermittent hypoxia during prolonged breath-hold activities, have reported mixed findings, ranging from preserved function to deficits. This is why a precise exploration of episodic memory with HS anatomy is necessary to clarify the impact of hypoxic training in this sport. While previous research has primarily focused on cognitive outcomes at a single time point after a freediving performance (maximal performance) in elite freedivers (considering several years of practice), a notable gap remains regarding the effects of a season of freediving training (several months) in recreational athletes. To date, no study has examined cognitive and anatomical changes before and after a structured training period.

The present study aimed to examine the effects of a freediving training season on HS volume and its relationship to performance in the PS task. To this end, 17 male

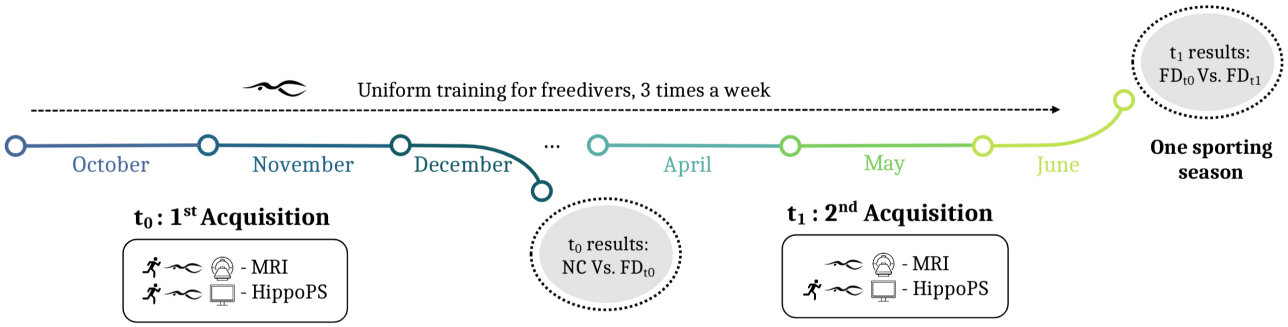


Fig. 1. Acquisitions calendar over one sporting season. 3T anatomical MRI and cognitive tests (HippoPS task) before and after homogeneous freediving training 3 times a week, including 1 hour 30 minutes of training for each session, and for non-freediver sport controls. FD, freedivers; NC, controls; MRI, magnetic resonance imaging; PS, pattern separation.

Table 1. Demographic data (FD and NC).

Characteristics	Freedivers (FD)	Controls (NC)
n	17	20
Sex	M	M
Age*	47.9 ± 4.8	44.8 ± 9.0
Years of study*	16.9 ± 1.7	16.5 ± 2.4
Training load	~5 h/week (aerobic & anaerobic)	~5 h/week (aerobic)

* Data are means ± standard deviation. M, Male.

freedivers were recruited during their training season and assessed at the beginning and end of a seven-month training period, which included three training sessions per week. Their results were compared to those of an age-matched control group of non-freediving male athletes. Data were collected at the beginning (F_{t0}) and at the end (F_{t1}) of the freediving training season. We employed Hippocampal Segmentation Factory (HSF© 4.0.0 CEA Saclay, Gif-sur-Yvette, France), an automatic MRI segmentation tool of the HS [27], and a PS task, HippoPS [28], to assess episodic memory. Given the role of the DG in neo-neurogenesis and its neuroprotective function for episodic memory, we hypothesized that freedivers would exhibit changes in the volume of DG and comparable PS scores to those of the control group between the beginning and the end of the training season, as no memory deficits have been previously reported in this population.

2. Materials and Methods

2.1 Participants

Data acquisition was performed following the Good Clinical Practice guidelines and approved by an appropriate Ethical Committee (2022-A01030-43). Written informed consent was obtained from each participant. Forty-seven male volunteers participated in this study, including 17 freedivers (FD) and 20 controls (NC) aged 27–55 years and recruited between 2022 and 2024 in the pools of Ile de France region (Paris, Yvelines, Hauts de Seine, France). A schematic of our protocol is shown in Fig. 1.

2.1.1 Freedivers

The FD selected for this study had prior experience with freediving as a hobby but were not professional athletes. After inclusion, FD participants underwent seven months of intense, regular, and uniform hypoxia training [29], including swimming pool sessions three times per week. Training sessions were made available through an application, where participants logged their performance immediately after completion or noted any exceptional absence. Swimming pool sessions lasted 1 hour and 30 minutes and consisted of repeated apnea series of varying durations interspersed with recovery periods of similar lengths. Typically, with bifins, 50-meter apnea series, used for hypercapnia training, lasted around 45–50 seconds with short recovery periods, while longer-distance apnea series, such as 100 meters (approximately 90–100 seconds), included a few minutes without breathing, followed by equivalent recovery periods. Throughout the season, training progressed from general physical preparation to more specific hypoxia exposure. By the end of the training period, all freedivers were able to complete dynamic apnea swims of 100 meters using fins, ensuring their physiological adaptation to hypoxia. All participants were members of a freediving club, ensuring consistent training throughout the year. Data collection was conducted at two time points: the first at the beginning of the training season (F_{t0}) and the second at the end of the training season (F_{t1}).

2.1.2 Controls

Age- and sex-matched controls with similar socio-cultural backgrounds were assessed under similar conditions (Table 1). These controls did not participate in free-diving but maintained a similar weekly training load (~5 hours per week) through physical activities such as swimming, running, or cycling (aerobic sports). Control participants underwent a single anatomical MRI assessment at t_0 and completed the memory task at t_0 and t_1.

2.2 MRI Acquisitions

Cerebral MRI was performed at 3T (VE11, 3T PRIMA Fit Siemens Healthineers, Erlangen, Germany) including the acquisition of T1 and high-resolution T2-weighted images of the HS. T1 parameters were Repetition Time (TR) = 2300 ms, Echo Time (TE) = 3.05 ms, 0.9 × 0.9 × 0.9 mm resolution, 176 slices, Time = 4.44′. T2-weighted MRI parameters were TR = 9600 ms, TE = 83 ms, Field of View (FOV) 192 mm, 0.5 × 0.5 × 1 mm resolution, 60 slices, Time = 6.46′.

2.3 MRI Segmentation: HS Volumes

The HS were automatically segmented using the Hippocampal Segmentation Factory (HSF©) software, a segmentation tool using deep learning. Starting with a preprocessing step where MRI scans are prepared for segmentation, the HSF© pipeline entails a standalone tool, ROILoc, to extract the left and right hippocampi from the raw T2 MRI. The hippocampi are cropped with a safety margin and normalized (Z-normalization). This preprocessing step also registers MRI data to a standardized template, enabling consistent localization of hippocampal regions. Additionally, the system incorporates test-time augmentation, generating multiple versions of each HS through flips, elastic deformations, and affine transformations, which are aggregated for final segmentation.

HSF© produces voxel-wise segmentation and uncertainty maps, assigning confidence levels to each voxel. It segments the major HS, including the DG, essential for PS processes; the CA1, CA2, CA3, and the subiculum, crucial regions in episodic memory.

This approach addresses challenges in segmenting every type of HS by leveraging high-quality datasets and an efficient training process. HSF© achieves results closer to manual segmentations than existing tools, ensuring accuracy and reproducibility while significantly reducing processing time. More details about this tool can be found at https://hsf.readthedocs.io/en/latest/ [27].

2.4 Cognitive Functions

2.4.1 Fluid Intelligence

We assessed fluid intelligence using the Raven's Progressive Matrices task [30], which evaluates logical reasoning and problem-solving skills. The task consists of five series (A, B, C, D, E) of twelve numbered items, with increasing difficulty. Participants were required to identify the missing piece to complete the logical sequence. A total score was computed to approximate the participant's intellectual capacity and subsequently compared to age- and socio-culturally adjusted normative data [31].

2.4.2 Digit-memory Span

To assess memory span, we used the digit span task, comprising two components: the forward span, measuring short-term memory, and the backward span, which requires more manipulation and visualization of numbers and measures working memory. Participants listened to a sequence of numbers and repeated it correctly. Sequence length increased progressively following each correct response. Each level included two trials with different sequences, and the task concluded when the participant failed both trials at a given level. The participant's span was defined as the level at which they made two consecutive errors. Performance was compared against normative data stratified by age [32].

The global intelligence scores indicated no cognitive deficits in either cohort (NC and FD), and the two populations had similar scores (Table 2) [31,32].

Table 2. Global intelligence results in the Raven's Progressive Matrices task and memory span task.

Tasks	Freedivers (FD)	Controls (NC)
Raven task (percentiles)*	88.9 ± 12.3	87.8 ± 12.6
Memory span (score)*		
Forwards	7.1 ± 1.1	7.4 ± 0.7
Backwards	6.4 ± 0.9	5.9 ± 1.6

*Data are means ± standard deviation.

2.5 Episodic Memory Task: HippoPS

Episodic memory was assessed using the HippoPS task [28] (Fig. 2), a validated ecological tool specifically designed to study PS. This task is particularly suited for evaluating episodic memory, as it provides a more precise assessment of its defining characteristics compared to methods commonly described in literature.

The experiment consists of two parts: the encoding phase and, after 15 minutes delay, the recognition phase. The experiment begins with an instruction: "*Lisa is a foreign tourist coming to Paris for the first time. She wants to show you around and associate a different gesture for each place she has visited. Watch the entire video carefully so that you can discuss it with her afterward. Do you recognize these places? Have you seen these gestures before?*".

In the encoding phase, participants watch a series of items presented on video, each comprising an image of a location associated with a gesture and a temporal context (morning, noon, afternoon). After 15 minutes, the recognition phase begins, with an instruction as a transition, asking

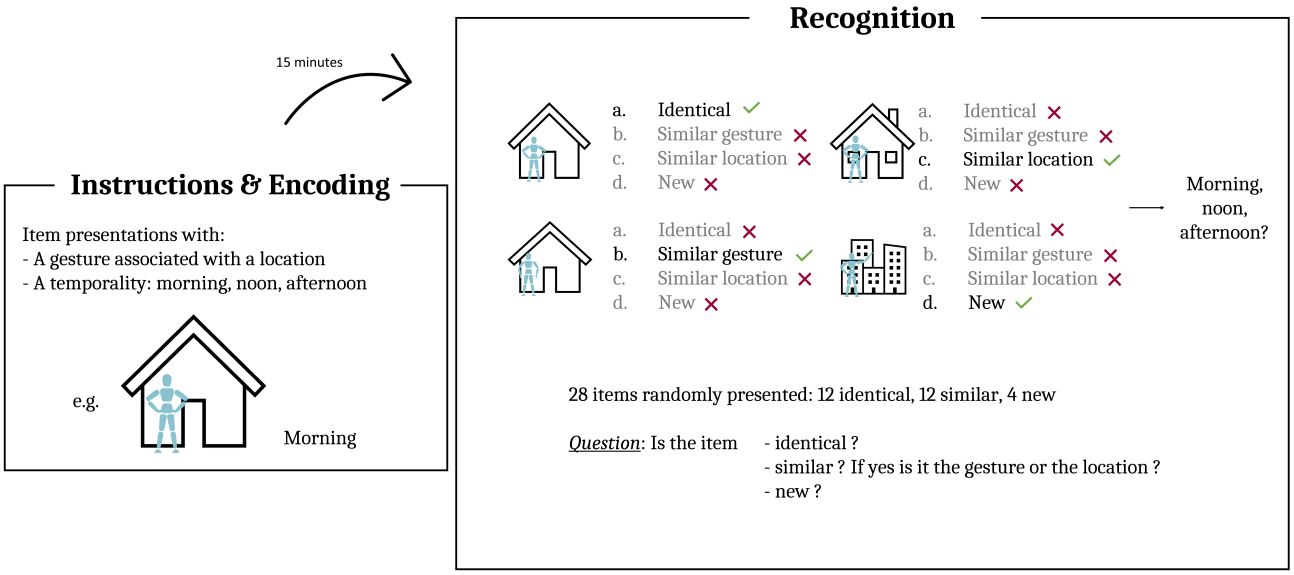


Fig. 2. Encoding and recollection phase of the HippoPS task. The encoding phase involves presenting images of a location paired with a gesture and a temporal context (morning, noon, or afternoon). The recognition phase takes place 15 minutes later and consists of 28 questions: is the item (i) identical? (ii) similar? (iii) new?

the participant to distinguish photos, with the question: (i) is it an event with the same gesture and the same location ('identical'), or (ii) is it an event with a different location but the same gesture or an event with the same location but a different gesture ('similar location' or 'similar gesture'), or (iii) is it an event with a different gesture and a different location ('new')?

Four examples are provided to ensure that the instructions are clearly understood. 28 items were randomly presented, 12 of which were 'identical' events, 12 'similar' events (i.e., 6 'similar location' and 6 'similar gesture'), and 4 'new' events. The results are calculated in percentage for (i) identical, (ii) similar, and (iii) new items.

2.6 Statistical Analysis

All statistical analyses were conducted using R Statistical Software 4.4.2 (https://cran.r-project.org/src/base/R-4/) and JASP Team (2024 0.19.1, https://jasp-stats.org/previous-versions/), with significance set at a 0.05 threshold. The volumes of the whole hippocampus and each HS were analyzed separately. Due to deviations from normality, a Mann-Whitney test was employed to NC and FD at F_{t0} (pre-training), and NC and FD at F_{t1} (post-training). Within the FD group, comparisons between F_{t0} and F_{t1} were performed using a Wilcoxon signed-rank test. Equality of variances was assessed using Levene's test, and an False Discovery Rate (FDR) correction was applied to account for multiple volume comparisons. Episodic memory (EM) scores were analyzed using a two-way repeated measures ANOVA. The factors included Group effect (FD vs. NC), Item effect (3 scores: (i) identical, (ii) similar, and (iii) new items), and Training effect for FD (FD_{t0} vs. FD_{t1}). Between-group contrasts (FD vs. NC) and within-group contrasts (FD_{t0} vs. FD_{t1}) were assessed. Levene's test confirmed the equality of variances. However, Mauchly's test revealed a violation of sphericity; therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity where necessary.

3. Results

3.1 MRI Segmentation: HS Volumes at t_0 and t_1

No significant differences were observed between the left and right hippocampal volumes; therefore, the two hippocampi were pooled for each subject (FD_{t0} $p = 0.455$; FD_{t1} $p = 0.567$; NC $p = 0.250$). At the beginning of training (t_0), the FD and NC groups showed comparable hippocampal anatomy, regardless of the HS volume considered (NC ($M = 3.69$, $SD = 0.37$) $\approx$ FD_{t0} ($M = 3.67$, $SD = 0.31$), $p = 0.552$, $d = 0.12$). This was a crucial prerequisite for the study, ensuring the validity of the comparison of anatomical changes over the seven months of training.

At the end of the training season (t_1), no significant differences were observed either within the freediver group or between freedivers and controls, whether in specific HS regions or the whole hippocampus (FD_{t0} ($M = 3.67$, $SD = 0.31$) $\approx$ FD_{t1} ($M = 3.62$, $SD = 0.36$), $p = 0.691$, $d = 0.13$; NC ($M = 3.69$, $SD = 0.37$) $\approx$ FD_{t1} ($M = 3.62$, $SD = 0.36$), $p = 0.532$, $d = 0.12$). These results indicate that hippocampal volumes remained stable despite repeated voluntary exposure to hypoxia during training (Figs. 3,4).

In addition, there was no change in the variability whether examining specific HS volumes or the whole hippocampus before (t_0) and after (t_1) training (Fig. 4).

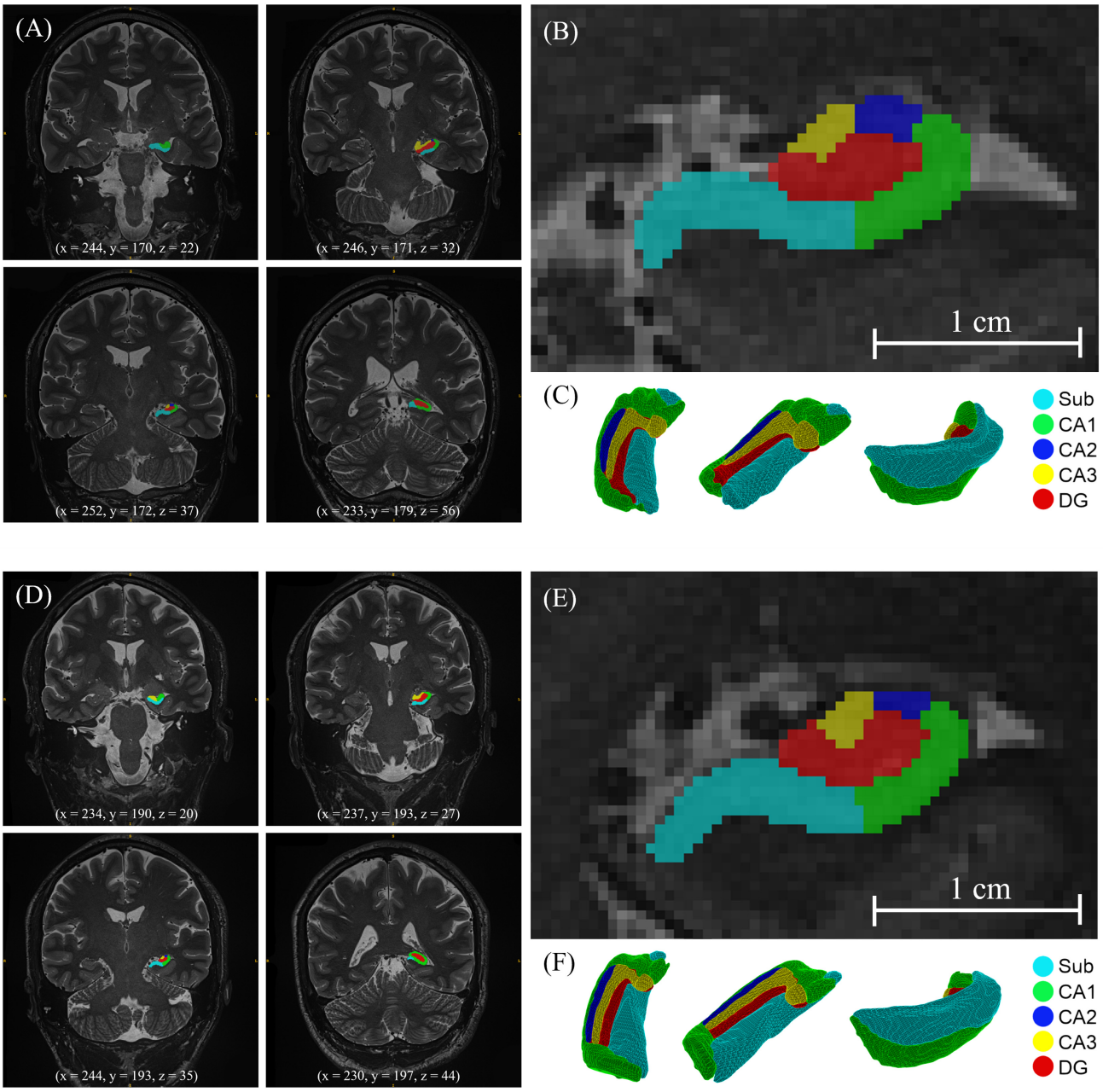


Fig. 3. Automatic HS segmentation of an NC (A–C) and FD (D–F) obtained with HSF©: dentate gyrus, CA1, CA2, CA3 regions and subiculum. (A,D) Coronal MRI slices at MNI coordinates (B,E) Zoom of a coronal MRI slice at MNI coordinates (x = 244, y = 193, z = 35) (C,F) 3D volume rendering. HS, hippocampal subfields; HSF©, Hippocampal Segmentation Factory; DG, dentate gyrus; CA, Cornu Ammonis; Sub, subiculum; MNI, Montreal Neurological Institute.

3.2 Episodic Memory: HippoPS Task

The Group effect was not significant before (t_0) or after training (t_1), indicating comparable scores between FD and NC ($p = 0.397$, $\eta^2 = 0.01$). The Item effect was significant ($p < 0.001$, $\eta^2 = 0.38$), regardless of the group or training ((i) identical items M = 71.79, SD = 22; (ii) similar items M = 48.92, SD = 19 and (iii) new items M = 74.22, SD = 25). No significant interactions were observed.

The Training effect was significant ($p = 0.002$, $\eta^2 = 0.11$), with PS memory scores for each item being significantly higher at t_1 (M = 71.24, SD = 21.73) than at t_0 (M = 62.90, SD = 24.19). Further analysis (post-hoc tests) revealed that, for both groups before and after training, memory scores were lower for (ii) similar items ($p < 0.001$), and higher for (i) identical items than (ii) similar items ($p < 0.001$) (Fig. 5).

4. Discussion

This study aimed to determine the impact of intermittent voluntary hypoxia through seven months of freediving

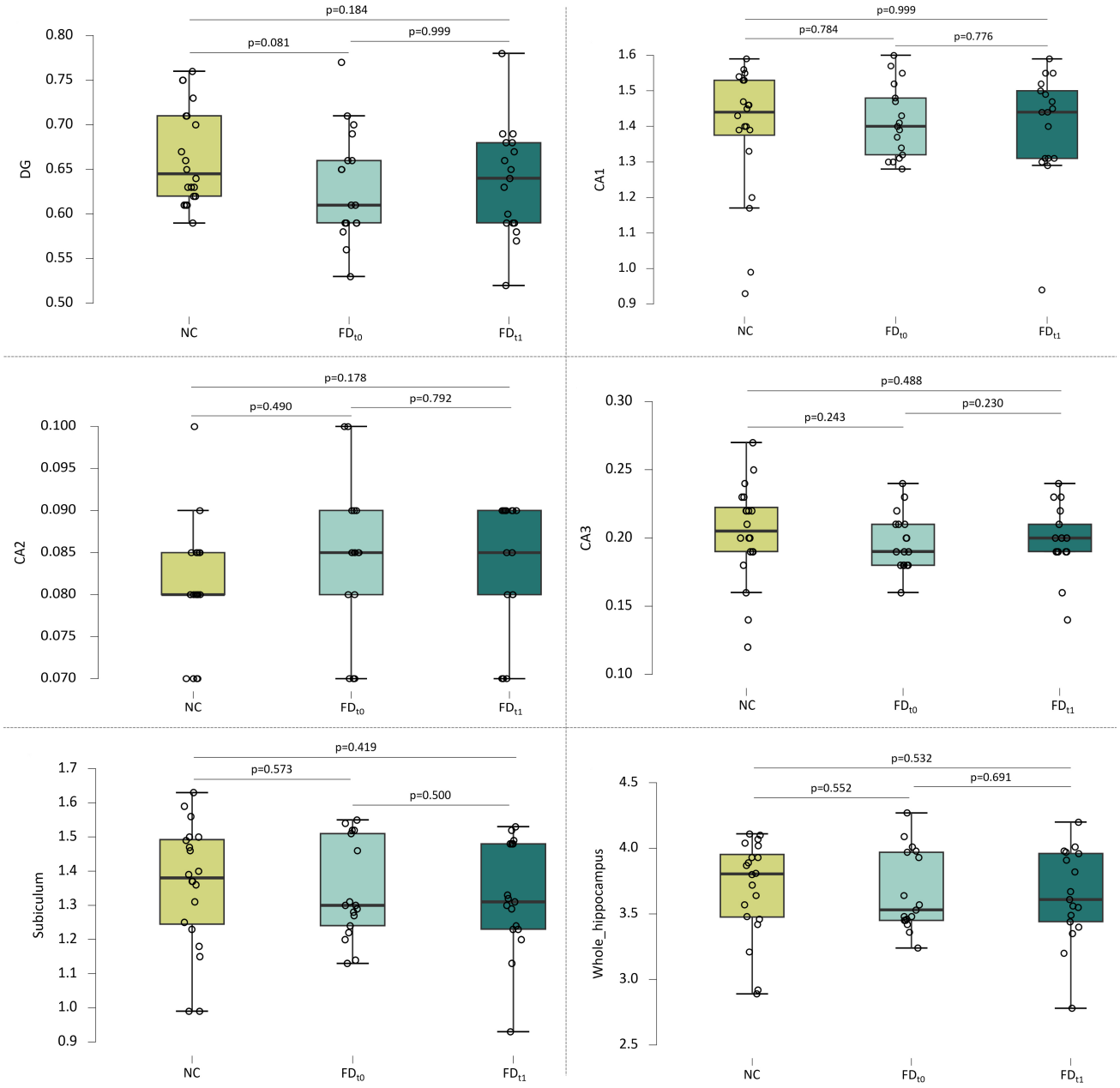


Fig. 4. HS volumes in cm^3 in the NC group before training and the FD group before and after training. *p*-values are the Mann-Whitney test and the Wilcoxon signed-rank test with FDR correction. Mean and standard deviation are indicated. FDR, False Discovery Rate.

training on HS volumes using MRI automatic segmentation by HSF© [27], and episodic memory scores using a sensitive ecological PS task [28].

Our results showed (1) no significant differences in HS volumes between freedivers and controls or between freedivers before and after training, regardless of the specific HS examined; (2) no significant differences in episodic memory performance between freedivers and controls, either before or after training. Both groups demonstrated similar performances in the PS task, with better accuracy for identical items compared to similar ones, and for new items compared to similar ones, showing improved performance at the second assessment. These findings suggest that male freedivers maintain hippocampal volume and function essential for episodic memory despite repeated voluntary exposure to hypoxia.

4.1 Hippocampal Stability in Response to Voluntary Hypoxia

Unlike studies reporting hippocampal atrophy in response to pathological or environmental hypoxia, such as COPD or high-altitude exposure [13,14,16,18,19], our results suggest that hippocampal anatomy remains stable in

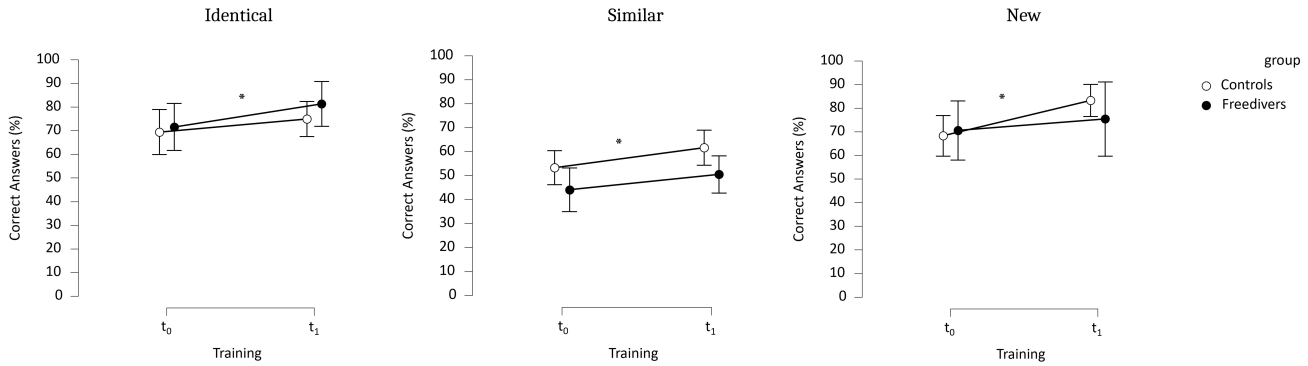


Fig. 5. Correct answers in % in the PS task before and after training, for items (i) identical, (ii) similar, (iii) new in both groups. *, significant differences between t_0 and t_1.

healthy individuals following repeated voluntary hypoxia during freediving training. This highlights the resilience of the hippocampus under controlled hypoxic conditions, warranting further confirmation in larger samples.

Previous studies on accidental hypoxia consistently highlight the vulnerability of the hippocampus to hypoxia, often leading to structural atrophy associated with memory impairments [15,17]. While many studies have focused on total hippocampal volumes or specific HS such as CA1 or the DG [4,33], few studies have systematically examined all HS using advanced segmentation methods. Recent improvements in segmentation techniques, such as HSF©, allow detailed analysis of HS, yet their application in hypoxia studies remains limited. By employing such methods, we ensured a comprehensive examination of CA1, CA2, CA3, DG, and subiculum. Despite their sensitivity to oxygen deprivation [13,19], no significant volume changes were detected across the freediving training period. This stability may reflect limitations in current segmentation approaches, which typically analyze the hippocampal head, body, and tail as separate regions. Further studies should consider more detailed analyses along the anterior-posterior axis or employ a gradient-based approach to better capture subtle adaptations. Furthermore, functional or microstructural changes may precede detectable volumetric changes, necessitating advanced imaging techniques for identification.

4.2 Episodic Memory Maintenance in Response to Voluntary Hypoxia

Our study also enhances the understanding of episodic memory performance under hypoxic conditions, particularly regarding PS, a process critical for distinguishing overlapping memories. The PS task assessed the hippocampus's ability to encode unique representations for each event and tested memory consolidation by evaluating participants' ability to distinguish between identical, similar, and new items after a 15-minute delay. Additionally, the task included associative learning components, linking actions to specific locations, and temporal contexts. Designed with ecologically valid stimuli, this task offers greater relevance to real-life memory functions compared to abstract or artificial cognitive assessments [28,34].

We observed no significant differences in memory performance between freedivers and controls, either before or after training. However, both groups improved their PS performance post-training, consistent with the established cognitive benefits of regular physical exercise [23]. In addition, regardless of training, both groups were less adept at identifying similar items and better at recognizing identical ones. This is understandable, as distinguishing between similar items is a more complex task than recognizing a previously seen item. Thus, freedivers and controls adopt the same approach to the task. These findings contrast with studies reporting hypoxia-induced memory deficits in clinical populations, such as those with OSA [16] or COPD [14], where PS impairments were linked to hippocampal damage. Unlike these pathological conditions, freedivers who are exposed to controlled, intermittent hypoxia, preserved their memory performance. This aligns with prior studies highlighting the neuroprotective effects of physical exercise and moderate hypoxia [22,26].

Our results are consistent with the literature on episodic memory in freedivers, involving similar cohorts in terms of the number of participants, freediving experience, age, and years of education. These studies have reported no memory deficits following hypoxemia exposure in freedivers. For instance, research using a 4-item memory task after at least 12 hours without freediving found that all divers performed within one standard deviation of published norms, suggesting no significant impairment despite years of hypoxemia exposure [21]. More recent work investigating PS performance using the Mnemonic Similarity Task (MST) found no decline in memory performance when participants completed the task 20 minutes before and 10 minutes after a freediving session [20], and testing divers 30 minutes post-exercise also reported no significant differences between freedivers and controls [35]. It is important to note that while these studies focused on acute effects, based on data collected during and immediately after performance, our study is the first to provide longitudinal data

on hippocampal volume and episodic memory in the context of repeated voluntary hypoxia, allowing us to isolate the effects of freediving training on hippocampal adaptability and cognitive function.

4.3 Potential Mechanisms of Hippocampal Adaptability in Response to Voluntary Hypoxia

Hippocampal plasticity is modulated by various factors, suggesting an adaptive mechanism that responds to environmental changes. Physical exercise, an intrinsic component of freediving training, plays a crucial role in hippocampal adaptability and episodic memory, promoting neurogenesis through different mechanisms [36–38]. The combination of hypoxia and physical exercise, as seen in freediving, may offer unique benefits for episodic memory, that exceed those of either factor alone. Moderate hypoxia during physical exercise has been shown to enhance episodic memory through mechanisms such as increased synaptic plasticity and neurotransmitter modulation [24]. However, the extent of hypoxia is critical; while moderate levels improve memory and neuroplasticity, severe hypoxia may impair cognitive functions [25]. The neuroadaptive benefits of freediving, who experience controlled and intermittent hypoxia, likely result from the interplay of these factors, optimizing hippocampal function while avoiding the detrimental effects associated with pathological or accidental hypoxia [39,40].

While the frequency and duration of apnea episodes in freedivers may resemble those observed in pathological conditions, some variations exist. Both freediving and involuntary hypoxia (e.g., OSA or COPD) expose the brain to repeated oxygen deprivation, a known risk factor for hippocampal atrophy and memory deficits [13,15]. However, the main distinction in our study lies in the voluntary nature of hypoxia during freediving, combined with regular physical exercise. This controlled exposure, paired with the physiological benefits of exercise, may explain the absence of detectable hippocampal damage or cognitive impairments in freedivers.

4.4 Implications for Future Research

A recent animal study [41] suggests that controlled, moderate exposure to intermittent hypoxia can yield significant neuroprotective effects, including enhanced hippocampal angiogenesis and neurogenesis, as well as reduced brain lesion size in neonatal mice, highlighting its potential to mitigate cognitive impairments and brain injuries. Thus, carefully calibrated intermittent hypoxia could be explored as a therapeutic strategy for conditions like hypoxic-ischemic encephalopathy or other neurological disorders, opening new avenues for translational research in human medicine.

While our findings provide valuable insights, several limitations must be acknowledged. Although the HSF© software proves highly effective, outperforming other known automatic segmentation models to date (HSF's dice coefficient compared to ASHS ($p < 0.001$; hedge's g = 1.64), HIPS ($p < 0.001$; hedge's g = 4.93), and HippUnfold ($p < 0.001$; hedge's g = 5.44)) [27], the MRI method and acquisition itself may lack the sensitivity needed to detect subtle changes in HS after seven months. Functional adaptations (e.g., changes in functional connectivity) might occur without being reflected in visible volumetric changes. Additionally, the stability of hippocampal volumes could reflect preserved structural homeostasis facilitated by the previously mentioned adaptations. Future studies should incorporate complementary measures such as functional connectivity (rs-fMRI), metabolic assessments (MRI spectroscopy), and cerebrovascular measurements (MRI ASL), to further explore the neurobiological mechanisms underlying adaptations to voluntary hypoxia. Another limitation is that all participants were recruited from the Île-de-France region, which may limit the generalizability of our findings to freedivers from other regions with different training regimens, and lifestyles. Additionally, including female participants in future studies could help identify potential sex differences in adaptation mechanisms and hippocampal function.

Our findings strongly suggest that hippocampal function and memory performance remain intact in recreational freedivers following repeated hypoxic exposure, ensuring that freediving, as an increasingly popular sport, does not negatively impact the hippocampus, a brain region particularly sensitive to oxygen deprivation. This raises the intriguing possibility of exploring voluntary, controlled intermittent hypoxia as a non-invasive therapeutic intervention. Whether combined with physical exercise or implemented through other protocols, moderate intermittent hypoxia holds promise as a potential strategy for enhancing neuroplasticity and cognitive resilience.

5. Conclusions

HS volumes and memory performance remained comparable between freedivers and controls before and after the seven-month training period. These findings suggest that repeated voluntary hypoxic training, as experienced in freediving, does not induce detectable hippocampal damage or memory deficits in recreational athletes. They highlight the potential neuroprotective effects of regular physical exercise, even under hypoxic conditions, and position freediving as a valuable natural model for investigating the impact of intermittent hypoxia on cognitive function. Moreover, this study provides insights into potential therapeutic applications for neurological conditions involving hippocampal dysfunction, such as stroke, perinatal hypoxia, and transient global amnesia. Future research should explore potential functional and metabolic adaptations to further elucidate the neurobiological mechanisms underlying these findings.

Abbreviations

DG, dentate gyrus; FD, freedivers; HS, hippocampal subfields; NC, controls; PS, pattern separation.

Availability of Data and Materials

The datasets referenced in this article are not publicly available, as participants consented to their data being used solely under the supervision of the principal investigator. Requests to access the datasets should be directed to MN.

Author Contributions

MN developed the research questions and the design of experiment (PI). The HSF software was developed by CP and MN. The HippoPS task was developed by JZ and MN. FM, FB and MN designed the MRI sequences. CC made substantial contributions to the acquisition of data as the medical investigator and was responsible for overseeing the project's ethical compliance. Recruitment and data collection were conducted by JM, AEH, MT and MN. Data analyses and results interpretation were led by JM under the supervision of MN. JM and MN drafted the manuscript, ATH contributed to statistical analysis and edited the English language. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and the research protocol is adhering to ethical guidelines for research involving humans and was approved by the Ethics Committee (Committee for the Protection of Persons Ile de France II, Ethic Approval Number: 2022-A01030-43). All participants provided signed informed consent.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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Conclusion

Over a seven-month freediving season, hippocampal subfield volumes remained stable in freedivers, with no significant changes relative to controls. Performance on the pattern separation task was also preserved, with both groups showing the expected pattern of higher accuracy for identical and novel items than for similar lures, and no evidence of decline.

These findings are in sharp contrast with the anatomical atrophy and cognitive deficits consistently reported in models of involuntary hypoxia. They suggest that voluntary, intermittent hypoxia, when combined with regular exercise training, does not compromise hippocampal integrity and instead promotes hippocampal resilience.

In the context of this thesis, these results indicate that any functional reorganization observed in the following chapter is unlikely to reflect compensatory responses to anatomical damage, but rather adaptive network changes occurring on a preserved anatomical and cognitive background. The next section will examine resting-state functional connectivity to identify potential neural signatures of this preserved performance under voluntary hypoxic stress. Because hippocampal volumes and episodic memory scores remained stable over time, no direct correlation analysis was conducted at this stage.

3. Functional connectivity and episodic memory

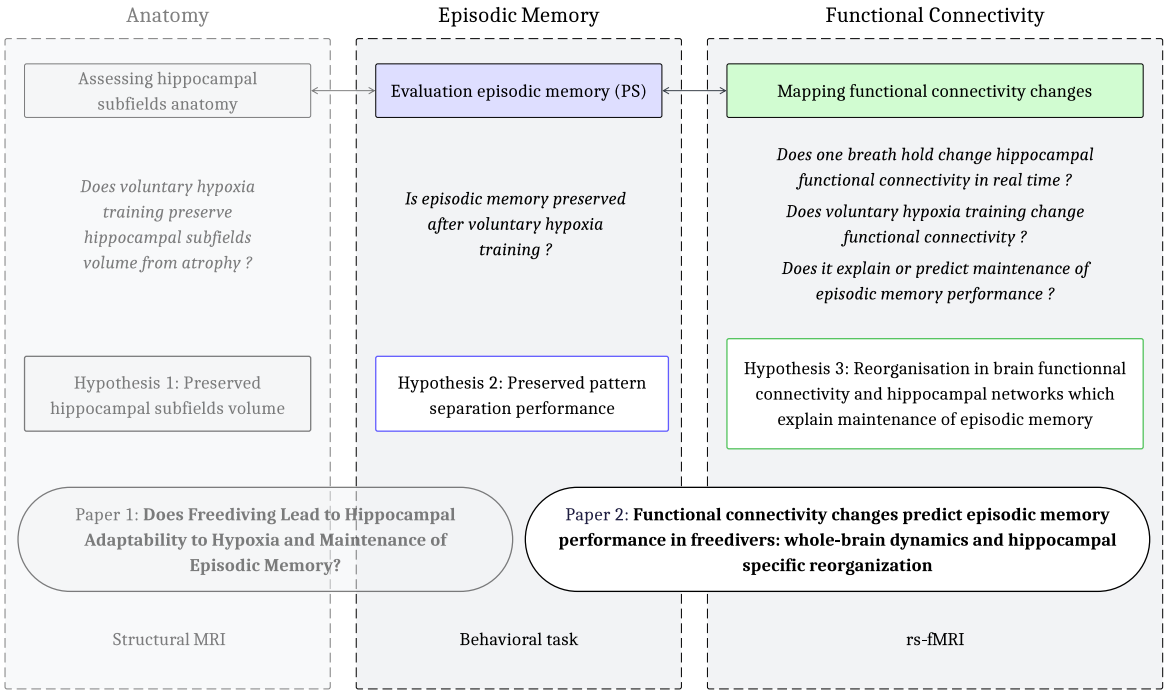


Figure 15: Architecture of the Ph.D. dissertation: episodic memory performance and brain functional reorganization at rest. PS: Pattern Separation.

Functional connectivity changes predict episodic memory performance in freedivers: whole-brain dynamics and hippocampal specific reorganization

Micaux, J., Habibi, A. T., Mauconduit, F., Noulhiane, M. *In Submission for Human Brain Mapping.*

The previous chapter of this thesis demonstrated that seven months of freediving training did not lead to hippocampal volume loss or episodic memory decline. These results established that voluntary hypoxia, under controlled and intermittent conditions, does not induce the anatomical and cognitive deterioration typically associated with involuntary hypoxia.
Nevertheless, the absence of anatomical change doesn't necessarily imply the absence of neural adaptation. Here, functional neuroimaging can detect network-level plasticity that is invisible to anatomical measures: rs-fMRI provides a non-invasive approach to investigate how the hippocampus reorganizes its connectivity profile in response to environmental challenges. Functional connectivity patterns reflect the coordinated activity between brain regions and can be shaped by metabolic stress, but also training and cognitive engagement (Bakker *et al.*, 2023; Neubauer and Fink, 2009; Raichlen *et al.*, 2016).
In involuntary hypoxia, functional connectivity across large-scale networks is disrupted (Bakker *et al.*, 2023; Chen *et al.*, 2018). In contrast, athletes typically show connectivity patterns consistent with more efficient and targeted neural resource allocation (Heller-Wight

et al., 2023; Ko *et al.*, 2023; Wang and Lu, 2022). Voluntary hypoxia during freediving combines features of both contexts, yet its functional effects on hippocampal networks remain unknown.

Investigating hippocampal functional connectivity in this context is crucial for two reasons: first, it enables us to determine whether preserved anatomy and memory function are supported by stable or reorganized functional networks; second, it provides insight into the neural strategies that may sustain cognitive performance under metabolic constraint.

The present study examined hippocampal functional connectivity in freedivers before and after a seven-month training season, and compared with controls (Figure 15). Using ROI-to-ROI and seed-based rs-fMRI analysis, we assessed whole-brain connectivity patterns from the hippocampus and related changes to episodic memory performance. We hypothesized that freedivers would show selective reorganization of hippocampal connectivity, associated with preserved memory performance.

By integrating functional connectivity analysis into the framework established in the previous chapter, this work extends our understanding from anatomical and cognitive stability to the dynamic network processes that may support resilience under voluntary hypoxia. Together, these findings contribute to the central objective of this thesis: identifying the neural adaptations that distinguish voluntary, intermittent hypoxia from its pathological counterparts.

Original research

Functional connectivity changes predict episodic memory performance in freedivers: whole-brain dynamics and hippocampal specific reorganization

Julia Micaux[1,2], Abir Troudi Habibi[1,2], Franck Mauconduit[3], Catherine Chiron[1,2], Marion Noulhiane[1,2*]

[1]Université Paris-Saclay, CEA, Joliot Institute, NeuroSpin, UNIACT, Gif-sur-Yvette, France
[2]Université Paris Cité, Inserm, U1141 NeuroDiderot, InDev team, Paris, France
[3]CEA, NeuroSpin, CNRS, Université Paris-Saclay, Gif-sur-Yvette, France
*Corresponding Author: marion.noulhiane@cea.fr

Abstract: Accidental hypoxia has detrimental effects on the brain, particularly on the hippocampus, which is highly sensitive to oxygen deprivation. Most resting-state functional MRI (rs-fMRI) studies on accidental hypoxia report altered brain connectivity, including changes in hippocampal resting-state functional connectivity (rs-FC). However, freedivers (FD), who regularly experience voluntary hypoxia, do not appear to exhibit such deficits. Our previous work also found no anatomical changes in the hippocampus or impairments in episodic memory, a key hippocampal function, in this population. This raises the question: does voluntary intermittent hypoxia in freediving training lead to changes in brain connectivity, particularly hippocampal rs-FC? If so, could these changes explain the preservation of episodic memory? This study investigated whole-brain and hippocampal rs-FC in a cohort of FD during apnea and rest, before (t_0) and after (t_1) a 7-month uniform freediving training program, and compared them to aerobic-trained controls (NC). Using CONN Toolbox, we analyzed (1) whole-brain ROI-to-ROI rs-FC; (2) seed-to-voxel rs-FC from the bilateral hippocampus and additional selected ROIs (frontal pole, frontoparietal region, occipital pole, and Default Mode Network -DMN-); and (3) hippocampal rs-FC and episodic memory scores correlations. Main results showed: (1) Whole-brain FC analyses revealed a reorganization involving salience, frontoparietal, sensorimotor and cerebellar networks at rest after training. (2) Seed to voxel analysis revealed hypoconnectivity between the hippocampus and both the DMN and sensorimotor networks, alongside hyperconnectivity in cerebellar and visual regions after training. Interestingly, the other ROIs exhibited the opposite pattern, i.e., decreased connectivity with the cerebellum. (3) Hippocampal rs-FC correlated with episodic memory scores after training, providing evidence for a link between adaptive plasticity and preserved cognitive function. These findings suggest that repeated voluntary hypoxia during freediving training induces specific patterns of rs-FC reorganization, especially within the hippocampus, supporting brain resilience and episodic memory preservation despite intermittent oxygen deprivation. This unique model in healthy individuals may offer valuable insights for developing therapeutic strategies for neurological conditions involving hippocampal damage.

Keywords: Freediving · Hypoxia · Brain Plasticity · Hippocampus · rs-fMRI · Episodic Memory

Key points

- Voluntary intermittent hypoxia in FD leads to specific hippocampal FC reorganization, with reduced coupling to both sensorimotor and DMN networks and increased connectivity with the cerebellum, this effect becomes more pronounced after freediving training.
- Freediving training also drives large-scale FC changes across sensorimotor, salience, attention networks, frontoparietal and visual regions, reflecting adaptive redistribution of neural resources under hypoxia.
- Post-training hippocampal FC predicts episodic memory performance, suggesting a compensatory mechanism that supports memory preservation despite repeated oxygen deprivation.

INTRODUCTION

The hippocampus plays a central role in episodic memory by supporting the encoding, storage, and retrieval of experiences in specific spatial and temporal context. A key process that supports this function is pattern separation, which allows the distinction between similar but distinct events, relying on the dentate gyrus and CA3 region (Castillon et al., 2018). This mechanism prevents interference between overlapping memory traces and is essential for accurate episodic recall. Since the HM case (Scoville and Milner, 1957), it has been widely recognized that many pathologies affecting the hippocampus are known to generate episodic memory disorders, and among the latter are pathologies linked to hypoxia.

Involuntary hypoxia, a reduction in oxygen availability caused by pathological or environmental conditions, represents a significant clinical challenge, and can lead to widespread disruptions in brain function. Among brain regions, the hippocampus is especially vulnerable to hypoxia due to its high metabolic demand and complex vascularization (Spallazzi et al., 2019), making it one of the first structures affected by oxygen deprivation in multiple clinical contexts (Lu et al., 2025; McKeown et al., 2025). This results in memory deficits, as shown for instance by Olaithe et al. (2018) in sleep apnea and by Zhang et al. (2022) in high-altitude residents. These changes are associated with macroanatomical alterations, primarily hippocampal atrophy (Li and Fei, 2013; Olaithe et al., 2018; Pfister et al., 2023), as well as microanatomical alterations such as reduced neurogenesis and neuronal necrosis, decreased synaptic plasticity and dendritic spine density, impaired cerebral perfusion, and increased oxidative stress (Khuu et al., 2019; Lu et al., 2025), whose extent strongly depends on the type and severity of hypoxia. A

better understanding of functional reorganization after accidental hypoxia is therefore a relevant avenue.

rs-FC is recognized as a key marker of neurophysiological adaptations to various environmental challenges. It provides a non-invasive method to study how brain networks reorganize in response to specific physiological conditions, making FC analysis relevant for assessing the brain's response to hypoxia. Looking at rs-fMRI data, involuntary hypoxia is consistently associated with a decrease in FC and disorganization of large-scale networks (Bakker et al., 2023). It is especially evident in the hippocampus, which shows functional vulnerability to both acute and chronic exposure to hypoxia, impairing episodic memory performance (Micaux et al., 2025b; Song et al., 2018). However, these damage are often accompanied by many other cognitive impairments, particularly in learning and memory, attention, processing speed, and executive control (McKeown et al., 2025; Wang et al., 2022). This results in alterations in networks such as the default mode network (DMN), sensorimotor, frontoparietal (FPN) and attention networks (DAN / VAN), as well as visual and auditory circuits (Chang et al., 2020; Liu et al., 2022; Wang et al., 2023). However, the effects of voluntary hypoxia, as seen in freediving, remain largely unclear.

FD, who experience voluntary intermittent hypoxia during training, do not seem to have the same cognitive impairments after prolonged apneas (Allinger et al., 2024; Ridgway and McFarland, 2006). This sport therefore provide a unique model to investigate the impact of hypoxia on episodic memory and hippocampal FC under controlled conditions, highlighting potentially distinct adaptive mechanisms (Micaux et al., 2025)
Interestingly, freediving combines hypoxia exposure with exercise training. Studies on athletes with a regular endurance training have shown different FC patterns, suggesting a more specialized and efficient brain organization depending on the type of sport. W. Li et al. (2023) reported reduced motor cortex FC in individuals with higher fitness compared to those with lower fitness, while Raichlen et al. (2016) observed increased FC between the FPN and frontal cortex in runners, along with decreased FC between the DMN and sensorimotor, and the occipital cortex. Remarkably, even light physical activity appears to promote functional plasticity specifically in the hippocampus (Heller-Wight et al., 2023), and enhances hippocampal memory function (Suwabe et al., 2018). These reorganizations may reflect increased automaticity and reduced cognitive load in task execution, and could promote brain functional specialization.

In FD, a study by Annen et al. (2021) suggest a similar pattern of adaptation. Increased FC was observed during apnea in subcortical regions (bilateral thalamus, caudate, right amygdala) and in cortical territories involving the DMN and executive control networks. In parallel, decreased FC was mainly found in sensorimotor regions but also in temporal, parietal, insular and occipital cortices.

The observed connectivity shifts may reflect an optimization of brain function to tolerate controlled hypoxia more effectively, as seen in exercise training.

Freediving may therefore induce a complex pattern of brain adaptation and FC changes, combining beneficial reorganization associated with training and specific compensatory mechanisms to cope with hypoxia. This idea is supported by our previous work where we found that FD did not show any difference in hippocampal volume with the NC group, and their pattern separation scores were comparable (Micaux et al., 2025). Allinger et al. (2024), found similar results and demonstrated that elite divers maintain intact episodic memory despite repeated hypoxic challenges. Notably, however, no study has specifically examined hippocampal FC, leaving a major gap in understanding its role in freediving adaptations, despite its known sensitivity to hypoxia and modulation by exercise training.
This study investigated whole-brain and hippocampal rs-FC in a group of 17 male FD during apnea and rest, and before (t_0) and after (t_1) a 7-month uniform freediving training, compared to a group of 20 athletes practicing aerobic sports. We expected that: (1) Whole-brain ROI-to-ROI FC changes observed in the freediving group would reflect a specific adaptive response to hypoxia, suggesting that freediving training could transform a hypoxic stressor into a beneficial modulatory process and lead to functional plasticity and resource redistribution. (2) Seed-to-voxel hippocampal FC would be reinforced, to sustain memory function. (3) This FC reorganization may explain the preservation of episodic memory performance observed in our cohort. Additionally, FC patterns might predict inter-individual variability in memory performance, even within a population exhibiting normal cognitive function.

MATERIAL AND METHODS

1. Participants

Data acquisition was performed under the regulations of an appropriate Ethical Committee board (CPP 2022-A01030-43), and written informed consent was obtained from each participant. Forty-seven men participated to this study, including 17 FD matched to 20 NC aged from 27-55 years old and recruited between 2022 and 2024 in the pools of Ile de France region (Paris, Yvelines, Hauts de Seine, FRANCE). NC performed one rs-fMRI acquisition and FD performed 2 rs-fMRI before and after 7 months of regular uniform freediving training.

The FD group consisted of experienced recreational FD, all affiliated with a freediving club to ensure consistent, structured training. They followed an intense, regular, and uniform 7-month freediving training (Micaux et al., 2025), with data collected at the start (FD_{t0}) and end (FD_{t1}) of the training period. NC were age- and sex-matched individuals with comparable socio-cultural backgrounds (Table 1). Although not engaged in freediving, they maintained a similar weekly exercise

training load (~5 hours per week) through aerobic sports. NC had an MRI at t_0 and completed the memory task at both t_0 and t_1.

Table 1: Demographic data (FD and NC)

Characteristics	Freedivers (FD)	Controls (C)
n	17	20
sex	H	H
age*	47.9 ± 4.8	44.8 ± 9
years of study*	16.9 ± 1.7	16.5 ± 2.4
Training load	~ 5 h/week (aerobic & anaerobic)	~ 5h/week (aerobic)

* Data are means ± standard deviation.

2. Episodic memory

Episodic memory was assessed using the HippoPS task (Micaux et al., 2025; Zhao & Noulhiane, In Prep), an ecological and validated tool specifically designed to study PS. The task includes two phases: encoding and recognition (after a 15-minute delay). During encoding, participants watch videos showing 28 pictures of a location associated with a gesture. During recognition, they categorize each photo as: i. 'identical' (same gesture and location), ii. 'similar' (same gesture or same location), or iii. 'new' (different gesture and location). These scores were correlated to hippocampal FC (Figure 1). Global intelligence was also assessed, revealing no cognitive deficits in either group (NC or FD), with comparable scores between cohorts (Micaux et al., 2025).

3. Rs-fMRI acquisitions

Cerebral MRI was performed at 3T (Magnetom Prisma, Siemens Healthineers) including acquisition of T1 and T2-weighted images of the hippocampus (Figure 1). T2-weighted parameters were TR=9600ms, TE=83ms, FOV 192mm, 0.5 x 0.5 x 1mm resolution, 60 slices, Time=6.46'. Functional MRI was acquired using a multiband EPI sequence (MB factor = 2): TR = 2500 ms, TE = 26 ms, flip angle = 71°, voxel size = 1.7 × 1.7 × 1.8 mm^3, 68 slices, 80 volumes, FOV = 192 mm, scan time = 3.20'. Two spin-echo EPI acquisitions with opposite phase-encoding directions (PA and AP) were acquired for distortion correction: TR = 3510 ms, TE = 55.4 ms, voxel size = 1.7 × 1.7 × 1.8 mm^3, 68 slices, MB factor = 2. The BOLD sequence included 20 blocs time points (10 baseline, 10 active), with high-pass temporal filtering and a paradigm length of 3 time points.

We acquired 4 resting-state fMRI runs, each lasting 3 minutes and 30 seconds. During each run, participants underwent a 2-minute apnea period followed by 1 minute and 30 seconds of regular breathing. A 1-minute rest period was included between runs. Throughout each run, participants watched a movie adapted from (Vanderwal et al., 2015), which included on-screen instructions for the apnea task. Each movie began with a countdown displaying the message "Apnea in 10s" down

to “Apnea” at 0. After 2 minutes, the message “End of apnea” was displayed. A different movie was shown for each run.

4. Rs-fMRI preprocessing

Rs-fMRI data was preprocessed using the default preprocessing pipeline of the CONN Toolbox (version 20.b) (Figure 1). Functional volumes were first realigned and unwrapped to correct for subject motion and geometric distortions. Outlier scans were identified using the ART toolbox, based on both framewise displacement thresholds (0.9 mm) and global signal Z-value thresholding (95th percentile), with additional detection of volumes falling outside the MNI space. Functional and anatomical images were segmented and normalized to MNI space. A spatial smoothing step was applied using an 8 mm FWHM Gaussian kernel to reduce anatomical variability and enhance signal-to-noise ratio. During denoising, temporal pass-band filtering (0.008–0.09 Hz) was performed to retain low-frequency resting-state fluctuations, and physiological noise was removed using aCompCor by regressing out confounding signals from white matter, CSF, and motion parameters. Visual inspection and quality control were conducted at each stage of preprocessing.

5. Statistical analysis

All statistical analyses were performed using CONN Toolbox on MATLAB, with a significance threshold set at 0.05 (Figure 1). For FD, each of the four rs-fMRI runs was split into two separate runs (apnea and rest) based on each participant’s individual apnea duration (if they stopped before the 2min instruction). We analyzed FC of the hippocampus, and four other regions of interest (ROIs) were selected based on the networks most affected by hypoxia according to the literature: the frontal pole, the frontoparietal pole and the default mode network (DMN). The occipital pole was added as a control region, since participants were watching a movie during voluntary apnea. We first computed whole-brain ROI-to ROI FC to assess global brain connectivity patterns, followed by seed-to-voxel analyses to evaluate the connectivity between each chosen ROI and all other voxels in the brain. We used the Harvard-Oxford atlas, covering the entire brain, and computed connectivity matrices and seed-to-voxel connectivity maps for each hemisphere. After performing the standard second-level analysis separately for each condition and group, we used CONN’s second-level covariates tool to conduct direct comparisons between conditions. The contrasts we chose enabled the extraction of difference maps and corresponding connectivity matrices that captured condition-specific changes. The following comparisons were conducted: (1) $FDt_{0apnea} > FDt_{0rest}$, (2) $FDt_{1apnea} > FDt_{1rest}$, (3) $FDt_{0apnea} > FDt_{1apnea}$, (4) $FDt_{0rest} > FDt_{1rest}$, and (5) all of the above conditions were also compared with the NC group ($FDt_{0apnea} > NC$, $FDt_{1apnea} > NC$, $FDt_{0rest} > NC$, and $FDt_{1rest} > NC$).

Using CONN Toolbox, we also performed correlations between FC of the left and right hippocampus and episodic memory scores obtained in our previous study (Micaux et al., 2025), using a pattern separation task involving three item types: i.

identical, ii. similar, and iii. new. Each score was correlated with the hippocampal FC of both the NC group and the FD group, during apnea and rest, before and after training.
For all analysis, FDR correction was applied.

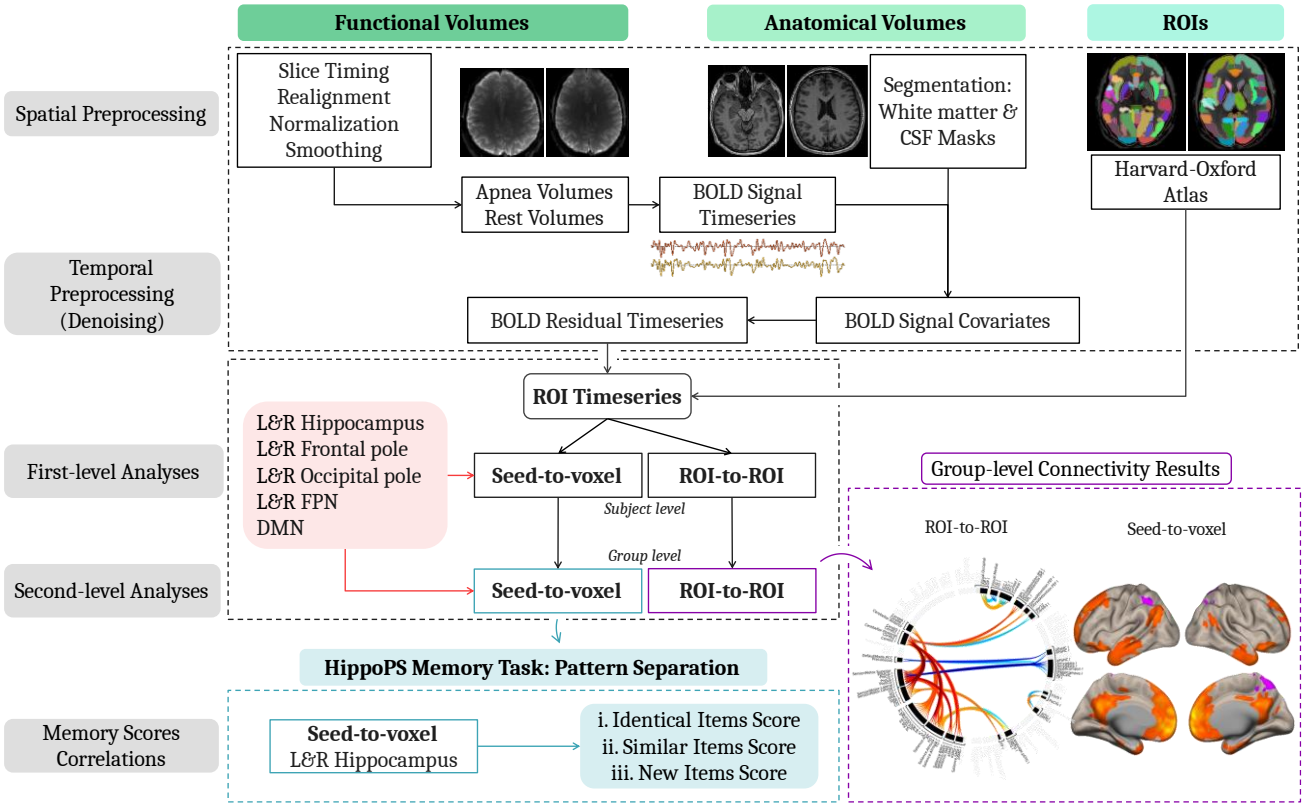


Figure 1: Schematic representation of acquisitions, preprocessing pipeline and analysis using CONN toolbox on MATLAB. L&R: Left and right.

RESULTS

1. Rs-fMRI functional connectivity: ROI-to-ROI whole brain analysis

Whole-brain ROI-to-ROI analysis revealed several significant differences in FC between the NC and FD conditions, during both apnea and rest (only significant results are presented) (Figure 2).

During apnea

a. Before training season (FDt_{0apnea} > NC), hyperconnectivity was found between the cerebellum and the sensorimotor network (notably the supplementary motor area -SMA-), the dorsal attention network, and the salience network. In contrast, hypoconnectivity was found between the hippocampal network and both the default mode network (DMN) and the sensorimotor network.
b. At the end of the training season (FDt_{1apnea} > NC), hyperconnectivity was found between the salience network and the sensorimotor/dorsal attention networks, as well as between the hippocampus and the cerebellum, and between the sensorimotor network and subcortical structures (thalamus, caudate, putamen). In

parallel, hypoconnectivity was found between the hippocampal and sensorimotor networks.

During rest

c. Before training season (FDt_{0rest} > NC), hyperconnectivity was found between the caudate and the sensorimotor network, the caudate and the SMA, the caudate and the superior temporal gyrus (STG), and between the visual network and both the middle temporal gyrus (MTG) and the frontoparietal networks. In contrast, marked hypoconnectivity was found between the cerebellum and several networks, including the frontoparietal network (FPN), visual network, salience network, and language network, as well as specific regions such as the right angular gyrus, thalamus, caudate, and insular cortex (ICC).

d. After training season (FDt_{1rest} > NC), hyperconnectivity was found between the sensorimotor network and the putamen/salience network, between the cerebellum and the right angular gyrus, and between the cerebellum and the salience network. In contrast, hypoconnectivity was found between the cerebellum and both the frontoparietal and salience networks.

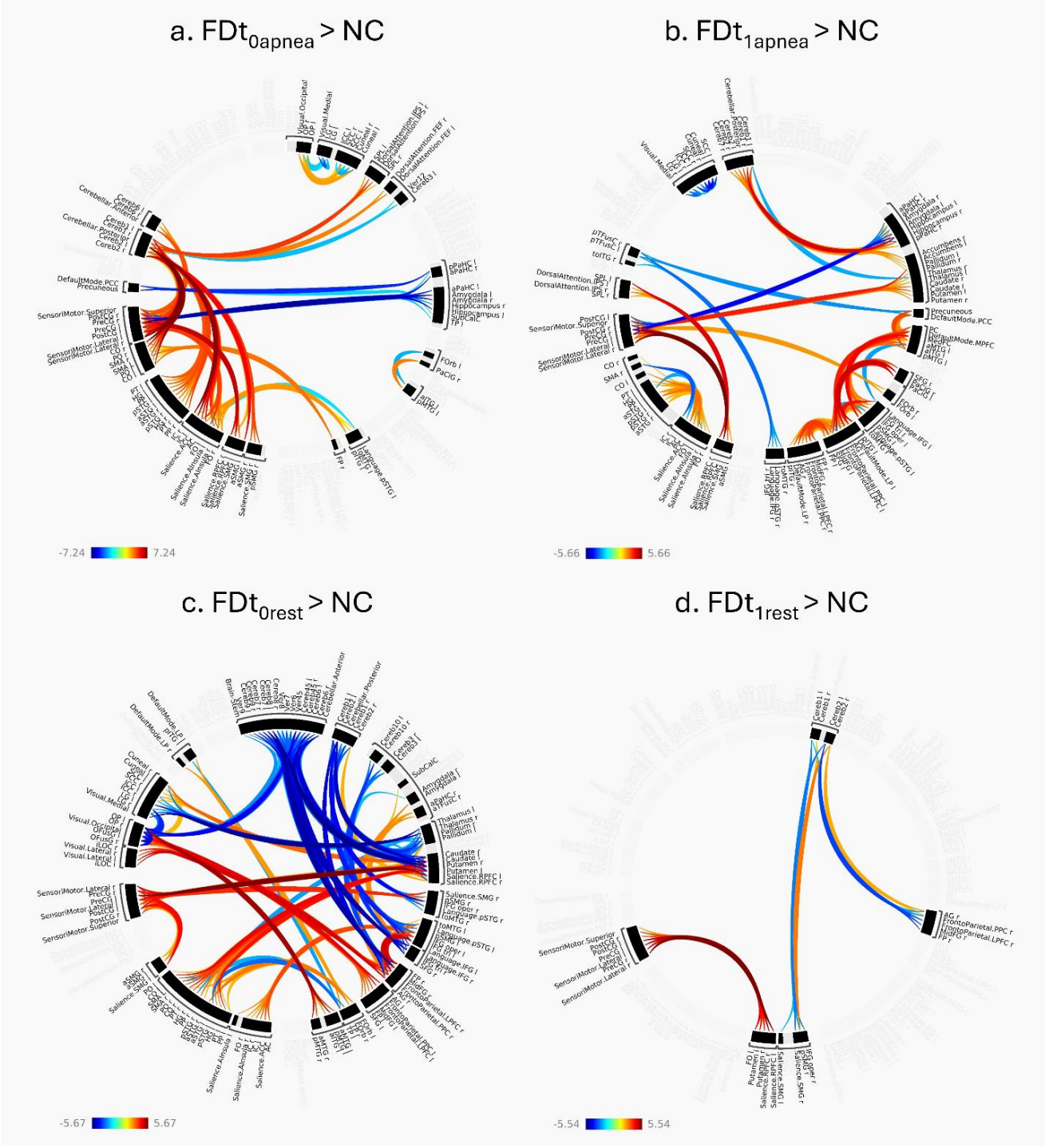


Figure 2: *FC matrices showing differences in whole brain hypoconnectivity and hyperconnectivity comparing different conditions (NC versus FD during apnea and rest, before and after training): ROI-to-ROI analysis using CONN toolbox on MATLAB. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. N= 17 FD and 20 NC. FDR correction applied. FD: Freedivers, NC: Controls.*

Before training: apnea vs. rest

We found significant FC differences between apnea and rest before training (FDt_{0apnea} > FDt_{0rest}), including hyperconnectivity between the cerebellum and both

the salience and sensorimotor networks. Conversely, hypoconnectivity was found between the visual cortex and the frontoparietal network (FPN)/MTG (Figure S1).

2. Rs-fMRI functional connectivity: Seed-to-Voxel

Only significant results are presented, and p-values are available in Table S1 and S2.

2.1 HIPPOCAMPUS (Figure 3)

Left Hippocampus

During apnea

a. Before training (FDt_{0apnea} > NC), hypoconnectivity was found between the left hippocampus and bilateral precentral and postcentral gyri, bilateral supplementary motor area (SMA), right superior parietal lobule (SPL), and left paracingulate gyrus.

b. After training (FDt_{1apnea} > NC), hypoconnectivity was found between bilateral precentral and postcentral gyri, and bilateral SMA. Hyperconnectivity was noted with bilateral cerebellum, right temporal occipital fusiform cortex, and right temporal fusiform cortex.

During rest

c. Before training (FDt_{0rest} > NC), hypoconnectivity was found with bilateral temporal pole, right middle temporal gyrus, and frontal medial cortex. Hyperconnectivity was limited to the left cerebellum.

d. After training (FDt_{1rest} > NC), hypoconnectivity was found between the frontal medial cortex, left precentral gyrus, bilateral postcentral gyri, bilateral SPL, bilateral superior temporal gyri, bilateral planum polare, right central opercular cortex, and precuneus cortex. Increased FC was found with bilateral cerebellum.

Right Hippocampus

During apnea

a. Before training (FDt_{0apnea} > NC), no hypoconnectivity was found. Hyperconnectivity was found exclusively with the right cerebellum.

b. After training (FDt_{1apnea} > NC), hypoconnectivity was found with the left precentral gyrus. Hyperconnectivity was found with bilateral cerebellum.

During rest

c. Before training (FDt_{0rest} > NC), no significant differences in FC were found.

d. After training (FDt_{1rest} > NC), hypoconnectivity was found with left precentral and postcentral gyri, right planum temporale, right planum polare, and right central opercular cortex. Hyperconnectivity was found with the right cerebellum.

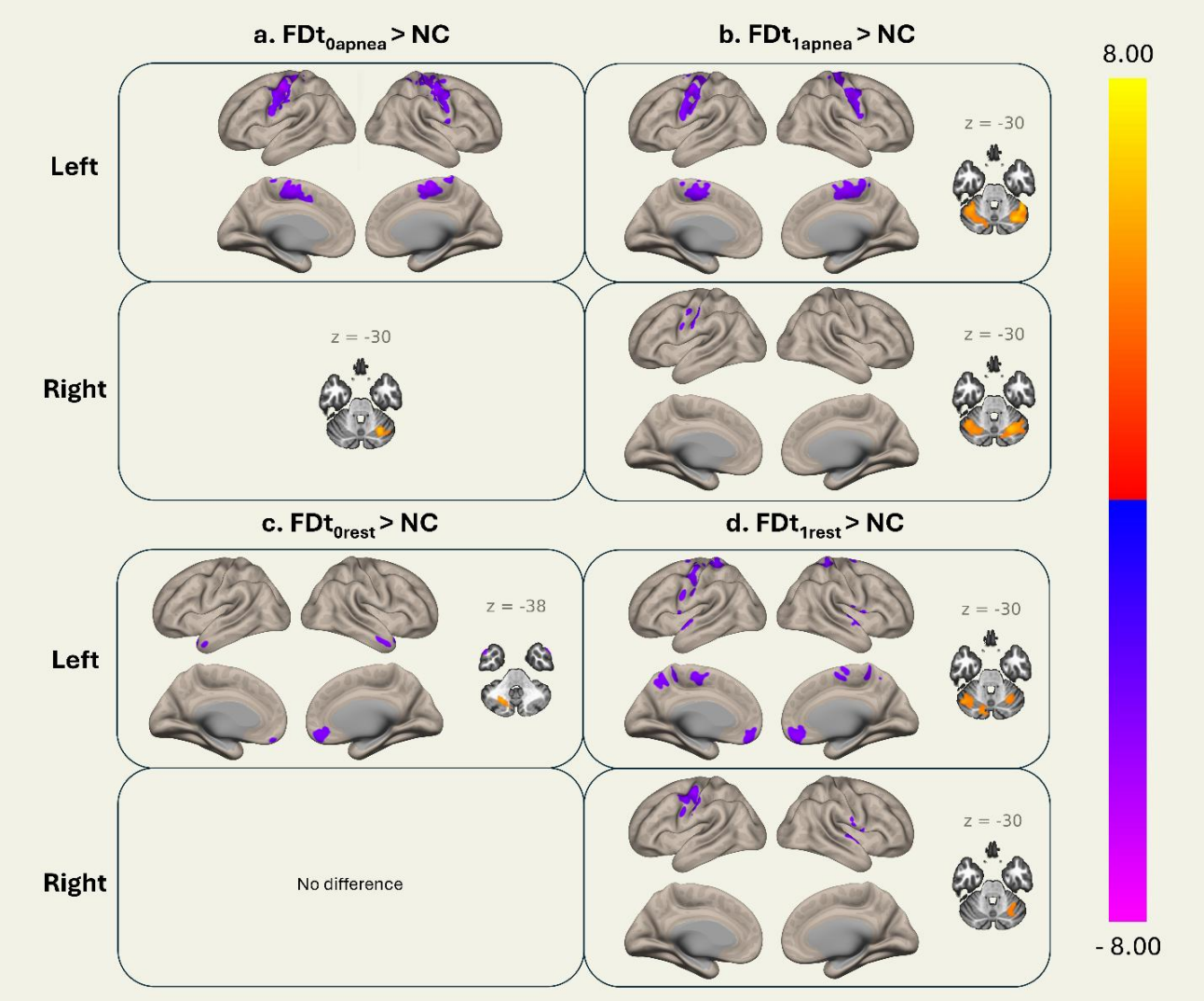


Figure 3: *Left and right hippocampal FC differences between conditions (NC versus FD during apnea and rest, before and after training): Seed-to-Voxel analysis using CONN toolbox on MATLAB, FDR correction applied. 2D slices and 3D view. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. n = 17 FD and 20 NC. FD: Freedivers, NC: Controls.*

2.2 ADDITIONNAL ROIs

Default mode network

During apnea

a. No significant results before training.

b. After training season (FDt1apnea > NC), hypoconnectivity was found with the left occipital pole, left intracalcarine cortex, left supracalcarine cortex, right lingual gyrus, right occipital fusiform gyrus, and right cerebellum (Figure S2).

During rest

c. and d. No significant results before or after training.

Left frontal cortex

During apnea

a. Before training season (FDt0apnea > NC), hyperconnectivity was found with the right central opercular cortex, left postcentral gyrus, and right precentral gyrus.

b. After training (FDt1apnea > NC), hyperconnectivity was found with the left precentral gyrus and right postcentral gyrus.

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found with the right cerebellum.

d. After training (FDt1rest > NC), hypoconnectivity was found with the right intracalcarine cortex. Hyperconnectivity was found with the right frontal pole, right middle frontal gyrus, and right superior frontal gyrus (Figure S3).

Right frontal cortex

During apnea

a. Before training (FDt0apnea > NC), hyperconnectivity was found with bilateral precentral gyri, bilateral postcentral gyri, bilateral central opercular cortex, left superior temporal gyrus, left middle temporal gyrus, left planum temporale, right insular cortex, and right planum polare.

b. After training (FDt1apnea > NC), hyperconnectivity was found between bilateral precentral gyri, bilateral postcentral gyri, left middle frontal gyrus, left inferior temporal gyrus, right insular cortex, right central opercular cortex, and right parietal operculum cortex.

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found with bilateral cerebellum. Hyperconnectivity occurred with the left inferior frontal gyrus and left frontal orbital cortex.

d. After training (FDt1rest > NC), hypoconnectivity was found with the right intracalcarine cortex. Hyperconnectivity emerged with bilateral precentral gyri, bilateral postcentral gyri, and left inferior temporal gyrus (Figure S3).

Left frontoparietal network

During apnea

a. Before training (FDt0apnea > NC), hyperconnectivity was found with the right precentral gyrus.

b. After training (FDt1apnea > NC), hyperconnectivity was found with bilateral frontal pole, bilateral paracingulate gyrus, cingulate gyrus (anterior division), left postcentral gyrus, and cingulate gyrus (posterior division).

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found between bilateral cerebellum and left thalamus. Hyperconnectivity was foundin cingulate gyrus (posterior division) and bilateral paracingulate gyrus.

d. After training (FDt1rest > NC), hypoconnectivity was found with the right intracalcarine cortex (Figure S4).

Right frontoparietal network

During apnea

a. Before training (FDt0apnea > NC), hyperconnectivity was found with bilateral precentral gyri, bilateral postcentral gyri, right superior parietal lobule, bilateral SMA, cingulate gyrus (anterior division), left planum temporale, and left Heschl's gyrus.

b. After training (FDt1apnea > NC), hypoconnectivity was found with the left caudate. Hyperconnectivity was found in bilateral precentral gyri, bilateral postcentral gyri, left frontal pole, bilateral central opercular cortex, bilateral parietal operculum cortex, bilateral insular cortex, bilateral Heschl's gyrus, left planum temporale, and left paracingulate gyrus.

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found with bilateral cerebellum. Hyperconnectivity was found with bilateral precentral gyri, bilateral postcentral gyri, left occipital pole, left lateral occipital cortex, left inferior frontal gyrus, left frontal operculum cortex, left paracingulate gyrus, left middle temporal gyrus, and left superior temporal gyrus.

d. After training (FDt1rest > NC), hypoconnectivity was found in left cerebellum and right thalamus. Hyperconnectivity was found in bilateral precentral gyri, right postcentral gyrus, and left frontal pole (Figure S4).

Left occipital cortex

During apnea

a. Before training (FDt0apnea > NC), hypoconnectivity was found with the brain stem, frontal medial cortex, and right occipital fusiform gyrus.

b. After training (FDt1apnea > NC), hypoconnectivity was found with the left paracingulate gyrus and cingulate gyrus (anterior division).

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found in bilateral lingual gyri, bilateral occipital fusiform gyri, bilateral cerebellum, bilateral occipital poles, vermis, right thalamus, and brain stem. Hyperconnectivity was found with bilateral middle temporal gyri, bilateral inferior temporal gyri, bilateral superior temporal gyri, bilateral angular gyri, bilateral supramarginal gyri, bilateral superior parietal lobules, bilateral lateral occipital cortices, and right middle frontal gyrus.

d. No significant results after training (Figure S5).

Right occipital cortex

During apnea

a. Before training (FDt0apnea > NC), hypoconnectivity was found with the right occipital fusiform gyrus, right lingual gyrus, right occipital pole, right cerebellum, vermis, brain stem, left putamen, and left insular cortex. Hyperconnectivity was

found with bilateral precentral gyri, bilateral superior frontal gyri, and left middle frontal gyrus/SMA.
b. No significant results after training.

During rest

c. Before training (FDt0rest > NC), hypoconnectivity was found bilateral lingual gyri, bilateral occipital fusiform gyri, left cerebellum, right occipital pole, vermis, right thalamus, and brain stem. Hyperconnectivity was found with bilateral middle temporal gyri, bilateral inferior temporal gyri, bilateral superior temporal gyri, bilateral angular gyri, bilateral supramarginal gyri, bilateral superior parietal lobules, and right middle frontal gyrus.
d. No significant results after training (Figure S5).

3. Correlations with episodic memory scores

Left hippocampus

FD group, rest after training

We found a significant positive correlation between EM scores of ii. similar items and the FC of the left hippocampus with the right cerebellum (r = 0.89, p<0.001, n = 17) and the left hippocampus (r = 0.88, p = 0.044, n = 17). We also found a significant positive correlation between EM scores of iii.new items and the FC of the left hippocampus with the right cerebellum (r = 0.90, p<0.001, n = 17).
No other significant correlations were found in the other conditions.

NC group

We found a significant positive correlation between EM scores of ii. similar items and the FC of the left hippocampus with the frontal medial cortex and the paracingulate gyrus (r = 0.79, p = 0.045, n = 20) (Figure 4).

Right hippocampus

FD group, rest after training

We found a significant negative correlation between EM scores of i. identical items and the FC of the right hippocampus with the left postcentral gyrus (r = -0.91, p<0.001, n = 17), the left precentral cortex and left central opercular cortex (r = -0.85, p<0.01, n = 17), and the right pre and postcentral gyrus (r = -0.83, p = 0.011, n = 17). No other significant correlations were found in other conditions.

NC group

We found a significant positive correlation between EM scores of iii. new items and the FC of the right hippocampus with the frontal medial cortex (r = 0.83, p = 0.017, n = 20) (Figure 4).

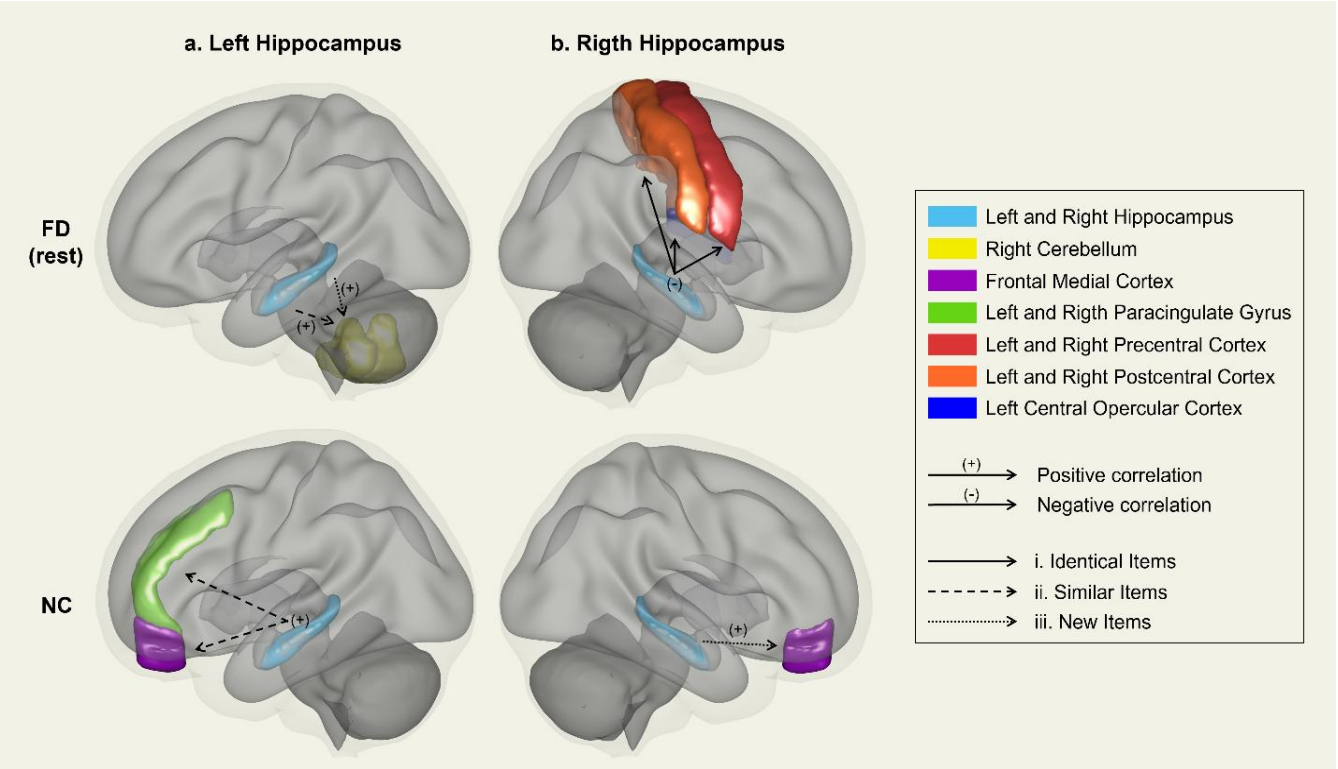


Figure 4: *Correlations result between left and right hippocampal FC across conditions (NC and FD during rest after training) and episodic memory scores: GLM with FDR correction using CONN toolbox on MATLAB. a. Left hippocampus b. Right hippocampus. FD: Freedivers, NC: Controls.*

DISCUSSION

This study investigated the impact of voluntary intermittent hypoxia on rs-FC, in the hippocampus and whole-brain networks in male FD. The main results showed: (1) Whole-brain FC analyses revealed reorganization within the salience, frontoparietal, sensorimotor and cerebellar networks at rest after training. (2) Hippocampal FC of FD revealed before training hypoconnectivity between the hippocampus and both the DMN and sensorimotor areas, alongside hyperconnectivity in cerebellar and visual regions, that increased after training. (3) Hippocampal rs-FC was significantly correlated with episodic memory performance, especially after training, suggesting a compensatory functional adaptation to preserve cognitive abilities.

Our results indicate that freediving training leads to specific patterns of functional reorganization, both within the hippocampus and across large-scale brain networks. Unlike the widespread disruptions reported for involuntary hypoxia, particularly in the DMN, FPN, attentional and hippocampal networks (Micaux et al., 2025b; Song et al., 2018), this reorganization appears to reflect an adaptive redistribution of neural resources that supports, and possibly enhances, functional efficiency.

1. FC in response to freediving training: whole-brain reorganization

At the whole-brain level, freediving training was associated with large-scale FC reorganization. We examined these changes in relation to the major resting-state networks (RSNs) typically activated at rest and impaired under involuntary hypoxia (Micaux et al., 2025b). Specifically, we observed hyperconnectivity within the FPN, and between frontal/FPN regions and the sensorimotor network (notably the SMA), DMN, salience network (SN), and visual regions. These effects were present both before and after training, with an increase following training. We also observed hyperconnectivity between the occipital cortex and sensorimotor, DMN, attention networks, FPN, and visual regions, but only before training.

In contrast, hypoconnectivity predominantly involved occipital regions and the cerebellum. Before training, during apnea, we found hypoconnectivity between occipital regions and the DMN, VAN, SN, FPN, and cerebellum. After training, hypoconnectivity was found between the cerebellum and frontal/FPN as well as DMN regions.

Taken together, these findings suggest that freediving training reshapes brain connectivity toward a pattern characterized by stronger interactions between frontal control regions and sensorimotor areas, and reduced interactions involving occipital regions and the cerebellum. The SMA involvement is particularly relevant for freediving, as it supports motor planning, imagery, and the voluntary control required to suppress automatic breathing reflexes during apnea.

2. FC in response to freediving training: hippocampal reorganization

The hippocampus plays a central role in this functional reorganization, as a region highly vulnerable to hypoxia, yet also plastic in response to exercise training (Heller-Wight et al., 2023; Suwabe et al., 2018). Our findings show consistent hypoconnectivity between the left hippocampus and the sensorimotor cortex across all conditions, more pronounced after training. We also found hypoconnectivity between the hippocampus and DMN networks, mainly at rest. Simultaneously, we observed increased hyperconnectivity between the hippocampus and the cerebellum, as well as visual regions, particularly after training as well. This suggests a shift from sensorimotor coupling toward cerebellar and visual integration. The right hippocampus exhibited a more stable pattern, with only minimal changes in FC and persistent cerebellar coupling.

This profile may reflect an optimized hippocampal response to apnea: disengagement from sensory inputs, reduced involvement in motor coordination, and increased interaction with regions supporting internal visualization and autonomic regulation. The increased hippocampal connectivity with cerebellar regions suggests a stronger interaction between cognitive and autonomic processes, potentially facilitating motor inhibition during freediving. In addition, the cerebellum emerges as a central contributor to memory-related processes. It is anatomically and functionally linked with the hippocampus and other cortical memory networks, supports episodic memory through its synaptic adaptation, and

shows increased activation under stress or pathology (Almeida et al., 2023; D'Angelo et al., 2016; Nettekoven et al., 2024; Zuo et al., 2025). Enhanced hippocampo-cerebellar connectivity observed in our study may therefore represent a functional reorganization that helps maintain memory encoding under metabolic stress.

When considering whole-brain adaptations alongside this hippocampal FC profile, we observe an opposite trend: while the hippocampus disengages from sensorimotor and DMN coupling and reinforce his connections with the cerebellum, large-scale networks show increased connectivity in these regions, and decreased connectivity with the cerebellum. This contrast highlights a dual adaptation, with localized hippocampal reorganization favoring memory preservation, and global network reorganization reinforcing voluntary motor control and attentional regulation essential to freediving practice.

These findings align with those of Annen et al. (2021), who examined a world-class FD and observed that apnea strengthens the connectivity of circuits involved in regulation, control, and emotional integration, while at the same time it reduces connectivity in regions related to sensory processing. The authors interpreted this as evidence of a brain state characterized by enhanced internal focus, reduced somatosensory interference, and optimized cognitive control, similar to meditation, but specifically associated with the physiological demands of apnea. Our data extends and refine these findings to a group level and further reveal hippocampal and cerebellar dynamics, suggesting that freediving not only modifies introspective networks but also reorganizes memory networks to sustain cognitive function under intermittent voluntary hypoxia.

Our findings are also similar to prior research in exercise training (with hypoxia, as in synchronized swimming, or without), and low-dose hypoxia, each offering insight into different mechanisms that may contribute to memory preservation in FD.
Research in synchronized swimmers indeed supports our results. Jones & Cooper, (2018) showed preserved oxygenation in the prefrontal cortex during maximal apneas, despite severe muscle deoxygenation, indicating prioritized cerebral protection.
As outlined in the introduction, endurance training is known to promote brain efficiency through reduced global FC in non-essential regions and selective strengthening of networks relevant for a specific task (Li et al., 2023; Raichlen et al., 2016), similar to what we observed in our FD group. However, this is not unique to endurance exercise. For instance, research on skeleton athletes illustrates a clear case of specialization: increased rs-FC in regions involved in cognitive and motor control, reward learning, visual processing, spatial cognition, and emotional regulation, all of which are essential in their discipline.

A distinct line of research on intermittent hypoxic training (IHT) suggests that low-dose hypoxia, when paired with exercise, could have neuroprotective effects (boost production of BDNF), and a beneficial impact on cognition (Boulares et al., 2024; Damgaard et al., 2023; Rybnikova et al., 2022). Our results support this: hippocampal FC patterns became more predictive of cognitive performance only after training, suggesting that hypoxia alone is not sufficient; adaptation depends on repeated, controlled exposure combined with exercise training. Not surprisingly, the impact of IHT depends on hypoxia intensity, with moderate levels promoting beneficial effects while more severe exposure leads to detrimental outcomes (Damgaard et al., 2023; Navarrete-Opazo and Mitchell, 2014).

Overall, neuroplasticity induced by freediving appears to reflect a unique convergence of sport and hypoxia adaptation. This combination led to a functional reorganization that prioritizes internal regulation, memory preservation, and network efficiency. Our data suggests therefore that under controlled and repeated exposure, voluntary hypoxia may support neural resilience. Notably, the cerebellum, often overlooked in rs-fMRI studies, emerged as a central adaptive hub connected to the hippocampus.

3. Hippocampal FC predict episodic memory scores

Our results reveal strong correlations between hippocampal FC and episodic memory performance, particularly after training. These correlations were more pronounced in the left hippocampus, which is typically associated with semantic and episodic processing, and involved enhanced FC with the cerebellum. This suggests that freediving practice could lead to new hippocampal-cerebellar loops supporting cognitive performance under physiological stress.

For similar item recognition, a process specifically linked to hippocampal pattern separation (Zhao & Noulhiane, In Press), FD after training showed stronger correlations with left hippocampal FC than both before training and with NC participants. This suggests that freediving enhances the recruitment of hippocampal networks to maintain the same performance as NC, validating our hypothesis of compensatory functional plasticity. For new items, left hippocampal–cerebellar FC was associated with episodic memory performance in FD, whereas NC showed right hippocampal–medial prefrontal involvement. This shift may reflect a redistributed encoding strategy following training. Finally, for identical items, a negative correlation with right hippocampal-sensorimotor FC was found, suggesting that sensorimotor disengagement may reduce interference and support accurate recognition; consistent with Simons & Spiers, (2003), who proposed that disengagement of irrelevant networks can facilitate memory by preventing information overload or cognitive noise.

These results suggest that hippocampal FC, especially in the left hippocampus, can predict episodic memory performance in FD, with higher values than in NC before training and a further increase after training. These findings align with Maeshima et al. (2017) who reported beneficial effects of regular

synchronized swimming practice on memory, suggesting that freediving training may similarly lead to long-term cognitive improvements. However, in healthy individuals performing a pattern separation task in normal conditions, the hippocampus shows enhanced and complex FC with multiple neocortical regions (Amer and Davachi, 2023; Stevenson et al., 2020). In contrast, our results reveal a reorganization of hippocampal FC that also engages subcortical structures such as the cerebellum, suggesting the emergence of a compensatory mechanism specific to hypoxia training.

4. Future directions and perspectives

Overall, our study supports the hypothesis of FC reorganization in FD. In addition to the absence of detectable anatomical changes or memory impairments (Micaux et al., 2025), we observed significant FC changes that may reflect compensatory mechanisms helping to preserve memory performance under repeated hypoxic exposure. Hippocampal plasticity reveals how voluntary intermittent hypoxia promotes resilience without anatomical decline, positioning hippocampal FC as a marker of adaptability under extreme environmental conditions such as freediving. These findings fit with the concept of cognitive reserve, where adaptive plasticity can preserve brain performance despite aging and pathology (Barulli and Stern, 2013; Verkhratsky and Zorec, 2024).

The longitudinal design represents a central advantage of our study, allowing us to separate transient fluctuations from lasting neural adaptations. This supports the interpretation of hippocampal functional reorganization as a plastic process. However, several limitations about our cohort should be considered when interpreting these findings. All participants were recruited from the Île-de-France region, which may limit the generalizability to FD from other backgrounds. The sample also included only male participants; future studies should include females to explore potential sex differences in FC changes (Jung et al., 2020). In addition, it would be relevant to explore whether the observed FC changes are associated with additional cerebral adaptations, such as, for instance, alterations in the hemodynamic response (HRF) of cerebral blood flow (ASL MRI) (Troudi Habibi et al., In Press), or even metabolic changes (MRS), particularly in the hippocampus. Longitudinal studies are also needed to assess the persistence and reversibility of these changes after training has stopped (Blackmore et al., 2024). Finally, assessing a broader range of cognitive functions would help determine whether hypoxia-related FC changes extend beyond memory processes (McKeown et al., 2025).

CONCLUSION

Freediving represents a unique healthy human model to study intermittent, voluntary hypoxia combined with training. Our findings suggest that freediving training induces a complex pattern of functional brain network reorganization, combining resource redistribution that supports cognitive resilience and compensatory mechanisms for the physiological challenges posed by hypoxia. The

hippocampus and cerebellum appear to play a key role in this process, integrating memory, motor control, and autonomic regulation. Finally, these adaptive changes may reflect a broader mechanism by which mild hypoxic stress promotes FC plasticity and enhances brain efficiency, opening avenues for potential applications in therapeutic contexts involving hippocampal vulnerability.

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Availability of Data and Materials

The datasets referenced in this article are not publicly available, as participants consented to their data being used solely under the supervision of the principal investigator. Requests to access the datasets should be directed to MN.

Author Contributions

Conceptualization: MN developed the research questions and experimental design (PI). Methodology: FM and MN designed the MRI sequences. Investigation: CC was the medical investigator of the project. Recruitment: JM and MN conducted participant recruitment and data collection. Formal analysis: JM led data analyses and results interpretation with ATH. Supervision: MN supervised the analyses and the overall project. Visualization: JM, ATH and MN created the figures. Writing – original draft: JM drafted the manuscript. Writing – review & editing: JM and MN did the review and editing, and all co-authors contributed critical revisions. Approval: All authors approved the final version of the manuscript for submission.

Ethics Approval and Participant Consent to Participate

The research protocol is adhering to ethical guidelines for research involving humans and was approved by the Ethics Committee (Ethic Approval Number: 2022-A01030-43). All participants provided signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1: Significant p-values of seed-to-voxel comparison (hyperconnectivity) with FDR correction. AD: Anterior Division; PD: Posterior Division. FD: Freedivers, NC, Controls.

Seed Region	Comparison	Hyperconnectivity	p-FDR
Hippocampus_Left	FDt_{1apnea} > NC	Left & Right Cerebellum	< 0.001
Hippocampus_Left	FDt_{1apnea} > NC	Right Temporal Occipital Fusiform Cortex	< 0.001
Hippocampus_Left	FDt_{1apnea} > NC	Right Temporal Fusiform Cortex	< 0.001
Hippocampus_Left	FDt_{0rest} > NC	Left Cerebellum	0.009
Hippocampus_Left	FDt_{1rest} > NC	Left & Right Cerebellum	0.003; 0.01
Hippocampus_Right	FDt_{0apnea} > NC	Right Cerebellum	< 0.001
Hippocampus_Right	FDt_{1apnea} > NC	Left & Right Cerebellum	< 0.001
Hippocampus_Right	FDt_{1rest} > NC	Right Cerebellum	0.026
FP_Left	FDt_{1apnea} > FDt_{1rest}	Left & Right Intracalcarine Cortex	< 0.001; 0.003
FP_Left	FDt_{1apnea} > FDt_{1rest}	Right Cuneal Cortex	< 0.001
FP_Left	FDt_{1apnea} > FDt_{1rest}	Left & Right Lingual Gyrus	< 0.001; 0.003
FP_Left	FDt_{0apnea} > NC	Left & Right Central Opercular Cortex	0.016
FP_Left	FDt_{0apnea} > NC	Left Postcentral Gyrus	0.016
FP_Left	FDt_{0apnea} > NC	Right Precentral Gyrus	0.028
FP_Left	FDt_{1apnea} > NC	Left Precentral Gyrus	0.048
FP_Left	FDt_{1apnea} > NC	Right Postcentral Gyrus	0.48
FP_Left	FDt_{1rest} > NC	Right Frontal Pole	0.044
FP_Left	FDt_{1rest} > NC	Right Middle Frontal Gyrus	0.044
FP_Left	FDt_{1rest} > NC	Right Superior Frontal Gyrus	0.044
FP_Right	FDt_{0apnea} > NC	Left & Right Precentral Gyrus	< 0.001
FP_Right	FDt_{0apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
FP_Right	FDt_{0apnea} > NC	Left & Right Central Opercular Cortex	< 0.001
FP_Right	FDt_{0apnea} > NC	Left Superior Temporal Gyrus	< 0.001
FP_Right	FDt_{0apnea} > NC	Left Middle Temporal Gyrus	< 0.001
FP_Right	FDt_{0apnea} > NC	Left Planum Temporal	< 0.001
FP_Right	FDt_{0apnea} > NC	Right Insular Cortex	< 0.001
FP_Right	FDt_{0apnea} > NC	Right Planum Polare	< 0.001
FP_Right	FDt_{1apnea} > NC	Left & Right Precentral Gyrus	< 0.001
FP_Right	FDt_{1apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
FP_Right	FDt_{1apnea} > NC	Left Middle Frontal Gyrus	< 0.001
FP_Right	FDt_{1apnea} > NC	Left Inferior Temporal Gyrus	0.041
FP_Right	FDt_{1apnea} > NC	Right Insular Cortex	0.047
FP_Right	FDt_{1apnea} > NC	Right Central Opercular Cortex	0.047
FP_Right	FDt_{1apnea} > NC	Right Parietal Operculum Cortex	0.047

FP_Right	FDt_{0rest} > NC	Left Inferior Frontal Gyrus	0.01
FP_Right	FDt_{0rest} > NC	Left Frontal Orbital Cortex	0.01
FP_Right	FDt_{1rest} > NC	Left & Right Precentral Gyrus	< 0.001
FP_Right	FDt_{1rest} > NC	Left & Right Postcentral Gyrus	< 0.001
FP_Right	FDt_{1rest} > NC	Left Inferior Temporal Gyrus	0.049
FPN_Left	FDt_{0apnea} > NC	Right Precentral Gyrus	0.006
FPN_Left	FDt_{1apnea} > NC	Left & Right Frontal Pole	< 0.001
FPN_Left	FDt_{1apnea} > NC	Left & Right Paracingulate Gyrus	< 0.001
FPN_Left	FDt_{1apnea} > NC	Cingulate Gyrus AD	< 0.001
FPN_Left	FDt_{1apnea} > NC	Left Postcentral Gyrus	0.039
FPN_Left	FDt_{1apnea} > NC	Cingulate Gyrus PD	0.039
FPN_Left	FDt_{0rest} > NC	Cingulate Gyrus PD	0.003
FPN_Left	FDt_{0rest} > NC	Left & Right Paracingulate Gyrus	0.032; 0.49
FPN_Right	FDt_{0apnea} > NC	Left & Right Precentral Gyrus	< 0.001
FPN_Right	FDt_{0apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
FPN_Right	FDt_{0apnea} > NC	Right Superior Parietal Lobule	< 0.001
FPN_Right	FDt_{0apnea} > NC	Left & Right Supplementary Motor Area	< 0.001
FPN_Right	FDt_{0apnea} > NC	Cingulate Gyrus AD	< 0.001
FPN_Right	FDt_{0apnea} > NC	Left Planum Temporal	0.006
FPN_Right	FDt_{0apnea} > NC	Left Heschl's Gyrus	0.006
FPN_Right	FDt_{1apnea} > NC	Left & Right Precentral Gyrus	< 0.001
FPN_Right	FDt_{1apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
FPN_Right	FDt_{1apnea} > NC	Left Frontal Pole	0.003
FPN_Right	FDt_{1apnea} > NC	Left & Right Central Opercular Cortex	0.005; 0.008
FPN_Right	FDt_{1apnea} > NC	Left & Right Parietal Operculum Cortex	0.005; 0.008
FPN_Right	FDt_{1apnea} > NC	Left & Right Insular Cortex	0.005; 0.008
FPN_Right	FDt_{1apnea} > NC	Left & Right Heschl's Gyrus	0.005; 0.008
FPN_Right	FDt_{1apnea} > NC	Left Planum Temporal	0.008
FPN_Right	FDt_{1apnea} > NC	Left Paracingulate Gyrus	0.022
FPN_Right	FDt_{0rest} > NC	Left & Right Precentral Gyrus	< 0.001
FPN_Right	FDt_{0rest} > NC	Left & Right Postcentral Gyrus	< 0.001
FPN_Right	FDt_{0rest} > NC	Left Occipital Pole	< 0.001
FPN_Right	FDt_{0rest} > NC	Left Lateral Occipital Cortex	< 0.001
FPN_Right	FDt_{0rest} > NC	Left Inferior Frontal Gyrus	< 0.001
FPN_Right	FDt_{0rest} > NC	Left Frontal Operculum Cortex	< 0.001
FPN_Right	FDt_{0rest} > NC	Left Paracingulate Gyrus	0.007
FPN_Right	FDt_{0rest} > NC	Left Middle Temporal Gyrus	0.028

FPN_Right	FDt_{0rest} > NC	Left Superior Temporal Gyrus	0.028
FPN_Right	FDt_{1rest} > NC	Left & Right Precentral Gyrus	< 0.001; 0.037
FPN_Right	FDt_{1rest} > NC	Right Postcentral Gyrus	< 0.001
FPN_Right	FDt_{1apnea} > NC	Left Frontal Pole	0.004
OP_Left	FDt_{0rest} > NC	Left & Right Middle Temporal Gyrus	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Inferior Temporal Gyrus	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Superior Temporal Gyrus	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Angular Gyrus	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Supramarginal Gyrus	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Superior Parietal Lobule	< 0.001
OP_Left	FDt_{0rest} > NC	Left & Right Lateral Occipital Cortex	< 0.001; 0.03
OP_Left	FDt_{0rest} > NC	Right Middle Frontal Gyrus	< 0.001
OP_Right	FDt_{0apnea} > NC	Left & Right Precentral Gyrus	< 0.001
OP_Right	FDt_{0apnea} > NC	Left & Right Superior Frontal Gyrus	< 0.001
OP_Right	FDt_{0apnea} > NC	Left Middle Frontal Gyrus	< 0.001
OP_Right	FDt_{0apnea} > NC	Left Supplementary Motor Area	< 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Middle Temporal Gyrus	< 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Inferior Temporal Gyrus	< 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Superior Temporal Gyrus	< 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Angular Gyrus	< 0.001; 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Supramarginal Gyrus	< 0.001; 0.001
OP_Right	FDt_{0rest} > NC	Left & Right Superior Parietal Lobule	< 0.001; 0.001
OP_Right	FDt_{0rest} > NC	Right Middle Frontal Gyrus	0.014

Table S2: Significant p-values of seed-to-voxel comparison (hypoconnectivity) with FDR correction. AD: Anterior Division; PD: Posterior Division. FD: Freedivers, NC, Controls.

Seed Region	Comparison	Hypoconnectivity	p-FDR
DMN	FDt_{1apnea} > FDt_{1rest}	Left & Right Lateral Occipital Cortex	0.034
DMN	FDt_{1apnea} > FDt_{1rest}	Left Occipital Pole	0.034
DMN	FDt_{1apnea} > NC	Left Occipital Pole	< 0.001
DMN	FDt_{1apnea} > NC	Left Intracalcarine Cortex	< 0.001
DMN	FDt_{1apnea} > NC	Left Supracalcarine Cortex	< 0.001
DMN	FDt_{1apnea} > NC	Right Lingual Gyrus	0.007
DMN	FDt_{1apnea} > NC	Right Occipital Fusiform Gyrus	0.007
DMN	FDt_{1apnea} > NC	Right Cerebellum	0.007
Hippocampus_Left	FDt_{0apnea} > NC	Left & Right Precentral Gyrus	< 0.001
Hippocampus_Left	FDt_{0apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
Hippocampus_Left	FDt_{0apnea} > NC	Left & Right Supplementary Motor Area	< 0.001

Hippocampus_Left	FDt_{0apnea} > NC	Right Superior Parietal Lobule	< 0.001
Hippocampus_Left	FDt_{0apnea} > NC	Left Paracingulate Gyrus	< 0.001
Hippocampus_Left	FDt_{1apnea} > NC	Left & Right Precentral Gyrus	< 0.001
Hippocampus_Left	FDt_{1apnea} > NC	Left & Right Postcentral Gyrus	< 0.001
Hippocampus_Left	FDt_{1apnea} > NC	Left & Right Supplementary Motor Area	< 0.001
Hippocampus_Left	FDt_{0rest} > NC	Left & Right Temporal Pole	0.009; 0.047
Hippocampus_Left	FDt_{0rest} > NC	Right Middle Temporal Gyrus	0.009
Hippocampus_Left	FDt_{0rest} > NC	Frontal Medial Cortex	0.047
Hippocampus_Left	FDt_{1rest} > NC	Frontal Medial Cortex	< 0.001
Hippocampus_Left	FDt_{1rest} > NC	Left Precentral Gyrus	0.041
Hippocampus_Left	FDt_{1rest} > NC	Left & Right Postcentral Gyrus	0.008; 0.006
Hippocampus_Left	FDt_{1rest} > NC	Left & Right Superior Parietal Lobule	0.006
Hippocampus_Left	FDt_{1rest} > NC	Left & Right Superior Temporal Gyrus	0.013; 0.018
Hippocampus_Left	FDt_{1rest} > NC	Left & Right Planum Polare	0.037; 0.018
Hippocampus_Left	FDt_{1rest} > NC	Right Central Opercular Cortex	0.018
Hippocampus_Left	FDt_{1rest} > NC	Precuneus Cortex	0.041
Hippocampus_Right	FDt_{1apnea} > NC	Left Precentral Gyrus	0.039
Hippocampus_Right	FDt_{1rest} > NC	Left Postcentral Gyrus	< 0.001
Hippocampus_Right	FDt_{1rest} > NC	Left Precentral Gyrus	< 0.001
Hippocampus_Right	FDt_{1rest} > NC	Right Planum Temporal	0.046
Hippocampus_Right	FDt_{1rest} > NC	Right Planum Polare	0.046
Hippocampus_Right	FDt_{1rest} > NC	Right Central Opercular Cortex	0.046
FP_Left	FDt_{0rest} > NC	Right Cerebellum	< 0.001
FP_Left	FDt_{1rest} > NC	Right Intracalcarine Cortex	0.001
FP_Right	FDt_{0rest} > NC	Left & Right Cerebellum	< 0.001
FP_Right	FDt_{1rest} > NC	Right Intracalcarine Cortex	0.049
FPN_Left	FDt_{0rest} > NC	Left & Right Cerebellum	< 0.001; 0.045
FPN_Left	FDt_{0rest} > NC	Left Thalamus	0.045
FPN_Left	FDt_{1rest} > NC	Right Intracalcarine Cortex	0.044
FPN_Right	FDt_{1apnea} > NC	Left Caudate	0.045
FPN_Right	FDt_{0rest} > NC	Left & Right Cerebellum	0.024
FPN_Right	FDt_{1rest} > NC	Left Cerebellum	0.004
FPN_Right	FDt_{1rest} > NC	Right Thalamus	0.037
OP_Left	FDt_{0apnea} > FDt_{0rest}	Left & Right Middle Temporal Gyrus	< 0.001; 0.001
OP_Left	FDt_{0apnea} > FDt_{0rest}	Left Inferior Temporal Gyrus	< 0.001
OP_Left	FDt_{0apnea} > FDt_{0rest}	Left Angular Gyrus	< 0.001
OP_Left	FDt_{0apnea} > FDt_{0rest}	Left Lateral Occipital Cortex	< 0.001

OP_Left	$FDt_{0apnea} > FDt_{0rest}$	Left Supramarginal Gyrus	< 0.001
OP_Left	$FDt_{0apnea} > FDt_{0rest}$	Cingulate Gyrus PD	0.001
OP_Left	$FDt_{0apnea} > FDt_{0rest}$	Left Frontal Pole	0.038
OP_Left	$FDt_{0apnea} > FDt_{0rest}$	Left Paracingulate Gyrus	0.038
OP_Left	$FDt_{1apnea} > FDt_{1rest}$	Left Lateral Occipital Cortex	0.005
OP_Left	$FDt_{1apnea} > FDt_{1rest}$	Precuneus Cortex	0.007
OP_Left	$FDt_{1apnea} > FDt_{1rest}$	Cingulate Gyrus PD	0.007
OP_Left	$FDt_{0apnea} > NC$	Brain Stem	0.049
OP_Left	$FDt_{0apnea} > NC$	Frontal Medial Cortex	0.049
OP_Left	$FDt_{0apnea} > NC$	Right Occipital Fusiform Gyrus	0.049
OP_Left	$FDt_{1apnea} > NC$	Left Paracingulate Gyrus	0.001
OP_Left	$FDt_{1apnea} > NC$	Cingulate Gyrus AD	0.001
OP_Left	$FDt_{0rest} > NC$	Left & Right Lingual Gyrus	< 0.001
OP_Left	$FDt_{0rest} > NC$	Left & Right Occipital Fusiform Gyrus	< 0.001
OP_Left	$FDt_{0rest} > NC$	Left & Right Cerebellum	< 0.001
OP_Left	$FDt_{0rest} > NC$	Left & Right Occipital Pole	< 0.001
OP_Left	$FDt_{0rest} > NC$	Vermis	< 0.001
OP_Left	$FDt_{0rest} > NC$	Right Thalamus	< 0.001
OP_Left	$FDt_{0rest} > NC$	Brain Stem	< 0.001
OP_Right	$FDt_{0apnea} > FDt_{0rest}$	Right Middle Temporal Gyrus	0.047
OP_Right	$FDt_{0apnea} > FDt_{0rest}$	Right Cerebellum	0.047
OP_Right	$FDt_{0apnea} > NC$	Right Occipital Fusiform Gyrus	< 0.001
OP_Right	$FDt_{0apnea} > NC$	Right Lingual Gyrus	< 0.001
OP_Right	$FDt_{0apnea} > NC$	Right Occipital Pole	< 0.001
OP_Right	$FDt_{0apnea} > NC$	Right Cerebellum	< 0.001
OP_Right	$FDt_{0apnea} > NC$	Vermis	< 0.001
OP_Right	$FDt_{0apnea} > NC$	Brain Stem	0.011
OP_Right	$FDt_{0apnea} > NC$	Left Putamen	0.02
OP_Right	$FDt_{0apnea} > NC$	Left Insular Cortex	0.02
OP_Right	$FDt_{0rest} > NC$	Left & Right Lingual Gyrus	< 0.001
OP_Right	$FDt_{0rest} > NC$	Left & Right Occipital Fusiform Gyrus	< 0.001
OP_Right	$FDt_{0rest} > NC$	Left Cerebellum	< 0.001
OP_Right	$FDt_{0rest} > NC$	Right Occipital Pole	< 0.001
OP_Right	$FDt_{0rest} > NC$	Vermis	< 0.001
OP_Right	$FDt_{0rest} > NC$	Right Thalamus	< 0.001
OP_Right	$FDt_{0rest} > NC$	Brain Stem	< 0.001

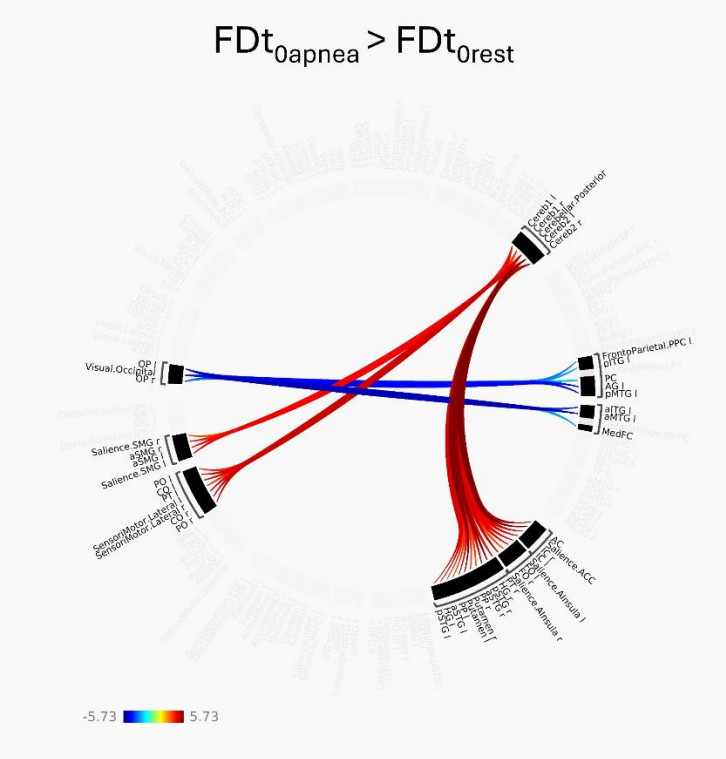


***Figure S1**: FC matrice showing differences in whole brain hypoconnectivity and hyperconnectivity comparing FDt_{0apnea} > FDt_{0rest}. ROI-to-ROI analysis using CONN toolbox on MATLAB. N= 17 FD and 20 NC. FDR correction applied. FD: Freedivers.*

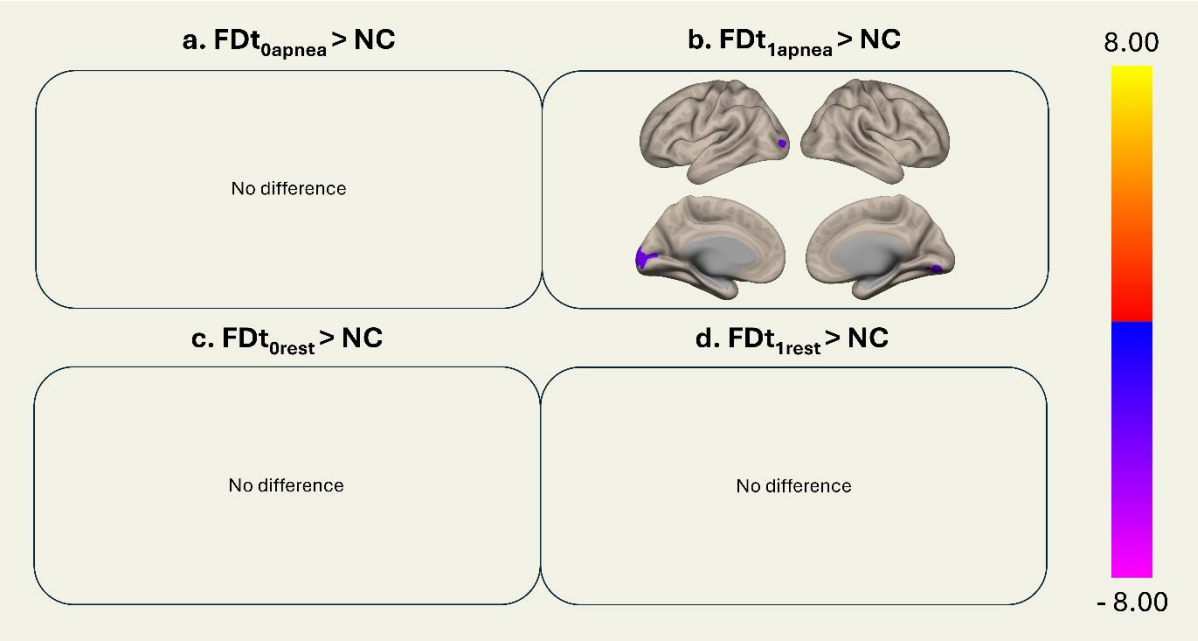


***Figure S2**: DMN FC differences between conditions (NC versus FD during apnea and rest, before and after training): Seed-to-Voxel analysis using CONN toolbox on MATLAB, FDR correction applied. 2D slices and 3D view. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. N= 17 FD and 20 NC. FD: Freedivers, NC, Controls.*

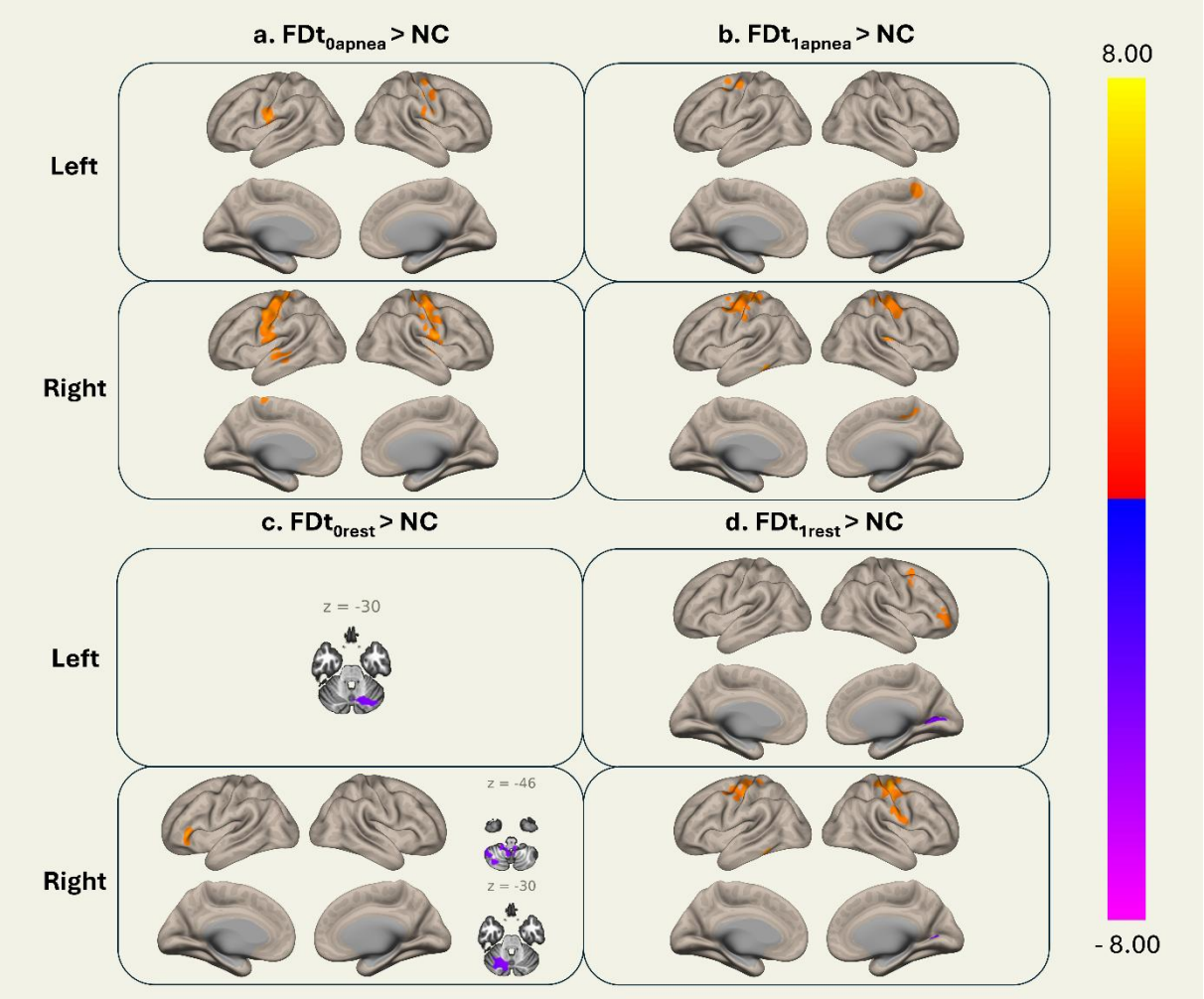


***Figure S1**: Left and right frontal FC differences between conditions (NC versus FD during apnea and rest, before and after training): Seed-to-Voxel analysis using CONN toolbox on MATLAB*, FDR correction applied. 2D slices and 3D view. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. N= 17 FD and 20 NC. FD: Freedivers, NC, Controls.

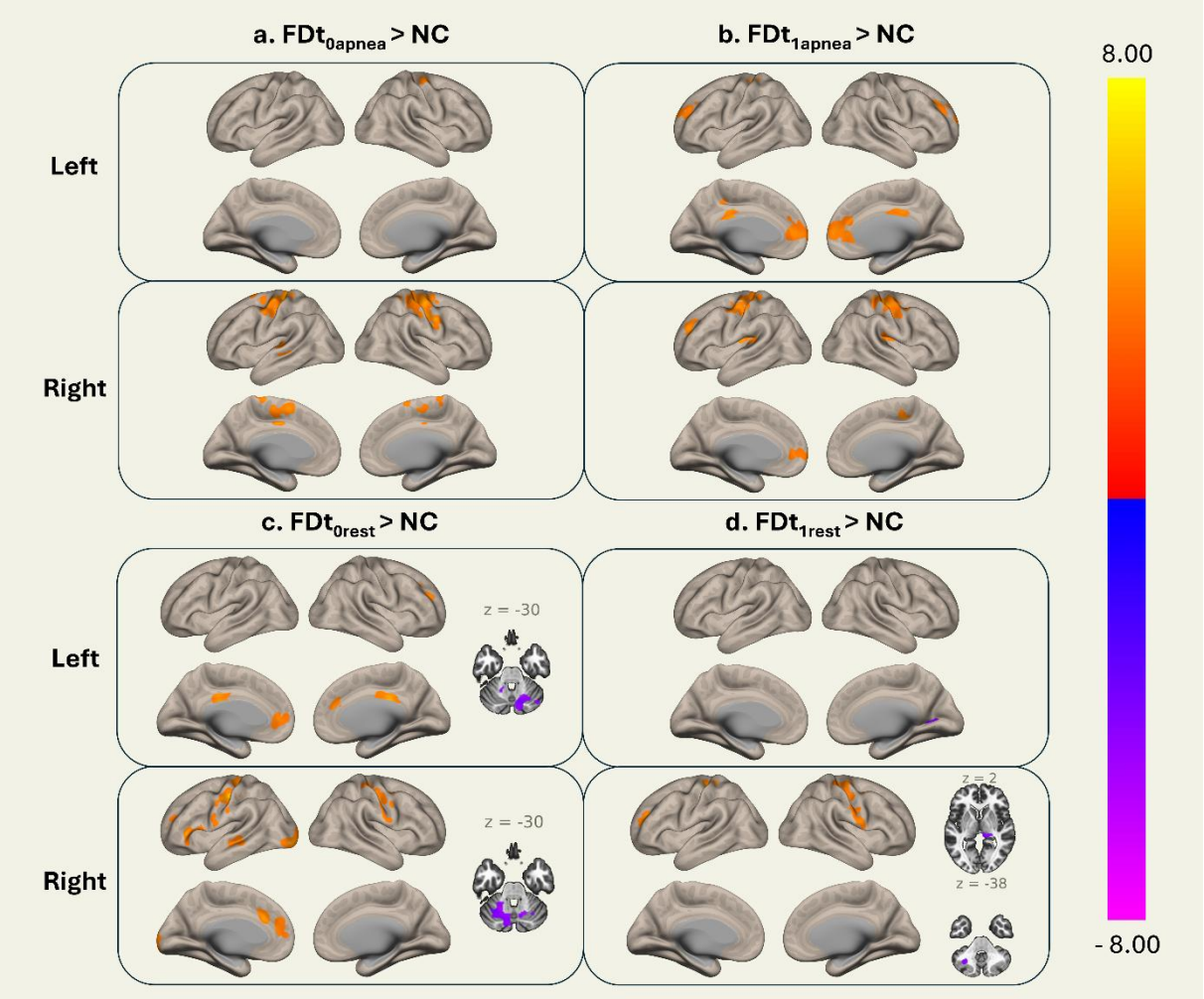


***Figure S4**: Left and right frontoparietal FC differences between conditions (NC versus FD during apnea and rest, before and after training): Seed-to-Voxel analysis using CONN toolbox on MATLAB, FDR correction applied. 2D slices and 3D view. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. N= 17 FD and 20 NC. FD: Freedivers, NC, Controls.*

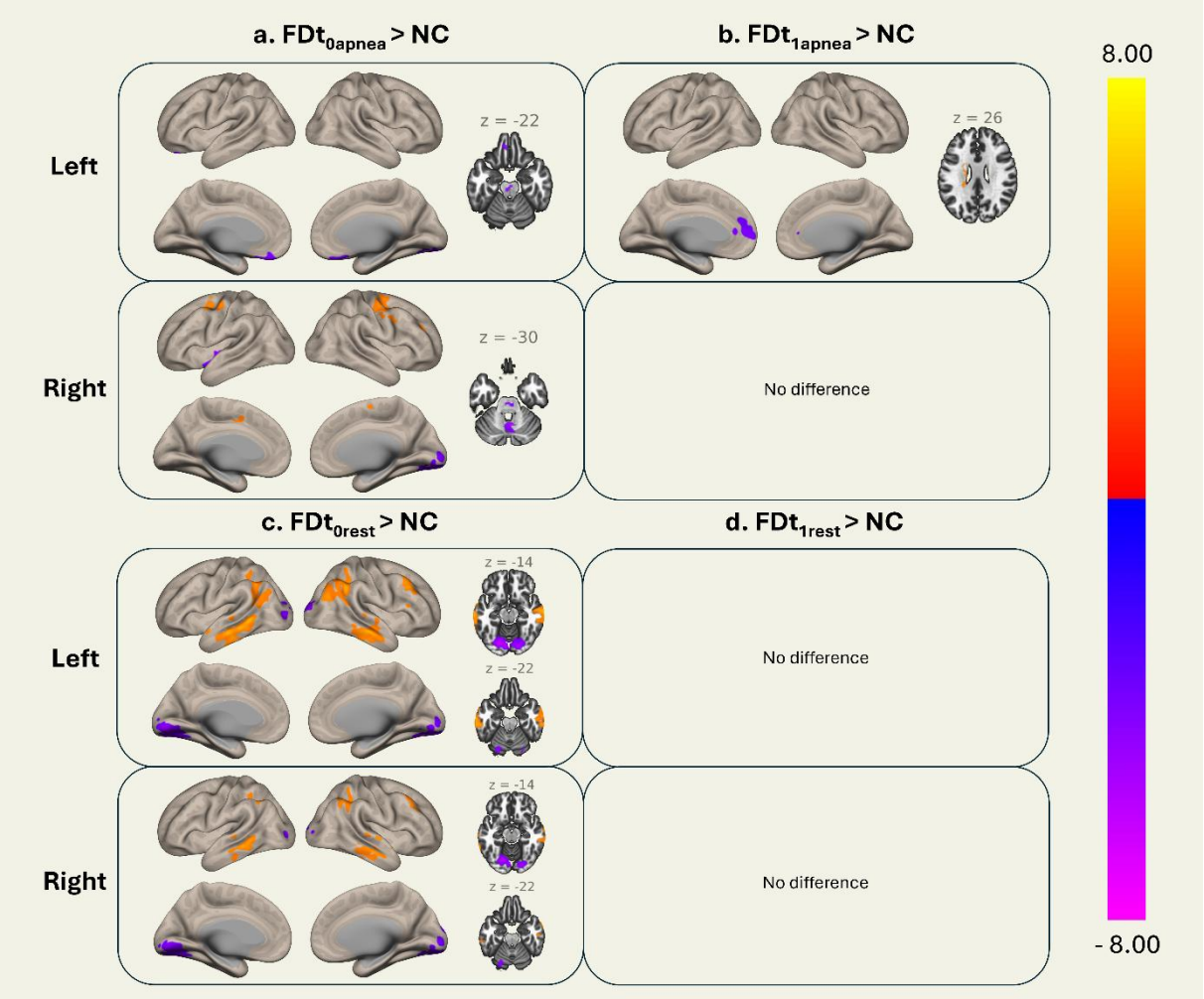


***Figure S5**: Left and right occipital FC differences between conditions (NC versus FD during apnea and rest, before and after training): Seed-to-Voxel analysis using CONN toolbox on MATLAB, FDR correction applied. 2D slices and 3D view. a. FDt_{0apnea} > NC b. FDt_{1apnea} > NC c. FDt_{0rest} > NC d. FDt_{1rest} > NC. N= 17 FD and 20 NC. FD: Freedivers, NC, Controls.*

Conclusion

This study showed that seven months of freediving training induced a selective reorganization of hippocampal functional connectivity. Freedivers exhibited reduced coupling between the hippocampus and DMN and sensorimotor regions, and increased connectivity with cerebellar and visual areas. These changes were absent from controls, indicating that they are not attributable to generic training effects.

Importantly, increase in hippocampo-cerebellar connectivity was associated with better performance on the pattern separation task after training. This suggests that the observed reorganization is functionally relevant, supporting episodic memory resilience under repeated hypoxic stress. Functional connectivity changes align with models of network efficiency, where the brain reallocates resources toward pathways relevant to a certain task, while downregulating connections that are less essential (Barulli and Stern, 2013; Neubauer and Fink, 2009).

Within the context of this thesis, these results are a valuable complement to the anatomical and cognitive findings from the previous chapter. They clearly demonstrate that preserved hippocampal anatomy and memory function in freedivers are accompanied by measurable network-level adaptations, consistent with a model of functional plasticity under metabolic constraint. This supports the central proposition that voluntary, intermittent hypoxia associated with exercise training can promote adaptive reorganization without anatomical damage.

Chapter 4: Discussion

This thesis examined whether seven months of controlled freediving training promotes adaptive rather than degenerative brain changes. We focused on hippocampal anatomy, functional connectivity, and episodic memory, combining multimodal neuroimaging with a behavioral pattern separation task. These are the main results from this unique paradigm:

Anatomical preservation and episodic memory maintenance:

- We observed no evidence of anatomical alteration in the hippocampus. Automatic segmentation of hippocampal subfields with HSF© confirmed stable volumes between pre- and post-training of freedivers, with no significant differences relative to controls (Micaux *et al.*, 2025).
- We also found that episodic memory performance remained stable between pre- and post-training of freedivers, following the same trajectory as the control population. On the pattern separation task, both groups showed higher scores for identical and novel items than for similar lures, with improvements observed after seven months. This indicates preserved memory encoding and discrimination in freedivers, despite repeated hypoxic exposure.

These results demonstrate that voluntary, intermittent hypoxia in the context of freediving does not lead to hippocampal damage or cognitive decline. Instead, it appears to be compatible with stable anatomy and intact hippocampal-dependent memory.

Functional hippocampal reorganization supporting memory resilience:

- We observed a selective reorganization of hippocampal functional connectivity following freediving training. rs-fMRI revealed reduced hippocampal connectivity with DMN and sensorimotor regions, alongside increased connectivity with cerebellar and visual areas (Micaux *et al.*, In Prep). These modifications were absent from controls, indicating that they are not explained by exercise training alone.
- We also showed that the degree of functional change observed was linked to episodic memory performance. Individuals showing greater hippocampal reorganization, particularly increased cerebellar connectivity, performed better on the pattern separation task after exercise training. This reorganization likely supports the maintenance of episodic memory.

These findings suggest that repeated voluntary hypoxia triggers a targeted reallocation of neural resources, rather than a general increase in connectivity (Annen *et al.*, 2021), and that the hippocampus appears to adjust its network configuration in a way that preserves cognitive function under metabolic stress. Most importantly, this association demonstrates that functional plasticity directly supports memory resilience.

Our findings showed that the hippocampus can adapt to voluntary intermittent hypoxia without anatomical damage or memory impairment, and that functional reorganization

appears to support memory resilience. This contrasts with the classical view of hypoxia as being harmful to the brain, particularly to the hippocampus given its high metabolic demand and complex vascularization (Li *et al.*, 2024; Spallazzi *et al.*, 2019). Clinical and environmental evidence from involuntary hypoxia conditions, such as OSA, HIE, and high-altitude exposure, has consistently reported hippocampal atrophy, functional disruption, and episodic memory deficits (Micaux, Troudi Habibi, *et al.*, 2025; Olaithe *et al.*, 2018; Pfister *et al.*, 2023). However, hypoxia is not always detrimental, and its consequences depend on key contextual factors, including hypoxia type, duration, and controllability of exposure. We showed that freediving constitutes a unique model of voluntary intermittent hypoxia, combining repeated breath-holds with structured training and full recovery. Unlike pathological hypoxia, it was intermittent and self-regulated, providing an ecologically valid framework to examine how the hippocampus could adapt to controlled metabolic stress.

The originality of this work's methodology provided the necessary basis to capture and interpret hippocampal adaptations under voluntary intermittent hypoxia.
The longitudinal design represents a central advantage of our study, allowing us to separate transient fluctuations from lasting neural adaptations. This supports the interpretation of hippocampal functional reorganization as a plastic process. In addition, the multimodal design, combining anatomical MRI, rs-fMRI, and a hippocampal-dependent memory task, provided converging evidence across anatomical, functional, and behavioral domains. Our sample reinforces the robustness of the findings: both freedivers and controls were age- and education-matched, had comparable training loads, and showed highly similar performances on global intelligence tasks, ensuring homogeneity and comparability across groups. It is however important to note that participants were exclusively male, which may restrict generalization across sex. Considering reported sex differences in connectivity and hormonal modulation of hypoxic responses (Jung *et al.*, 2020; Takenouchi *et al.*, 2025), future studies should include female participants. Another important step will be to examine clinical populations with cognitive vulnerability (such as individuals with mild cognitive impairment) in order to assess the therapeutic potential of voluntary intermittent hypoxia.

Proposed hippocampal response to hypoxia: HippoXia-Induced Adaptability Model (HiAM)

1. Cognitive reserve theory

Our findings support a central proposition: voluntary intermittent hypoxia, when combined with regular exercise training, can lead to adaptive functional reorganization of brain networks in the absence of anatomical damage. Rather than a diffuse compensation, this reorganization appears selective and strategic, optimizing memory performance. This interpretation echoes the concept of cognitive reserve, first introduced by Stern (2002), who proposed that lifelong plasticity allows the brain to resist stress, aging, and pathology.
Barulli and Stern (2013) refined this theory by distinguishing five central processes of cognitive reserve: efficiency, capacity, compensation, maintenance, and plasticity. Usually

discussed in the context of aging and neurodegeneration, efficiency refers to the optimization of some neural networks, capacity to the ability of networks to maintain performance under higher demand, compensation to the recruitment of alternative pathways when primary routes become insufficient, maintenance to the preservation of network integrity over time, and plasticity to the dynamic reorganization of networks across domains.

More recently, Verkhratsky and Zorec (2024) proposed that cognitive reserve should be seen as an integrative concept, by highlighting the articulation between anatomy (brain reserve) and function (maintenance, resilience, compensation). They underline that these two aspects cannot be completely separated, and cognitive reserve emerges from the interplay between both, with one reinforcing the other.

Within this framework, efficiency is illustrated by the selective reorganization we observed: reduced hippocampal coupling with sensorimotor areas and enhanced connectivity with cerebellar and visual circuits. This form of neuroadaptation aligns with models of network efficiency, in which the brain strategically redistributes and reallocates its functional resources toward task-relevant pathways (Neubauer and Fink, 2009). Compensation is reflected in the recruitment of alternative connections (e.g., cerebellar contributions to memory processes), when established hippocampo-cortical routes might become insufficient under hypoxia. Maintenance and resilience concepts resonate with the protective role of combined exercise training and voluntary hypoxia, which appear to preserve network integrity under repeated stress. Finally, plasticity is shown for example in the flexible reorganization of hippocampal networks to preserve episodic memory.

In our study, the absence of volumetric changes accompanied by preserved hippocampal integrity under intermittent hypoxic exposure may reflect training-induced resilience. In this context, regular exposure to hypoxic stress, when buffered by exercise training, may reinforce cognitive reserve, allowing functional reorganization without anatomical compromise.

2. Voluntary hypoxia through the lens of cognitive reserve

In order to extend the conceptual basis of cognitive reserve to the context of voluntary intermittent hypoxia, we propose the HippoXia-Induced Adaptability Model (HiAM), which integrates multiple levels of hippocampal adaptability into one perspective. It is conceived as a heuristic framework, designed not only to integrate current findings but also to stimulate new hypotheses and open perspectives for future research on each of the proposed factors. As illustrated in Figure 16, this model identifies seven factors, grouped into three main categories. First, neurocognitive factors include the anatomy of hippocampal subfields (volume measures), the functional dynamics of hippocampal networks (resting-state functional connectivity patterns), and cognitive aspects such as episodic memory (pattern separation task) and emotional-motivational processes, which are particularly relevant in the context of freediving practice. Second, neurobiological factors highlight possible adaptations at the cellular and metabolic levels, which could provide a better understanding of plasticity and resilience under hypoxic conditions. Third, physical factors include physiological responses from the body to oxygen deprivation and the effects of exercise training, both of which can modulate hippocampal adaptability. Together, these interconnected domains form the basis

of the model. They support the view that hypoxia-induced plasticity arises from a dynamic interplay between neurocognitive, neurobiological, and physical dimensions.
This thesis specifically focused on the three neurocognitive factors, which will be discussed in detail in light of the experimental results, while the remaining factors are proposed based on existing literature on exercise training and IHT, both of which provide converging mechanisms of adaptation.

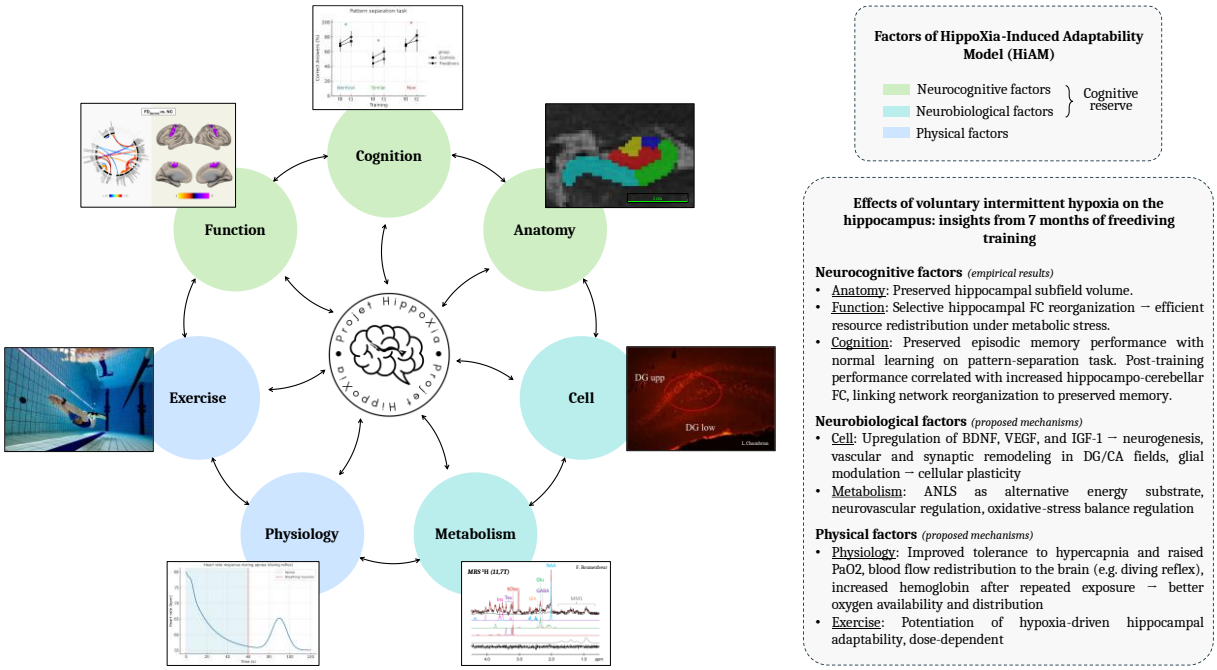


Figure 16: Schematic representation of the HippoXia-Induced Adaptability Model (HiAM). This model is composed of seven factors contributing to hippocampal adaptability under voluntary intermittent hypoxia, and grouped into three categories: neurocognitive factors (anatomy, function and cognition), neurobiological factors (cellular and metabolic adaptations), and physical factors (physiology and exercise training).

2.1 Neurocognitive factors: Main results of experimental contributions

The adaptive response observed in our cohort appears to follow a dual mechanism: anatomical stability combined with functional redistribution. We compared our findings on freediving with established knowledge in two contexts: healthy individuals, and involuntary hypoxia.

2.1.1 Anatomy

Unlike what is typically observed in involuntary hypoxia, we did not find any volumetric changes in hippocampal subfields. Freediving involves a combination of intermittent hypoxia, usually associated with DG atrophy in involuntary contexts, and acute hypoxia, which has been linked to global hippocampal atrophy with a particular vulnerability of CA1 (Figure 8). This contrast is striking, and it is important to highlight that there is growing evidence that low-dose intermittent hypoxia may actually have beneficial effects, which offers a compelling explanation for our results (Bouslama *et al.*, 2015; Damgaard *et al.*, 2023; Navarrete-Opazo and Mitchell, 2014).
In addition, as described above, the absence of anatomical differences does not necessarily imply a lack of underlying plasticity. Macroanatomical stability may mask subtle changes at

the microanatomical level (such as changes in synaptic density, dendritic complexity, or glial modulation) that remain undetectable with 3T MRI. These adaptations have been proposed as essential components of neuroplastic responses to metabolic or cognitive challenges. In this context, our findings should be interpreted cautiously, as volume preservation may coexist with biologically meaningful changes not captured by the tools used.
This anatomical stability could result from compensatory or protective mechanisms at a finer scale, which will be detailed in the next section (neurobiological factors).

It is also possible that our reliance on 3T imaging and automated segmentation limited sensitivity to subtle microanatomical effects. Hippocampal segmentation was performed using a state-of-the-art deep learning tool trained on manual delineations, yet recent assessments underscore inherent limitations of such methods. While deep learning–based segmentation improves reproducibility and efficiency compared to manual approaches, performance still varies across hippocampal subfields, particularly at 3T resolution (Sghirripa *et al.*, 2025). Boundaries with the DG for example remain difficult to delineate precisely, and postmortem comparisons have revealed spatial mismatches in some automated masks (Nirmala *et al.*, 2025). As a result, although our findings suggest no major volumetric alterations, we cannot exclude the possibility that more subtle anatomical changes went undetected due to segmentation imprecision. More sensitive approaches, such as higher field 7T imaging, may be required to detect changes hidden at the current resolution.

2.1.2 Function
Functional connectivity changes were more evident and readily measurable. After repeated exposure to voluntary hypoxia accompanied by a structured training framework, hippocampal connectivity patterns shifted selectively, decreasing links with sensorimotor areas and strengthening those with cerebellar and visual regions. As these changes were significantly correlated with episodic memory performance, this reorganization is coherent with our model presented above, suggesting a strategic redistribution of resources.

To better understand the functional specificity of this reorganization, we compared our results with classic RSN patterns in two contexts: resting state in healthy individuals, and resting state after involuntary hypoxia.

After training, freedivers exhibited decreased hippocampal connectivity with the sensorimotor network, consistent with disengagement from basic interoceptive systems typically active at rest. The DMN also showed reduced coupling with the hippocampus, suggesting a partial deactivation of introspective processes. In contrast, we observed increased connectivity between the hippocampus and cerebellar and visual regions. These shifts indicate a selective reallocation of hippocampal connectivity away from default and sensorimotor systems toward networks that facilitate memory preservation during apnea.

When compared to resting-state alterations typically observed in involuntary hypoxia (Micaux, Troudi Habibi, *et al.*, 2025), our results show both overlaps and divergences. Similar

to involuntary hypoxia, we observed reduced connectivity between the hippocampus and both the DMN and sensorimotor networks. However, unlike the usual hypoconnectivity found in the FPN and attention networks, our findings show increased connectivity in those, suggesting a distinct pattern of adaptation in voluntary hypoxia. Interestingly, the pattern of functional connectivity changes in freedivers appear to combine features of both acute and chronic hypoxia (Micaux, Troudi Habibi, *et al.*, 2025), despite freediving training being primarily an acute exposure. Notably, the case of acute intermittent hypoxia, as in freediving, is rarely represented in literature. In our review, acute hypoxia examples mostly involved continuous exposure (e.g., HIE), while chronic hypoxia included both continuous (e.g., high-altitude living) and intermittent (e.g., OSA) forms. It is therefore not surprising that freedivers show a mixed pattern combining features of both hypoxia types.

Beyond canonical RSNs, the cerebellum also emerged as a key feature of this adaptation. Buckner *et al.* (2011) and Nettekoven *et al.* (2024) demonstrated robust links between lobule VI, Crus I/II (D1 – D3) and memory-related cortical networks, including the MTL. Guell *et al.* (2018) confirms that Crus I and II support three distinct types of cognitive functions, including memory. Fastenrath *et al.* (2022) further showed that the cerebellar vermis emerges as a central hub within the brain network supporting emotional episodic memory. Almeida *et al.* (2023) indeed reported that non-invasive stimulation of right cerebellum enhances episodic memory performance in older adults, with simultaneous increases in connectivity between the cerebellum and memory-related hubs (e.g., the hippocampus). The cerebellum's ability to support such functions is rooted in its sectional and plastic architecture, as shown by D'Angelo *et al.* (2016) demonstrating that cerebellar plasticity allows the microcircuit to adapt and support learning and memory. In pathological contexts, Reumers *et al.* (2025) found that cerebellar disorders induce significant deficits across many cognitive domains, including episodic memory and working memory. Zuo *et al.* (2025) report that functional connectivity between cerebellar subregions (especially lobules IX, Crus I/II, and VI) and basal ganglia or cortical regions strongly correlates with episodic memory performance, highlighting the cerebellum's compensatory role in cognitive recovery after basal ganglia stroke, a role that resonates with our observation of compensatory cerebellar involvement in freedivers. In addition to these clinical findings, Katsumi *et al.* (2023) demonstrated that the functional connectivity gradients of the hippocampus and cerebellum align with those of the cortex, suggesting that both structures share a common organization and share a cooperative role in episodic memory. Altogether, these findings indicate that the cerebellum is not only anatomically connected to the hippocampus, but also capable of dynamic functional engagement and plasticity under physiological challenge.
In our study, enhanced hippocampo-cerebellar connectivity may similarly represent a compensatory, efficiency-driven shift toward circuits capable of maintaining memory encoding under metabolic stress.
These findings suggest that the functional reorganization observed here involves selective and efficient redistribution of hippocampal connectivity, most prominently with cerebellar and sensorimotor areas, which are tightly coupled to metabolic regulation and motor control.

Finally, with respect to cognitive reserve, our longitudinal design confirmed that changes in hippocampo-cerebellar connectivity emerged over time and correlated with memory improvements. Under usual circumstances, baseline cognitive reserve, linked to factors such as education, exercise, or premorbid ability, may still influence individual variability in adaptation (Barulli and Stern, 2013), with some individuals reorganizing more efficiently under metabolic stress than others. However, in our cohort, participants were highly comparable, suggesting that baseline reserve was likely very similar at the start of the protocol.
Taken together, these mechanisms illustrate how hippocampal reorganization can emerge alongside preserved anatomy, and explain the maintenance of episodic memory.

It should be noted that although segmentation was performed at the subfield level, functional connectivity analyses were conducted at the whole-hippocampus scale, and this choice reflects current limitations in subfield-specific functional connectivity mapping at standard 3T resolution. Acquisitions at high-resolution imaging will be required to examine plasticity at a finer scale. Additionally, exploring dynamic functional connectivity could provide more insight. Methods such as sliding-window analysis or time-varying functional connectivity would capture short-term fluctuations across apnea and recovery phases, offering a more granular view of network flexibility.

In addition, group differences in the hemodynamic response function (HRF) may also influence BOLD-based connectivity estimates. Both hypoxia and exercise can alter vascular dynamics, potentially modifying HRF latency or amplitude. Since standard resting-state analysis assumes a stable HRF across participants, group-level vascular differences could generate misleading correlations or mask neuronal effects. Although CONN does not explicitly model such variability, preliminary results from our ongoing work suggest HRF differences between groups, which will be further incorporated into subsequent modeling.

2.1.3 Cognitive factor

Episodic memory

Episodic memory emerged as a central dimension of hippocampal adaptability under voluntary intermittent hypoxia. While anatomical stability suggested preserved cognition, functional reorganization was directly linked to memory performance, particularly through enhanced hippocampo-cerebellar connectivity. Episodic memory provides here a relevant window into hippocampal plasticity, as its integrity closely reflects the efficiency of underlying anatomical and functional processes.

In this context, the pattern separation task used in this work provides a good basis to examine how voluntary intermittent hypoxia shapes episodic memory. By engaging hippocampal subfields sensitive to oxygen deprivation, the task directly challenges the DG and CA3 in their role of minimizing interference between overlapping experiences. Freedivers followed exactly the same performance profile as controls: better accuracy for identical items and lower accuracy for similar ones, and importantly equivalent learning and improvement across

sessions. Such findings reinforce the notion that controlled intermittent hypoxia, when coupled with exercise training, can be integrated into a broader model of positive hippocampal adaptability, linking functional resilience to potential clinical applications.

Because episodic memory is a core function of the hippocampus, we chose to emphasize this cognitive aspect, which helped clarify the adaptation of hippocampal connectivity under metabolic stress, in line with the hippocampus being the structure most vulnerable to hypoxia. Nevertheless, as voluntary hypoxia may also influence executive functions, attention, and emotion regulation (Boulares *et al.*, 2024), future protocols should expand the cognitive assessment to determine whether adaptive effects extend beyond memory.

Motivation and emotional modulation

Apart from the cognitive challenge, freediving has an important emotional and motivational dimension. Holding breath under water for extended periods requires managing strong affective states (such as anxiety, fear, and reward anticipation), linked to the decision to continue or resurface. This likely interacts with hippocampal adaptability, as emotional states are known to modulate memory consolidation processes (du Plessis and Lipinska, 2023). Positive mood, in particular, has been shown to increase brain network flexibility, notably within somatomotor systems, enhancing learning and cognitive adaptability (Betzel *et al.*, 2017). This flexibility could potentially support network reconfiguration under demanding conditions such as apnea. Moreover, task performance modulated by respiration can influence memory-related hippocampal dynamics (Heck *et al.*, 2022; Herrero *et al.*, 2018). Breathing at a specific rhythm, voluntarily slowed or consciously modulated in freediving, may act as an organizer for brain activity and affective regulation, possibly enhancing focus, stress resilience, and interoceptive awareness (Heck *et al.*, 2022; Herrero *et al.*, 2018). The ability to regulate affective states under hypoxia may act as a protective factor against anxiety-related dysregulation. Mechanisms of hypoxia adaptation are increasingly viewed as modifiable systems that interact with stress responses and may promote psychological resilience (Burtscher *et al.*, 2022). The motivational engagement, emotional intensity, and interoceptive demands of freediving could therefore contribute not only to cognitive and behavioral performance, but also to adaptive neural plasticity, particularly within the hippocampus, which is highly sensitive to both hypoxia and affective modulation.

2.2 Neurobiological factors: perspectives

Neurobiological factors refer to the cellular and metabolic processes that support hippocampal adaptation to hypoxia. They represent the biological foundation for the maintenance of episodic memory.

2.2.1 Cellular factors

At the cellular level, BDNF supports neurogenesis (especially in the DG, potentially offsetting neuronal loss) and enhances synaptic plasticity by promoting neuron survival and synapse formation (Miranda *et al.*, 2019). VEGF drives angiogenesis (which ultimately improves oxygen and nutrient delivery) and also contributes to neurogenic and neurotrophic effects

within the hippocampus (Licht *et al.*, 2011). IGF-1 supports both neurogenesis and synaptic plasticity (Nieto-Estévez *et al.*, 2016). Synaptic and dendritic remodeling may contribute to tissue integrity by strengthening local connectivity and improving metabolic efficiency, thereby preserving volume even under cellular stress (Dromard *et al.*, 2021). Finally, glial modulation has recently been recognized as an important contributor to cognitive reserve (Verkhratsky and Zorec, 2024). It enables the brain to adapt to life experience, maintain homeostasis, compensate for lesions and slow cognitive ageing, a perspective particularly relevant in adaptive contexts such as freediving.

Exercise training stimulates the cascades described above of central and peripheral growth factors, including BDNF, IGF-1, and VEGF, which act together to support brain plasticity (Cotman *et al.*, 2007; El-Sayes *et al.*, 2019; Luthra *et al.*, 2025). BDNF plays an essential role in the hippocampus during exercise by enhancing synaptic plasticity, memory consolidation, and functional adaptation. Regular training increases hippocampal neurogenesis, integrating new, highly excitable neurons that contribute to improved learning and episodic memory. In parallel, exercise induces angiogenesis through VEGF upregulation and its interaction with BDNF, leading to improved hippocampal vascularization and cerebral perfusion, possibly also under hypoxic conditions. The hormonal cascade involving growth hormone IGF-1 and VEGF supports cellular growth, neuronal survival, and repair, contributing to cognitive maintenance and neuroprotection. Altogether, these mechanisms illustrate that exercise acts at molecular, anatomical, and functional levels, with potential therapeutic implications.

An example of the interaction between exercise and hypoxia is provided by Żebrowska *et al.* (2020), who showed that moderate exercise under hypoxic conditions significantly increased circulating BDNF and IGF-1, with free IGF-1 remaining elevated up to 24 hours post-exercise in patients with type 1 diabetes. These results identify IGF-1 and BDNF as key molecular mediators of hippocampal adaptations to the combined effects of exercise and hypoxia.

These hypotheses, particularly those related to neurogenesis, will be directly tested in the animal component of the HippoXia project.

2.2.2 Metabolic factors

At the metabolic level, these changes have an effect on energy metabolism and vascular regulation, which reshape brain function under hypoxic conditions.

Among glial cells, astrocytes play a key role in sustaining neuronal metabolism, particularly under moderate hypoxia. Whereas neurons normally depend on oxidative phosphorylation and limited adaptation when oxygen is reduced, astrocytes rely more on glycolysis and can produce lactate, which can be shuttled to neurons as an alternative energy source. This concept, known as the astrocyte–neuron lactate shuttle model (ANLS model), highlights how astrocytes provide both energy and protective signals to neurons when oxygen levels are low (Figure A1 Appendix A p.158) (Magistretti and Allaman, 2018; Rose *et al.*, 2020). Human studies further confirm that astrocytes are not passive support cells but active partners in

maintaining brain energy balance (Pio *et al.*, 2024). In freediving, where exercise is combined with intermittent hypoxia, this astrocytic support likely provides effective protection, ensuring both endurance and stable brain function.
In the HippoXia project, this astrocytic contribution will be further explored using MRS, with a focus on assessing hippocampal metabolite composition (e.g., lactate) both in rats and in humans during apneas (acquisitions already performed during this PhD, in collaboration with F. Boumezbeur).

Regarding the vascular dimension, both exercise training and intermittent hypoxia have been shown to promote neurovascular plasticity and modulate cerebral blood flow, particularly in the hippocampus (Bouten *et al.*, 2020; Palmer *et al.*, 2023). These adaptations improve vascular reactivity and neurovascular coupling, ensuring that neuronal activity is supported by adequate oxygen and substrate supply. Repeated hypoxic exposure may then induce long-term adjustments in these mechanisms, helping to preserve hippocampal function under metabolic stress. Physiological strategies such as the diving reflex also play a role in optimizing oxygen distribution and will be addressed in the following section (Foster and Sheel, 2005). These vascular adjustments can now be quantified directly in humans using ASL, an MRI-based technique that non-invasively measures cerebral perfusion. ASL provides unique insight into how hypoxia and training reshape blood flow regulation in the hippocampus. In our review on ASL and hypoxia (Appendix B p.159, Troudi Habibi *et al.*, In Press), we show that this technique captures both acute compensatory hyperperfusion during transient hypoxia and long-term vascular remodeling under chronic exposure, offering sensitive biomarkers of neurovascular adaptation under metabolic stress. In this study, our fMRI analyses did not explicitly correct for vascular confounds such as perfusion changes or hemodynamic transit time, and vascular contributions to the observed functional changes cannot be ruled out. Ongoing ASL analyses within this cohort will therefore help determine whether changes in cerebral perfusion accompany the functional reorganization.

Finally, oxidative stress balance, another important metabolic factor, represents the equilibrium between reactive oxygen/nitrogen species (ROS/RNS) and antioxidant defenses of the body, aimed at preventing molecular damage. Under hypoxic conditions, both acute and prolonged exposures increase ROS production and disturb redox homeostasis, an effect particularly pronounced in hypobaric hypoxia and at high hypoxic doses. When combined with exercise, the response becomes dependent on the intensity: high-intensity exercise amplifies hypoxia-induced oxidative stress, whereas moderate exercise training stimulates antioxidant capacity and can attenuate the redox imbalance associated with altitude exposure (Debevec *et al.*, 2017).

2.3. Physiological and training factors

Physiological and training factors concern how the body responds to hypoxia and how exercise training can influence hippocampal adaptation.

2.3.1 Physiological

Partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) are key determinants of blood gas homeostasis. PaO_2 reflects the oxygen content available for tissue delivery, whereas $PaCO_2$ is a proxy of ventilatory efficiency and directly influences pH. Cerebral autoregulation refers to the ability of brain vessels to maintain a relatively stable blood flow despite changes in blood pressure, ensuring consistent oxygen supply to neural tissue (Willie *et al.*, 2014).

At the respiratory level, hypoxic exposure increases ventilation, which elevates PaO_2 and reduces $PaCO_2$. Over time, trained freedivers also develop greater tolerance to hypercapnia, allowing them to sustain longer apneas while limiting low cerebral oxygenation (Kyriakoulis, 2024). These ventilatory adjustments form the first line of defense against hypoxia, and have a direct impact on blood gas composition.

Cardiovascular and cerebrovascular mechanisms provide a complementary layer of adaptation, and the diving reflex provides a clear example of a vascular-metabolic strategy to cope with hypoxia. Its primary function is oxygen conservation, and it manifests as bradycardia, intense peripheral vasoconstriction, and a redistribution of blood flow toward the brain and the heart, reducing oxygen consumption in non-essential tissues and slowing arterial desaturation. In freedivers training regularly, repeated exposure enhances this reflex and is accompanied by additional adaptations, including splenic contraction that can increase circulating hemoglobin and lower oxidative stress after apneas. These changes illustrate how a reflex initially designed for short-term survival can, via training and repeated exposure, evolve into a reinforced mechanism that optimizes oxygen use and supports prolonged tolerance to hypoxia (Foster and Sheel, 2005). In addition to this reflex, autonomic regulation of heart rate and blood pressure becomes more flexible, while cerebrovascular vasodilation and autoregulation adjust regional perfusion according to fluctuations in PaO_2 and $PaCO_2$. Such mechanisms directly protect brain oxygenation, particularly in structures like the hippocampus that are highly sensitive to hypoxia.

Finally, hematological responses act on a slower timescale by increasing hemoglobin concentration after repeated hypoxic exposure (Kyriakoulis, 2024). These adjustments improve blood capacity to transport oxygen and provide an additional reserve that complements ventilatory and vascular adaptations. In sum, respiratory, cardiovascular, cerebrovascular, and hematological responses compensate with immediate adjustments in ventilation and circulation, which are progressively reinforced by longer-term changes in blood composition.

A strength of our study is that unlike hypoxic protocols in hypobaric chambers, where oxygen can be reduced while CO_2 remains constant, freediving combines progressive hypoxemia with rising CO_2, making it a more physiologically relevant challenge to cerebrovascular regulation. However, although heart rate was recorded with a finger pulse oximeter during MRI, the functional analyses did not systematically exploit this signal to assess variability. Incorporating continuous HRV measures, alongside SpO_2 and $PaCO_2$, would provide a clearer picture of both the hypoxic and hypercapnic loads. Linking such physiological markers to neural plasticity would help specify the contribution of systemic responses to the observed functional changes. Accordingly, future studies should integrate longitudinal neuroimaging

with real-time physiological monitoring to better characterize the dose–response profile of voluntary hypoxia.

2.3.2 Exercise training

Exercise training also influences hippocampal adaptability, across multiple levels. At the neurobiological scale, it stimulates neurogenesis, angiogenesis, and metabolic regulation, supported by trophic factors including BDNF, IGF-1, and growth hormones described above. At the anatomical and functional scales, training has been consistently associated with increases in hippocampal volume and with strengthened connectivity, particularly demonstrated by rs-fMRI studies. At the cognitive level, these adaptations are illustrated by improvements in episodic memory and motivational processes. In the context of freediving, those mechanisms are likely to act in synergy, potentially amplifying hippocampal adaptability.

We compared our neurocognitive findings with established knowledge in the contexts of exercise training, and athletes under involuntary hypoxia. This comparative framework allows us to disentangle which features reflect general adaptations and which define the specific adaptive profile of freedivers.

Anatomical adaptations and memory maintenance

Exercise has been reported to induce adaptations similar to the ones hypothesized as responsible for the maintenance of hippocampal subfields volume. In fact, regular exercise training has been repeatedly associated with hippocampal remodeling, particularly through neurogenesis in the DG and angiogenesis across the whole hippocampal formation (Ben-Zeev *et al.*, 2022). These processes improve metabolic support and circuit integration, compensating stress-related atrophy (Buenrostro-Jáuregui *et al.*, 2025). At the macroscopic level, exercise training has been associated with measurable increases in hippocampal subfield volumes, cortical thickness, and perfusion, particularly within the DG and CA1 (Erickson *et al.*, 2011; Farmand *et al.*, 2025; Firth *et al.*, 2018). However, these anatomical changes appear to depend on the duration and continuity of the intervention. In the meta-analysis by Firth *et al.* (2018), positive effects of aerobic exercise on hippocampal volume, notably in the left hemisphere, were mostly reported in studies lasting 6 to 24 months, with no significant effect found in shorter interventions. Erickson *et al.* (2011) reported a significant hippocampal volume increase after 12 months of aerobic training, with the first detectable gains emerging after approximately 6 months. In a different temporal profile, Farmand *et al.* (2025) reported temporary increases after only 6 weeks of training in young adults, which later returned to baseline, highlighting both the early plasticity and reversibility of these effects. In our study, despite a 7-month training period, falling within the range of interventions where effects have previously been observed, no volumetric changes were detected across hippocampal subfields. This absence of macroscopic variation does not exclude concurrent microanatomical, vascular, or functional adaptations, which may either precede volume changes or occur independently. Importantly, exercise training can trigger early vascular adaptations that may precede detectable anatomical changes (Palmer *et al.*,

2023). Together, these findings reinforce the notion that anatomical stability in our cohort does not exclude plasticity at a smaller scale, and that exercise training provides a relevant comparative model for understanding how such adaptations can occur without obvious volumetric differences.

Exercise combined with involuntary hypoxia presents a contrasting picture. Previous work consistently showed that involuntary hypoxia has deleterious effects on hippocampal anatomy and memory, with CA1 and DG being particularly vulnerable, and episodic memory impairments aligning with these anatomical alterations. In this context, exercise training emerges as a potential compensatory factor. Animal studies indicate that post-hypoxic training can reverse or attenuate hippocampal damage: voluntary wheel running mitigated spatial memory deficits induced by chronic intermittent hypoxia (Gozal *et al.*, 2010); acrobatic training following cerebral hypoperfusion restored hippocampal integrity and object recognition memory (de Almeida *et al.*, 2021); and exercise training promoted greater neuronal survival under chronic hypoxia (Martini *et al.*, 2022). Human studies similarly suggest protective effects: higher cardiorespiratory fitness correlated with preserved hippocampal volume in long-term high-altitude residents (Wang *et al.*, 2022), and aerobic exercise prior to hypoxic exposure prevented cognitive impairment in a young population (Chroboczek *et al.*, 2023). Even under acute normobaric hypoxia, submaximal exercise improved verbal working memory compared to rest (Seo *et al.*, 2017). However, this compensating role of exercise is not uniform: simultaneous and uncontrolled exposure, particularly at high intensity, may exacerbate anatomical decline and cognitive deficits. Moderating factors include hypoxia type (acute, chronic, intermittent, continuous), training intensity, timing relative to hypoxic exposure, and baseline fitness (Jung *et al.*, 2020). Overall, findings converge on a dose-dependent duality where exercise training can either mitigate or aggravate hypoxia-induced hippocampal damage and memory impairment.

Functional reorganization

The functional connectivity changes we observed align with findings from sports neuroscience, where trained individuals often show more focused and less redundant neural activation patterns (Li and Smith, 2021). While typically documented in motor or executive domains, our results suggest that similar mechanisms may apply to memory systems under metabolic constraint. We compared our results with classic RSN patterns in sport contexts: resting state in athletic population, and resting state after voluntary hypoxic training. To our knowledge, no study has yet assessed the effect of involuntary hypoxia on functional connectivity at rest in athletic populations. Nevertheless, this comparative framework aims at clarifying the uniqueness of the adaptation seen in freedivers.

Consistent with our hypothesis, our findings show strong convergence with RSN patterns reported in athletes. Increased connectivity within the FPN and DAN mirrors enhancements commonly seen in trained individuals, supporting improved executive and attentional functions. Similarly, stronger SN engagement aligns with the heightened interoceptive and alertness processes described in athletes. The reduced connectivity with the DMN is also

consistent with its relative deactivation during task-preparation states. In contrast, the hippocampal decoupling from the sensorimotor network differs from typical athlete profiles, possibly reflecting a unique aspect of freediving training.
Additionally, the RSN configuration we observed is highly consistent with previous findings in athletes exposed to voluntary hypoxia, as in the study of Annen *et al.* (2021) on freedivers. The same pattern, reduced default and sensorimotor connectivity alongside increased coupling with salience, executive, and attention networks, has been linked to adaptive neural strategies supporting cognitive efficiency.

These comparisons reveal that the profile observed in our cohort does not simply reflect resting-state dynamics, involuntary hypoxia, or exercise. Instead, it matches a specific reorganization pattern found only in voluntary intermittent hypoxia with exercise training, a condition specific to freediving, where both provides a dual adaptability stimulus, with exercise potentially amplifying the neurobiological mechanisms triggered by hypoxia.

Training load
Training load is another important factor to assess. It refers to the stress imposed on an athlete during practice and can be explained by two complementary dimensions: external load, which represents the amount of work performed (e.g., volume, distance, accelerations, lifted weight), and internal load, which reflects the individual's physiological and psychological responses to that work (e.g., heart rate, perceived exertion, biomarkers). Common monitoring tools include heart rate analysis, the session rating of perceived exertion (RPE), questionnaires, and physiological markers. The current literature highlights that the most reliable approach involves combining multiple indicators to capture both the external constraints applied and the internal response of the organism (Macedo *et al.*, 2024).
In our cohort, freedivers trained regularly over seven months, combining aerobic and anaerobic exercise. Since training load likely interacted with the hypoxic component to support reorganization, both its internal and external dimensions were assessed. Internal load was monitored via RPE and biological markers, while external load was standardized by providing all participants with identical swimming pool sessions (same distances, same apneas, and the same recovery intervals).

However, although training was uniform for the whole cohort and functional reorganization was already detectable, the moderate training dose (5 hours per week over 7 months) may not be sufficient to elicit subfield-level anatomical changes comparable to those observed after long-term pathological exposures.

2.4. The hippocampus as a functional sensor of hypoxic stress

Traditionally considered vulnerable to hypoxia, the hippocampus may instead function as a sensitive sensor capable of adaptive reconfiguration under metabolic challenge. In our study, repeated voluntary hypoxia did not alter hippocampal volume but led to selective redistribution of its functional connectivity. These changes were linked to memory

performance, suggesting that hippocampal functional connectivity may serve as a biomarker of strategic plasticity.

In the context of freediving, hypoxia consists of brief intentional apneas with recovery phases, a pattern that minimizes cumulative damage by allowing metabolic readjustment. Repeated over months, this exposure may act as a mild physiological stressor sufficient to trigger plasticity without inducing pathology. This interpretation aligns with preclinical dose–response models, which show that low to moderate hypoxic loads promote neurogenesis, angiogenesis, and synaptic remodeling, whereas excessive hypoxia leads to atrophy and cognitive impairment (Boulares *et al.*, 2024; Navarrete-Opazo and Mitchell, 2014). Our findings therefore occupy an intermediate position between deprivation and stimulation, which may explain why functional reorganization occurred in the absence of atrophy. Supporting this view, voluntary diving in rats has been shown to enhance hippocampus-dependent learning after 60 days of training (Hartantyo *et al.*, 2020). In humans, McKeown *et al.* (2025) showed that the cognitive effects of hypoxia were less pronounced during intermittent or hypobaric exposures. This attenuation was especially evident in executive and psychomotor tasks, and in studies involving repeated short exposures or moderate altitudes. These patterns suggest that such conditions engage adaptive mechanisms which can help maintain cognitive performance despite reduced oxygen availability. However, memory performance, and especially episodic memory, remains significantly impaired across conditions, likely reflecting the high vulnerability of the hippocampus to oxygen deprivation. Clinical longitudinal data also inform us on how hippocampal networks adapt after direct anatomical damage: Fleury *et al.* (2025) showed that in patients with anterior temporal lobe resection, long-term cognitive recovery was accompanied by progressive reorganization of hippocampal functional connectivity, including the strengthening of alternative pathways such as with the cerebellum. Huang *et al.* (2023) demonstrated that six months of CPAP therapy in sleep apnea patients partially restored hippocampal connectivity and improved cognitive outcomes. Finally, Won *et al.* (2024) found that in healthy individuals, hippocampal connectivity mediated the relationship between cardiorespiratory fitness and memory performance, indicating that exercise training and metabolic factors jointly shape memory-related networks.

Altogether, these findings position hippocampal functional connectivity as a dynamic and sensitive index of brain adaptation. In our cohort, its reorganization in the absence of anatomical decline suggests that functional remapping may precede or underlie behavioral stability. This strengthens its potential role as a biomarker for monitoring cerebral responses to controlled hypoxia.

Our ongoing analyses, including hippocampal perfusion (ASL) and spectroscopy (MRS), will allow further investigation into the vascular and metabolic mechanisms supporting this adaptation, and help define a more comprehensive model.

Potential therapeutic use of voluntary hypoxia?

Beyond its experimental implications, our findings suggest that structured voluntary intermittent hypoxia could hold clinical potential as a neuroprotective or cognitive-enhancing

approach. As seen above, and while preliminary, this hypothesis is supported by growing evidence that mild hypoxic exposure, especially when paired with exercise training, may trigger beneficial brain adaptations in humans (Boulares *et al.*, 2024; Damgaard *et al.*, 2023).

Preclinical research has highlighted several candidate mechanisms. Repeated hypoxic exposure has been associated with improved neurovascular plasticity, enhanced efficiency of cerebral metabolism, and adaptive changes in large-scale brain networks (Damgaard *et al.*, 2023; Millet *et al.*, 2010). Intermittent hypoxia has also been shown to promote vascular remodeling and support synaptic plasticity, adaptations particularly relevant in aging or neurodegenerative contexts (Baillieul *et al.*, 2017).

In this context, freedivers represent a unique human natural model of long-term adaptation to controlled, non-pathological hypoxic stress. Building on this paradigm, structured IHT protocols have been proposed as a clinical strategy. IHT typically combines short, regulated hypoxic episodes associated with exercise training and full recovery, closely mimicking the physiological conditions of freediving.
Although clinical implementation is still too early, our data supports the idea that carefully calibrated IHT protocols may facilitate cognitive resilience. Further research should assess how parameters like intensity, duration, and recovery influence outcomes. Neuroimaging tools such as hippocampal perfusion (ASL) and metabolism (MRS) could guide personalized monitoring and optimization.
Importantly, clinical application must proceed with caution. Not all forms of hypoxia are beneficial, and the threshold between adaptive and harmful responses remains narrow. However, under controlled conditions, voluntary hypoxic training may provide a novel means to enhance brain resilience and preserve cognitive function.

Conclusion

This thesis provides experimental evidence that the human hippocampus is not inevitably damaged by hypoxia, but can adapt to voluntary, intermittent exposure combined with exercise training. Our results converge across anatomical, functional, and cognitive levels, to show preserved hippocampal anatomy, stable episodic memory, and a strategic reorganization of hippocampal functional connectivity that supports resilience under metabolic stress.

We propose here the HippoXia-Induced Adaptability Model (HiAM), which positions the hippocampus as a sensitive adaptive hub. Rather than passively suffering from oxygen deprivation, this structure is capable of reallocating its network resources toward task-relevant circuits to maintain episodic memory performance. Our model integrates cognitive reserve theory with emerging concepts of neural efficiency, reframing hypoxia not as inherently harmful, but as a potential trigger for strategic plasticity.

These findings provide a foundation for future research, highlighting specific factors that will refine its mechanisms and boundaries. Additionally, while clinical applications remain exploratory, our data supports further investigation for translating this paradigm into controlled interventional protocols, where carefully calibrated hypoxic exposure may serve as a potential tool to enhance hippocampal resilience. Freediving thus emerges as more than an extreme sport. It offers a natural model of cerebral adaptation that invites us to rethink how the brain responds to extreme physiological demands: not merely as a vulnerable structure, but as a system capable of optimizing itself.

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Appendices

A. Brain metabolism in normoxia and hypoxia

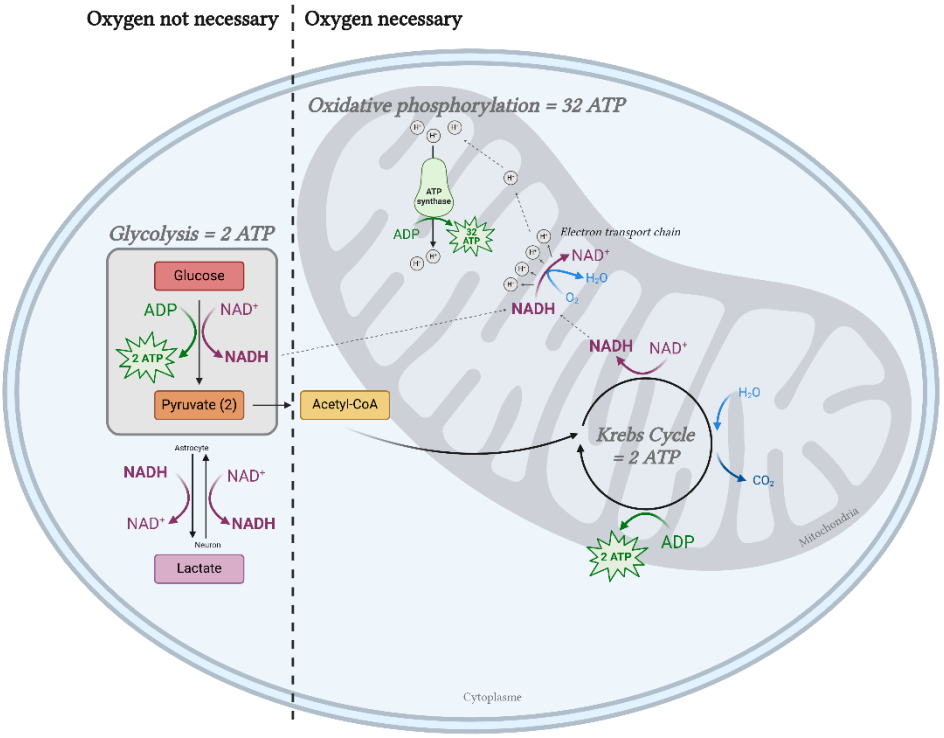


Figure A1: Energy production in the brain and ANLS Model: Under physiological conditions, neurons primarily rely on oxidative phosphorylation for ATP production, while astrocytes favor aerobic glycolysis, generating lactate that can be transferred to neurons. In the presence of oxygen (normoxia or moderate hypoxia), astrocyte-derived lactate is converted into pyruvate in neurons, fueling the Krebs cycle and oxidative phosphorylation, which allows efficient ATP production (rigth). In the absence of oxygen (severe hypoxia or anoxia), neurons can no longer use the Krebs cycle or oxidative phosphorylation, and glycolysis becomes their only source of ATP (left). Pyruvate is then reduced to lactate to regenerate of NAD^+, which is essential to sustain glycolysis. In this context, lactate may act as a signaling molecule for plasticity, and remains an immediately available substrate upon O_2 return.

B. ASL and involuntary hypoxia

Cerebrovascular Autoregulation in Hypoxia: Quantitative Insights from Arterial Spin Labeling

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This review provides a synthesis of how ASL has been applied to characterize cerebrovascular adaptation to hypoxia, detailing changes in cerebral blood flow and vascular regulation. ASL provides non-invasive, quantitative measures of perfusion and derived parameters such as arterial transit time, cerebrovascular reactivity, and oxygen metabolism. Across environmental and pathological contexts, it captures both acute compensatory hyperperfusion and long-term vascular remodeling, positioning ASL as a sensitive biomarker of neurovascular adaptation and dysfunction.

Within this thesis, this review serves as the rationale for including ASL next to anatomical MRI, and rs-fMRI. ASL data were collected but are not yet analyzed, representing a direction for future work. The review highlights how this technique can directly quantify hypoxia-induced perfusion changes in the hippocampus and opens a future perspective to assess the vascular component of hippocampal adaptation in voluntary hypoxia.

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EDITED BY
Johannes Boltze,
University of Warwick, United Kingdom

REVIEWED BY
Sabyasachi Dash,
AstraZeneca, United States
Spencer Waddle,
Philips, Netherlands

*CORRESPONDENCE
Marion Noulhiane
✉ marion.noulhiane@cea.fr
Abir Troudi Habibi
✉ abirtroudi1995@gmail.com

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Cerebrovascular autoregulation in hypoxia: quantitative insights from arterial spin labeling

Abir Troudi Habibi[1,2]*, Julia Micaux[1,2], Franck Mauconduit[3] and Marion Noulhiane[1,2]*

[1]Joliot Institute, University of Paris-Saclay, CEA, NeuroSpin, UNIACT, Gif-sur-Yvette, France, [2]University of Paris Cite, Inserm, U1141 NeuroDiderot, InDev Team, Paris, France, [3]CEA, NeuroSpin, CNRS, University of Paris-Saclay, Gif-sur-Yvette, France

Hypoxia, defined as an insufficient oxygen supply relative to metabolic demand, induces a cascade of cerebrovascular and metabolic responses aimed at preserving cerebral homeostasis. These responses vary depending on the temporal profile of exposure, with acute (e.g., hypoxic–ischemic encephalopathy, acute high-altitude exposure) versus chronic (e.g., obstructive sleep apnea, long-term altitude residence) conditions, and may range from compensatory vasodilation to long-term maladaptive remodeling. Arterial Spin Labeling (ASL) MRI offers a quantitative, non-invasive, and contrast-free method to assess cerebral perfusion, making it well-suited to characterize the spatial and temporal dynamics of these responses. This narrative review critically examines the application of ASL to quantify key hemodynamic parameters, including cerebral blood flow (CBF), arterial transit time (ATT), cerebrovascular reactivity (CVR), and, when integrated with complementary models, cerebral metabolic rate of oxygen consumption ($CMRO_2$), in the context of hypoxia. By synthesizing evidence from both environmental and pathological models induced by hypoxia, we highlight how ASL captures early signatures of cerebrovascular adaptation, impaired autoregulation, and emerging neurovascular dysfunction. Particular emphasis is placed on the potential of ASL-derived metrics to serve as early biomarkers for hypoxia-induced risk, enabling non-invasive longitudinal tracking of vascular integrity in both clinical and subclinical populations. Overall, ASL emerges as a powerful modality for elucidating the mechanisms of neurovascular adaptation to hypoxia and for supporting precision diagnostics in disorders where oxygen insufficiency constitutes a key pathophysiological driver.

KEYWORDS

perfusion MRI, ASL, CBF, hypoxia, cerebrovascular autoregulation

1 Introduction

Hypoxia, defined as an insufficient supply of oxygen to meet tissue metabolic demands, represents a fundamental physiological challenge for the brain, the organ with the highest oxygen consumption per unit mass. While hypoxia can arise as a gradual, chronic exposure or as an acute, transient episode, both scenarios act as aggressive etiological stressors on a brain initially functioning within homeostatic limits. In response, the brain mobilizes a series of tightly regulated compensatory mechanisms, such as cerebrovascular autoregulation, vasodilation, and metabolic adaptation, to preserve oxygen delivery and maintain neural viability (Mallat et al., 2022).

Arterial Spin Labeling (ASL) MRI has emerged as a powerful neuroimaging technique for investigating cerebral perfusion in both physiological and pathological states of hypoxia. By magnetically labeling arterial blood water as an endogenous tracer, ASL

provides a non-invasive, contrast-free, and quantitative assessment of cerebral blood flow (CBF) in absolute units (mL/100 g/min), with high regional specificity (Wang et al., 2002; Taso and Alsop, 2024; Wong and Maller, 2016). Importantly, beyond static measures of flow, ASL allows estimation of arterial transit time (ATT) and cerebrovascular reactivity (CVR), parameters that reflect vascular efficiency, reserve capacity, and autoregulatory integrity. These derived metrics enrich our understanding of the brain's dynamic vascular responses to hypoxia, including changes in the cerebral metabolic rate of oxygen ($CMRO_2$), which further illuminate the interplay between supply and demand under oxygen-limited conditions.

Originally developed for neurovascular and oncological applications such as neurodegeneration and tumor imaging (Noguchi et al., 2008; Troudi et al., 2023; Troudi et al., 2022), dementia (Grade et al., 2015), ASL has gained traction in conditions involving altered oxygen availability. In obstructive sleep apnea (OSA; Harris et al., 2013), chronic mountain sickness (Ainslie and Subudhi, 2014), and high-altitude adaptation, ASL studies consistently report perfusion changes in regions governing autonomic regulation, memory, and executive function. These findings support the idea that hypoxia induces region-specific cerebrovascular alterations that may precede overt structural damage. Furthermore, metrics such as prolonged ATT or reduced CVR have been linked to impaired vascular reserve and cognitive vulnerability in aging and small vessel disease (Dai et al., 2017; Neumann et al., 2022), underscoring clinically relevant biomarkers for hypoxia-induced neurovascular dysfunction.

Despite growing interest in ASL under hypoxic conditions, several key questions remain unresolved: How does cerebral autoregulation evolve during the transition from acute to chronic hypoxia? Can ASL detect early biomarkers of maladaptive vascular remodeling or incipient neurocognitive decline? What distinguishes *adaptive* from *pathological* perfusion responses at the regional level? most clinical imaging protocols still overlook subtle or dynamic cerebrovascular changes that occur in the absence of gross structural abnormalities, a gap that ASL, with its sensitivity to early hemodynamic shifts in structurally intact brain systems, may help bridge.

This narrative review synthesizes current evidence on the use of ASL to investigate the brain's vascular responses to hypoxia, both environmental and pathological. We focus on:

- The physiological basis of cerebrovascular responses to hypoxia and their detectability via ASL;
- The differential impact of acute vs. chronic hypoxia on CBF and related perfusion metrics;
- The potential of ASL-derived parameters (CBF, ATT, CVR, and $CMRO_2$) as biomarkers of cerebrovascular dysfunction;
- The translational implications of ASL in clinical diagnosis, risk stratification, and longitudinal monitoring in hypoxia-related brain disorders.

By consolidating findings across models, this review underscores ASL's unique ability to capture both early compensatory responses and later-stage perfusion deficits, offering a window into neurovascular vulnerability and resilience before irreversible damage occurs.

2 An overview of ASL perfusion imaging

2.1 Principles of ASL

ASL is a non-invasive MRI technique that measures cerebral perfusion using magnetically labeled arterial blood water as an endogenous tracer (Kwong et al., 1995). Labeling is achieved by applying a radiofrequency (RF) pulse upstream from the imaging volume, which inverts the magnetization of inflowing arterial blood. After a post-labeling delay (PLD), the labeled blood reaches the brain tissue and exchanges with tissue water, generating a signal change proportional to CBF (Figure 1; Williams et al., 1992). The standard ASL acquisition alternates between two conditions: *Label image*: arterial blood is inverted, leading to reduced tissue signal. *Control image*: no inversion is applied, serving as a baseline. By subtracting the label from the control image, a perfusion-weighted image (PWI) is obtained, isolating the signal difference related to tissue perfusion (Noguchi et al., 2008; Suzuki et al., 2024). This subtraction method

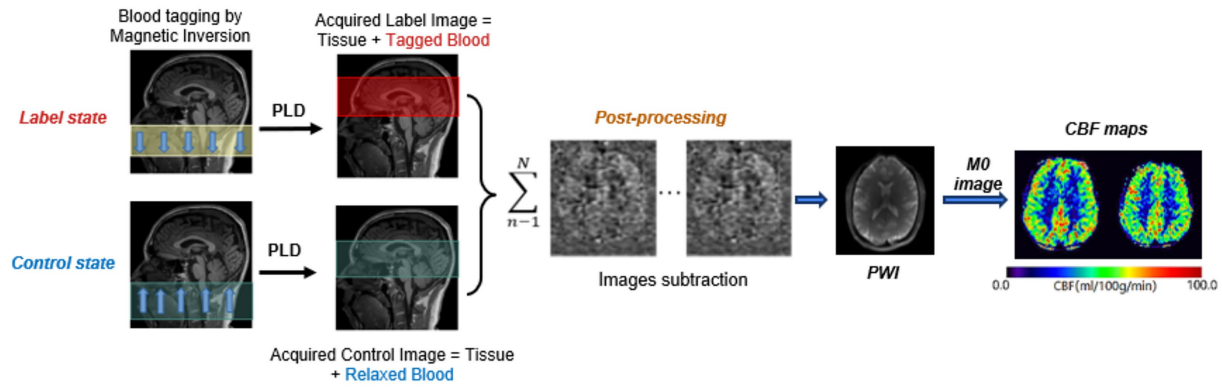


FIGURE 1
Illustration of the fundamental concept of ASL and subsequent image processing. PLD, post-labeling delay; PWI, perfusion weighted image; CBF, cerebral blood flow.

reduces static tissue contributions, enhancing sensitivity to flow-related changes.

Several ASL techniques exist, differing in labeling strategy, sequence design, and sensitivity to physiological conditions (Figure 2; Table 1):

- Pulsed ASL (PASL) uses short RF pulses to label a large arterial region, offering a simple and rapid acquisition. However, it typically produces a lower SNR and may be more sensitive to arterial transit time effects compared to continuous or pseudo-continuous ASL techniques (Golay et al., 2004).
- Continuous ASL (CASL), introduced by Williams et al. (1992), applies a long RF pulse (2–4 s) for sustained labeling, yielding higher signal but requiring hardware capable of handling prolonged RF exposure (Detre et al., 1992; Williams et al., 1992; Detre and Alsop, 1999; Wang et al., 2002).
- Pseudo-continuous ASL (pCASL) mimics CASL using rapid short pulses, offering high efficiency with lower specific absorption rate, and is now the clinical standard (Alsop et al., 2015; Suzuki et al., 2024; Dai et al., 2008).
- Multi-delay ASL (MDASL) acquires multiple PLDs, enabling better modeling of transit delays and more accurate CBF quantification, though with increased acquisition time and complexity (Ishida, 2023; Woods et al., 2024).
- Velocity-selective ASL (VSASL) tags blood based on velocity rather than location, improving sensitivity to slow-flow regions and enhancing microvascular assessments (Qin et al., 2022).
- Vessel-encoded ASL (VE-ASL) targets specific arteries to map territorial perfusion, valuable for studying vascular territories in stroke or malformations (Wong, 2007).

Despite its advantages, ASL perfusion MRI is highly sensitive to motion artifacts, susceptibility effects, partial volume errors, and low signal-to-noise ratio (SNR), all of which can hinder accurate CBF quantification. Motion artifacts cause geometric distortions and signal mismatches between the control and label images, and can be minimized using correction techniques, such as motion tracking or flow-triggered acquisitions, though patient cooperation remains essential (De Vis et al., 2014; Lu et al., 2012). Susceptibility artifacts, resulting from magnetic field inhomogeneities near tissue-air interfaces, can be reduced using techniques like VSASL or advanced post-processing algorithms such as Iterative Self-consistent Parallel Imaging Reconstruction (SPIRiT; Fan et al., 2021; Su et al., 2017; Inoue et al., 2014). Labeling efficiency and partial volume effects also impact CBF accuracy, with three-dimensional acquisitions helping to reduce these errors, albeit at the cost of longer scan times (McMorris et al., 2017; Hernandez-Garcia et al., 2022). Finally, the inherently low SNR of ASL, exacerbated by physiological and subtraction noise, can be improved through optimized acquisition protocols and digital filtering, ultimately enhancing measurement reliability (Grade et al., 2015).

2.2 Beyond CBF: ASL-derived physiological metrics

While CBF remains the core metric derived from ASL, other parameters accessible through tailored acquisition schemes or physiological challenges provide valuable insights into cerebrovascular health and adaptive capacity. These include arterial transit time (ATT), cerebrovascular reactivity (CVR), and cerebral metabolic rate of oxygen consumption ($CMRO_2$). These metrics expand the interpretive scope of ASL beyond perfusion alone, offering a more comprehensive view of brain hemodynamics and metabolism, particularly relevant in the context of hypoxic exposures (Table 2).

ATT is required for magnetically labeled blood to travel from the tagging plane to the tissue of interest. It reflects not only macrovascular transit but also microvascular flow resistance and collateral circulation status. ATT prolongation has been reported in conditions involving impaired vascular reserve, such as aging,

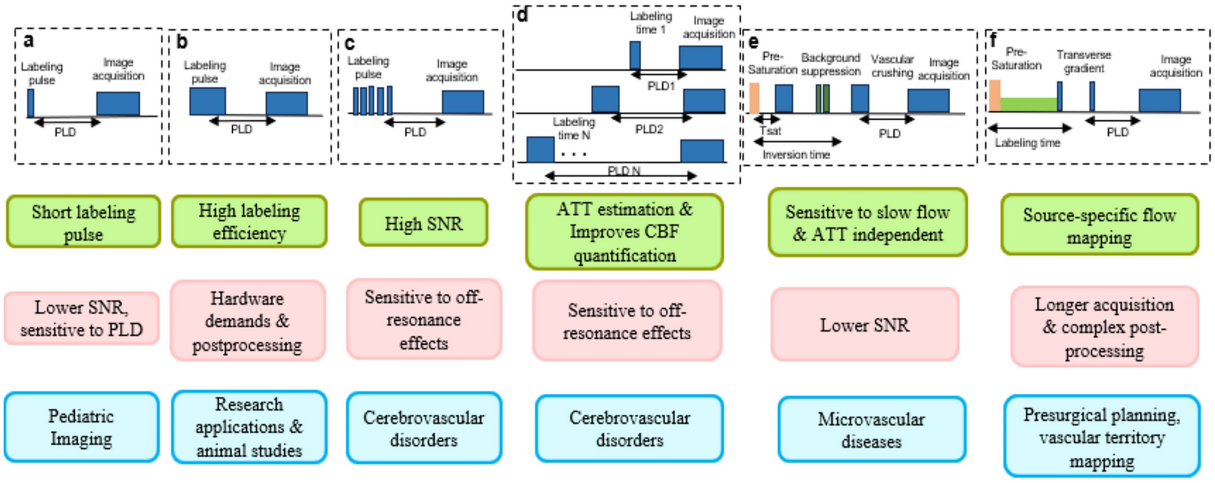


FIGURE 2
Arterial spin labeling techniques. PLD, post-labeling delay; **(a)** Pulsed ASL; **(b)** Continuous ASL; **(c)** Pseudo-Continuous ASL; **(d)** Multi-delay ASL; **(e)** Velocity selective ASL; **(f)** Vessel-encoded ASL. Green panels represent the Pros; Pink panels represent the Cons; blue panels represent the applications.

TABLE 1 Comparative summary of ASL techniques: advantages, limitations, and common applications.

Labeling technique	Advantages	Limitations	Applications
PASL	Short labeling pulse, no RF power deposition issues	Lower SNR, sensitive to PLD	Pediatric Imaging
CASL	High labeling efficiency	High RF power deposition, hardware demands	Research applications, animal studies
pCASL	High SNR, clinically recommended by ISMRM	Sensitive to off-resonance effects	Routine perfusion imaging, cerebrovascular disorders
Multi-delay ASL	Estimates ATT, improves CBF quantification	Longer acquisition	Chronic cerebrovascular disease, CVR studies
VSASL	Sensitive to slow flow, ATT-independent	Lower SNR	White matter perfusion, microvascular disease
VE-ASL	Source-specific flow mapping	Longer acquisition, complex post-processing	Pre-surgical planning, vascular territory mapping

PASL, pulsed ASL; CASL, Continuous ASL; pCASL, pseudo-Continuous ASL; VSASL, Velocity selective ASL; VE-ASL, Vessel-encoded ASL; PLD, post labeling delay; RF, radiofrequency; CBF, cerebral blood flow; ATT, arterial transit time; CVR, cerebrovascular reactivity.

TABLE 2 Summary of derived metrics from ASL data.

Metric	Definition	Main application
Cerebral blood flow (CBF)	Volume of blood supplied to the brain per unit time (mL/100 g/min)	Assessing cerebral perfusion, important in hypoxia and pathology
Arterial transit time (ATT)	Time taken for labeled blood to reach the imaging region	Optimizing post-labeling delay (PLD), assessing cerebrovascular reactivity
Oxygen extraction fraction (OEF)	Fraction of oxygen extracted by brain tissue	Evaluating cerebral hypoxia, metabolic dysfunction, and tissue viability in stroke
Cerebral metabolic rate of oxygen (CMRO2)	The rate of oxygen consumption by the brain	Robust indicator of tissue viability in acute stroke and other conditions.
Cerebrovascular reactivity (CVR)	Cerebral vascular response to vasoactive challenges (e.g., hypercapnia, breath-holding)	Diagnosing chronic vascular diseases, predicting stroke risk

cerebrovascular disease, and obstructive sleep apnea (Ishida, 2023; Woods et al., 2024; Li and Wang, 2023; Chen et al., 2012; Dai et al., 2017). Multi-delay ASL (MDASL) protocols are typically used to estimate ATT by acquiring signals at several PLDs, enabling robust modeling of the arrival time and separating it from true flow effects.

CVR measures the dynamic capacity of cerebral vessels to dilate or constrict in response to a vasoactive stimulus, such as CO_2 inhalation or breath-hold. ASL-based CVR mapping has been validated against BOLD-fMRI and PET techniques, and holds potential for detecting early dysfunction in neurovascular coupling. Reduced CVR may indicate compromised endothelial function, early vascular stiffness, or neuroinflammatory processes, particularly in chronic hypoxic conditions such as OSA or high-altitude exposure (Marshall et al., 2014; Solis-Barquero et al., 2021; Inoue et al., 2014). While CVR is not routinely measured in clinical ASL protocols, its incorporation is growing in advanced research settings due to its relevance in early diagnosis and intervention monitoring.

$CMRO_2$, the cerebral metabolic rate of oxygen consumption, provides a critical bridge between perfusion and metabolism. Although ASL does not directly measure $CMRO_2$, it can be estimated when ASL is combined with sequences that assess venous oxygenation, such as TRUST (T_2-Relaxation-Under-Spin-Tagging) or phase contrast MRI (Rodgers et al., 2015, 2016). These approaches exploit the Fick principle to estimate oxygen extraction fraction (OEF) and calculate $CMRO_2$ as the product of OEF and CBF. $CMRO_2$ mapping is particularly valuable in hypoxia, where perfusion increases may not always translate to metabolic sufficiency. For example, preserved or elevated CBF with reduced $CMRO_2$ may indicate luxury perfusion, while mismatched coupling could reflect tissue vulnerability or compensation failure (Jiang and Lu, 2022; De Vis et al., 2014; Lu et al., 2012; Hernandez-Garcia et al., 2022).

Taken together, these derived metrics position ASL as a multidimensional imaging technique capable of quantifying not only blood flow but also vascular timing, reactivity, and oxygen metabolism. This makes ASL particularly relevant for investigating hypoxia-induced neurovascular adaptations and dysfunctions across diverse contexts, from transient high-altitude exposure to chronic diseases like sleep apnea or cerebral small vessel disease.

3 ASL in environmental hypoxia

Hypoxia encountered in environmental contexts, such as high-altitude exposure or controlled experimental hypoxia, presents a valuable model for studying adaptive cerebrovascular responses in the

absence of overt brain pathology. This section discusses the use of ASL to investigate acute and chronic forms of environmental hypoxia, emphasizing individual variability, metabolic compensation, and longitudinal vascular adaptation.

3.1 Acute environmental hypoxia

Acute exposure to hypoxia, whether in hypobaric chambers or sudden ascent to high altitudes, elicits rapid physiological adaptations in the brain to preserve oxygen delivery. ASL has been instrumental in revealing interindividual differences in these early responses, particularly through the mapping of CBF and derived indices, such as ATT and CVR.

In anoxic brain injury, ASL measurements have consistently reported globally enhanced CBF compared to controls. Notably, regions with increased diffusion signals also exhibit hyperperfusion, suggesting compensatory vasodilation in response to oxygen deprivation (Li et al., 2020). The loss of cerebrovascular autoregulation in these patients results in excessive CBF (mean gray matter CBF 142.6 mL/100 g/min), which may reflect a protective mechanism but also poses risks of edema and secondary injury (Pollock et al., 2008).

Across various forms of acute hypoxia, CBF increases are accompanied by alterations in the blood oxygenation index, suggesting a compensatory response to maintain oxygen delivery despite reduced oxygen availability (average SpO2 of 83.4%; Harris et al., 2013). This cerebrovascular response is particularly pronounced in regions involved in sensory processing, motor control, and cognitive functions, indicating that these areas are more sensitive to hypoxic stress and require greater perfusion to sustain their activity.

Similarly, ASL studies in high-altitude exposure show increased regional CBF, particularly in frontal and sensorimotor cortices, areas involved in cognition and motor control (Pagani et al., 2011; Buck et al., 1998). These adaptations reflect the brain's attempt to maintain oxygen delivery despite reduced atmospheric pressure. Ventilatory and hematological compensations (e.g., hyperventilation, elevated hemoglobin levels) act synergistically to stabilize oxygen supply over time (Wang et al., 2018). In healthy subjects, this hyperperfusion correlates with elevated metabolic demand, reflected by increased $CMRO_2$ during initial hypoxic exposure (Dyer et al., 2008).

However, this balance is delicate. Studies indicate that CBF regulation may prioritize oxygen delivery over avoiding hyperperfusion, highlighting a flexible but imperfect adaptation strategy. For instance, under conflicting physiological demands, the brain may favor oxygen supply at the cost of higher perfusion pressure (Curtelin et al., 2018). This trade-off questions the reliability of using CBF alone as a proxy for cerebrovascular health during hypoxic stress.

Recent advances underscore the importance of integrating CBF, CVR, and $CMRO_2$ to capture the full spectrum of cerebrovascular adaptation. A multimodal MRI study by Deckers et al. (2022) combining ASL with venous oximetry showed that hypercapnia significantly increased CBF but reduced $CMRO_2$ when using CO_2 in air, challenging the assumption that such vasodilatory stimuli are metabolically inert. In contrast, carbogen ($CO_2 + O_2$) maintained $CMRO_2$ levels, suggesting that the addition of oxygen may buffer the metabolic consequences of vasodilation. These findings reveal that CVR and CBF changes can be decoupled from metabolic demand, and that measuring $CMRO_2$ is crucial for interpreting the physiological significance of perfusion alterations in hypoxia.

Furthermore, a recent systematic review emphasized that CVR is not a consistent predictor of CBF responses under hypoxia, pointing to distinct underlying mechanisms compared to hypercapnia-induced reactivity (Johnson et al., 2025). These insights challenge conventional interpretations of CVR and highlight the need for a multi-parametric approach to cerebrovascular assessment.

In contrast to hyperperfused states, mild hypoxia in pilots flying at high altitudes without supplemental oxygen presents a subtler yet concerning picture. Liu et al. (2021) reported decreased CBF in the right temporal, occipital, and cerebellar regions, areas critical for sensory integration, visuospatial processing, and motor coordination. This regional hypoperfusion, even before overt hypoxia symptoms, could impair reaction time, judgment, and flight safety. These findings raise operational concerns about subclinical cognitive deficits during prolonged exposure to mild hypoxia.

Taken together, these studies underscore the necessity of a dynamic, integrative framework, considering CBF, CVR, and $CMRO_2$, to understand environmental acute cerebrovascular responses to hypoxia. Such an approach provides a more physiologically grounded interpretation of ASL data and supports the development of robust biomarkers for monitoring cerebral resilience and vulnerability under environmental stress.

3.2 Chronic environmental hypoxia

Chronic exposure to environmental hypoxia, such as that experienced by high-altitude residents or through repeated hypoxic training such as in freediving (Micaux et al., 2025), induces long-term cerebrovascular adaptations that involve both vascular remodeling and metabolic reprogramming. Among the most consistently observed phenomena is the modulation of CBF and ATT, together providing a window into the evolving cerebrovascular status of the brain under sustained hypoxic stress.

Reductions in CBF are frequently reported during prolonged hypoxic exposure, especially in regions associated with the default mode network (DMN). Lawley et al. (2017) demonstrated that even short-term normobaric hypoxia (2–10 h) can lead to decreased perfusion in DMN hubs, an effect amplified over time and confirmed by hypercapnic challenges to be driven by vasoconstriction. This response may reflect a functional downregulation of resting-state activity under hypoxia, serving as an early indicator of cerebral adaptation. ATT, another crucial marker, may also be altered during chronic hypoxia. While some studies suggest a lengthening of ATT due to vascular rarefaction and reduced perfusion pressure, others report region-specific reductions in ATT driven by compensatory vasodilation and angiogenesis. The equation CBF = CBV / MTT (mean transit time), with ATT as a proxy for MTT in ASL protocols, illustrates how shifts in vessel diameter and volume dynamically impact cerebral hemodynamics. CO_2 accumulation, common in scenarios such as breath-holding, further modulates this relationship by acting as a potent vasodilator, simultaneously increasing cerebral blood volume and reducing ATT, thus amplifying CBF despite lowered oxygen availability (Keil et al., 2018).

Moreover, in chronic high-altitude conditions, inter-individual and ethnic variability in cerebrovascular responses becomes pronounced. For instance, Tibetans exhibit a 17% reduction in global CBF and a 22% increase in cerebrovascular resistance, in contrast to Han individuals who show more preserved CBF (Liu et al., 2016). Regionally, increased CBF has been observed in areas such as the inferior frontal gyrus and lentiform nucleus, possibly reflecting compensatory redistribution (Wang et al., 2018).

Additionally, animal models offer mechanistic insight into these adaptations. A murine study mimicking 5,000 m altitude exposure showed decreased hippocampal CBF, ventricular dilation, and white matter injury, alongside molecular evidence of neurovascular remodeling and myelin disruption (Cramer et al., 2019). Rats chronically exposed to 4,250 m similarly developed spatial memory impairments and hippocampal abnormalities that co-occurred with regional perfusion changes (Zhu et al., 2022).

Also, simulated microgravity studies using head-down tilt bed rest combined with elevated CO_2 (HDT + CO_2) have revealed differential CBF trajectories in individuals who developed spaceflight-associated neuro-ocular syndrome (SANS) compared to those who did not. While SANS participants showed an early drop in CBF followed by partial recovery, non-SANS individuals remained hypoperfused over 29 days, suggesting that chronic hypoxic and hypercapnic exposure unmask inter-individual differences in cerebrovascular regulation (Roberts et al., 2021).

These complex patterns underscore the inadequacy of considering CBF alone when evaluating cerebrovascular adaptation. Studies integrating hypercapnic reactivity and $CMRO_2$ measurements have shown that while some regions may exhibit increased perfusion, they do not always correspond to increased metabolic demand (Willie et al., 2014; Willie et al., 2015). Such dissociations highlight the importance of also quantifying ATT, CVR, and OEF to obtain a comprehensive understanding of neurovascular function.

Ultimately, the chronic hypoxia-induced modulation of CBF and ATT offers critical insights into the brain's capacity to recalibrate perfusion strategies over time. These parameters not only reflect the current state of vascular function but may also predict long-term consequences such as cognitive decline or structural degeneration. Their combined evaluation through multimodal neuroimaging approaches, incorporating ASL, venous oximetry, and diffusion tensor imaging, should be prioritized in future studies to better interpret the dynamic cerebrovascular responses and vulnerabilities associated with sustained environmental hypoxia (Figure 3; Table 2).

Key insights: ASL in environmental hypoxia

- Acute hypoxia triggers region-specific increases in CBF as a compensatory mechanism, particularly in sensory, motor, and cognitive regions.
- This hyperperfusion may not always align with metabolic demand, emphasizing the need to jointly assess CBF, CVR, and $CMRO_2$.
- Chronic environmental hypoxia leads to the region- and ethnicity-dependent cerebrovascular remodeling, involving both vascular (CBF, ATT) and metabolic ($CMRO_2$, OEF) adaptations.
- Multimodal ASL studies reveal that traditional CVR markers may not fully capture the dynamic cerebrovascular responses to environmental hypoxic stress.

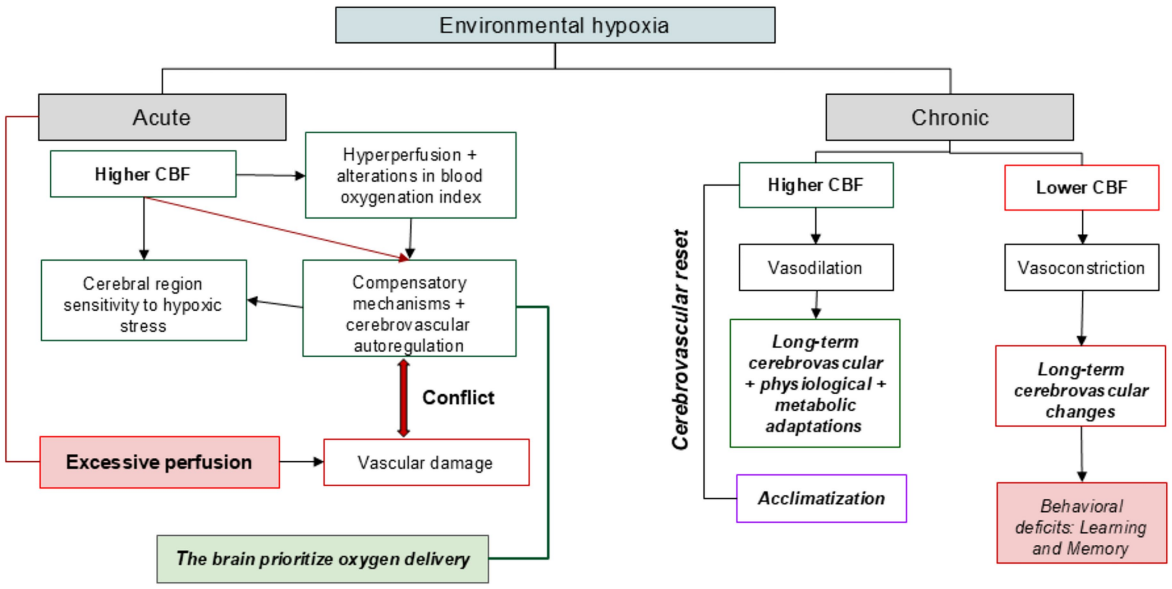


FIGURE 3
The brain's vascular responses to environmental hypoxia under acute and chronic conditions. The color coding highlights the nature of each physiological process: Green: Positive adaptive responses or compensatory mechanisms that support cerebral oxygen delivery or neurovascular regulation (e.g., increased CBF, autoregulation). Red: Maladaptive responses or negative outcomes (e.g., excessive perfusion, vascular damage, behavioral deficits). Blue: Long-term adaptive changes involving cerebrovascular, physiological, and metabolic adjustments under chronic hypoxia. Purple: Acclimatization processes reflecting a specific type of long-term adaptation to hypoxic environments.

4 Hypoxia-induced pathological conditions

4.1 Acute hypoxia: pathophysiological insights from ASL

Acute hypoxia, as experienced in high-altitude exposure or perinatal asphyxia, elicits rapid cerebrovascular adaptations aiming to preserve oxygen delivery to metabolically active regions. This section explores the utility of ASL in two pathological contexts of acute hypoxia: high-altitude illness and HIE in neonates. It aims to determine (i) whether ASL-derived CBF metrics distinguish between vulnerable and resilient phenotypes, (ii) how CBF evolves dynamically with exposure duration, and (iii) whether ASL can capture compensatory or maladaptive responses contributing to neurological outcomes.

With increased human activity at high altitudes, AMS, and its severe form, high-altitude cerebral edema (HACE), have become prominent neurological syndromes (Lafuente et al., 2016). ASL studies have revealed potential predictive biomarkers of AMS, particularly through resting-state perfusion patterns at sea level. In a recent large-scale study, Zhang et al. (2024) demonstrated sex-specific predictors: men with higher cortical CBF, notably in the posterior circulation (e.g., right posterior cerebral artery), were more likely to develop AMS, while women exhibited a predictive asymmetry in anterior cerebral artery perfusion. These findings suggest that baseline CBF may reflect an individual's vulnerability to AMS, although the mechanistic underpinnings remain unclear. Importantly, ASL also detects regional flow differences not captured by EEG or pulse oximetry, reinforcing its complementary diagnostic role (Feddersen et al., 2015). Also, AMS presents significant cerebrovascular challenges as demonstrated by Dyer et al. (2008). Despite no notable differences in oxygen saturation (SaO2) between AMS-susceptible (AMS-S) and AMS-resistant (AMS-R) individuals (87 ± 4% vs. 89 ± 3%, respectively), both groups exhibited increased whole-brain CBF during hypoxia.

Despite global increases in CBF during acute hypoxia, regional differences have not reliably distinguished AMS-S from resistant individuals. Liu et al. (2017) showed similar increases in both gray and white matter CBF between groups. However, magnetic resonance angiography indicated that individuals who developed AMS exhibited greater perfusion in large anterior vascular territories, suggesting that elevated flow in major arteries may relate to AMS symptoms, possibly through altered pressure gradients or venous outflow resistance. In parallel, CVR to CO_2 decreased significantly post-exposure, pointing to impaired vasodilatory capacity. These findings challenge earlier assumptions that linked AMS exclusively to hypoxia severity or oxygen saturation, instead highlighting the nuanced interplay between flow regulation and vascular reserve capacity.

The dynamics of CBF during and after high-altitude exposure reflect the transition from acute adaptation to long-term acclimatization. Initially, hypoxia-driven vasodilation predominates, leading to transient arterial enlargement despite hypocapnia-induced vasoconstriction. Over time, as ventilatory adaptation normalizes oxygenation, both CBF and artery diameters return toward sea-level baselines. Notably, Liu et al. (2023) reported a prolonged decline in regional CBF post-return, particularly in regions linked to neurocognitive symptoms. This decline correlated with elevated blood pressure, suggesting an interaction between systemic and cerebral hemodynamics (Liu et al., 2023). This post-hypoxic hypoperfusion raises concerns about long-term effects on brain function, emphasizing the need to monitor delayed cerebrovascular changes even after apparent acclimatization.

To better understand metabolic demand, Smith et al. (2013) assessed cerebral $CMRO_2$ and found increased values after 2 days at 3800 m, regardless of AMS status. This elevation may reflect heightened neural excitability due to reduced CO_2 from hyperventilation, but it does not appear to distinguish between affected and unaffected individuals. Consequently, while $CMRO_2$ increases are a general feature of acute hypoxia, they may not directly drive AMS development (Smith et al., 2013).

A critical yet understudied mechanism in AMS progression to HACE is venous compression. Using MRI over 22 h of high-altitude exposure, Sagoo et al. (2017) documented a progressive increase in white matter volume, correlated with AMS severity, and linked to restricted venous drainage in deep cerebral veins. This study underscores the contribution of venous outflow resistance to cerebral edema, a dimension not captured by arterial-focused metrics such as CBF alone (Sagoo et al., 2017).

ASL imaging reveals that high-altitude exposure triggers complex, regionally variable cerebrovascular responses. While elevated CBF is common, it does not reliably differentiate AMS risk. Instead, vulnerability appears linked to large-artery perfusion patterns, impaired CVR, and, potentially, venous drainage inefficiencies. The trajectory from hyperperfusion to post-exposure hypoperfusion, modulated by systemic factors such as blood pressure, suggests persistent brain vulnerability.

Furthermore, neonatal HIE represents another archetypal model of acute hypoxia with dynamic CBF changes caused by a lack of oxygen and/or blood flow to the brain around the time of birth. It represents a major cause of neonatal morbidity and mortality and is associated with long-term neurodevelopmental impairments (Greco et al., 2020).

ASL has revealed a characteristic evolution: an initial hypoperfusion phase (within 24 h), followed by compensatory hyperperfusion (days 1–3), and then region-specific persistence or normalization over the subacute period (days 4–28). These transitions reflect impaired autoregulation and vascular remodeling (Tang et al., 2019). The phase of hypoperfusion is followed by a period of compensatory hyperperfusion between days 1 and 3, where CBF rises markedly in most brain regions, excluding the frontal lobe, likely due to reactive vasodilation and blood flow redistribution toward metabolically vital deep structures (Tang et al., 2019; Wang et al., 2022; Meng et al., 2021). During the subsequent subacute stage (days 4 to 11), elevated CBF persists in selective areas, particularly the basal ganglia and temporal lobes, indicating ongoing vascular adaptation or delayed injury evolution (Proisy et al., 2019). From day 7 onward, and particularly between 15 to 28, studies report normalization of CBF across most brain regions, suggesting partial recovery of cerebral oxygenation and perfusion response to therapeutic interventions (Tang et al., 2019; Wang et al., 2022; Meng et al., 2021; Proisy et al., 2019).

Also, infants with severe HIE demonstrate the highest perfusion levels in the basal ganglia and thalamus, followed by those with moderate and mild injury. These deep regions are especially

susceptible to hypoxic damage, and early CBF elevations, quantified using ASL, correlate with the degree of functional impairment, providing objective, visual indicators of injury severity and prognosis (Zheng et al., 2021b; Wang et al., 2021; Ji et al., 2023). Hypoperfusion in vital structures like the brainstem, cerebellum, and deep nuclei has been associated with poor neurodevelopmental scores (Bayley-III < 80), while hyperperfusion in these same regions correlates with more favorable outcomes (Zheng et al., 2020).

Beyond group-level findings, ASL holds strong prognostic potential. Studies report high diagnostic accuracy (AUC 0.97–0.99) when combining CBF metrics in deep structures with behavioral scores like NBNA (Liu et al., 2023). Moreover, ASL can detect perfusion changes even in HIE infants with normal conventional MRI, especially in regions linked to motor and language development (e.g., caudate, precentral gyrus; Cao et al., 2022).

Finally, sex-specific differences further refine interpretation: thalamic perfusion tends to be lower in male neonates, potentially contributing to higher vulnerability (Zheng et al., 2021a).

ASL provides a dynamic and sensitive biomarker of evolving brain perfusion in neonatal HIE. By characterizing the spatiotemporal trajectory of CBF, ASL helps distinguish between reversible versus progressive injury and predicts neurodevelopmental outcomes with high reliability (Figure 4).

4.1.1 Chronic hypoxia in obstructive sleep apnea

OSA is characterized by recurrent upper airway obstruction during sleep, resulting in cycles of hypoxia and reoxygenation. These cycles can induce vascular oxidative stress, endothelial dysfunction, and impaired cerebral autoregulation (Claassen et al., 2021).

ASL studies have demonstrated both global and regional hypoperfusion in OSA patients, particularly those with moderate to severe disease (Chen et al., 2017). These reductions are frequently localized to functionally critical brain areas, including the corticospinal tracts, superior cerebellar peduncles, pontocerebellar fibers, thalamus, hippocampus, and insula, many of which are involved in motor control, arousal, and sensorimotor integration (Yadav et al., 2013). The asymmetrical nature of these impairments, such as lateralized hypoperfusion in the cerebellar peduncles, red nucleus, and midbrain, suggests localized vulnerability of motor coordination circuits, which may underlie the disordered synchrony between upper airway and diaphragmatic muscles characteristic of OSA.

Furthermore, perfusion deficits extend to cortical networks implicated in higher cognitive function. Decreased CBF has been observed in the DMN and central executive network (CEN), including the posterior cingulate cortex, dorsolateral parietal cortex, lateral prefrontal cortex, and inferior temporal lobes. These regions have been repeatedly linked to executive dysfunction, attention deficits, and memory impairments in OSA patients. Notably, CBF in memory-related areas such as the bilateral inferior temporal and left lingual gyri correlates positively with performance on delayed memory and attention tasks, suggesting a perfusion-based mechanism underlying cognitive decline (Nie et al., 2017; Yan et al., 2024). Moreover, hypoperfusion in deep gray matter structures, particularly the thalamus, caudate nucleus, and parahippocampal gyri, further implicates disrupted subcortical processing in the pathogenesis of neurobehavioral deficits (Yan et al., 2021).

Importantly, these perfusion abnormalities appear to be disease-severity dependent. While individuals with mild OSA often exhibit no significant differences in CBF compared to healthy controls, moderate to severe OSA is associated with extensive and consistent reductions in regional perfusion, particularly in areas already known to undergo structural degeneration (Innes et al., 2015). In some cases, such as the superior frontal gyrus, increased CBF has also been reported and shown to correlate with the longest apnea duration, possibly reflecting maladaptive or compensatory vasodilatory responses.

Compounding these changes, OSA patients demonstrate impaired CVR, especially in white matter, as evidenced by blunted CBF responses to hypercapnic challenges. This vascular

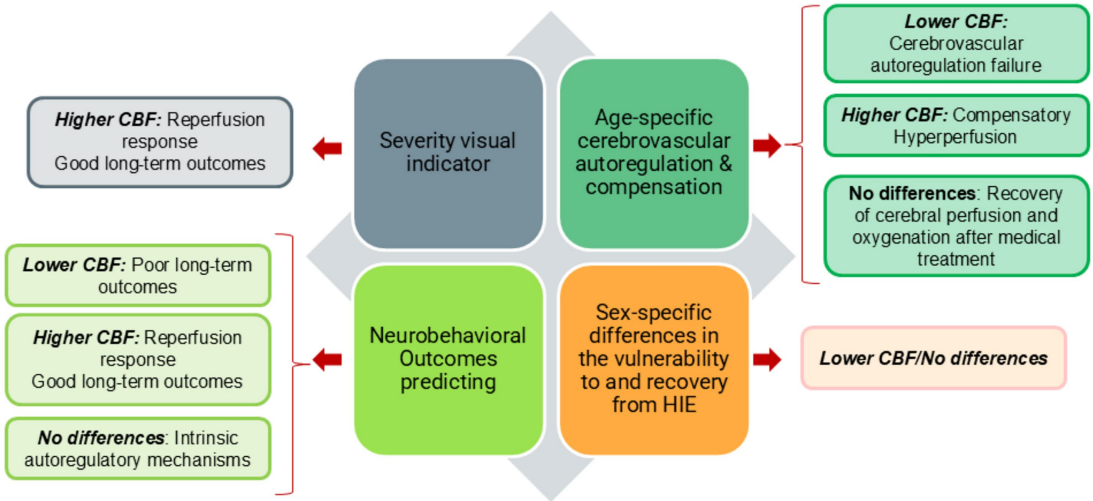


FIGURE 4
Cerebral blood flow (CBF) variations in hypoxic ischemic encephalopathy (HIE).

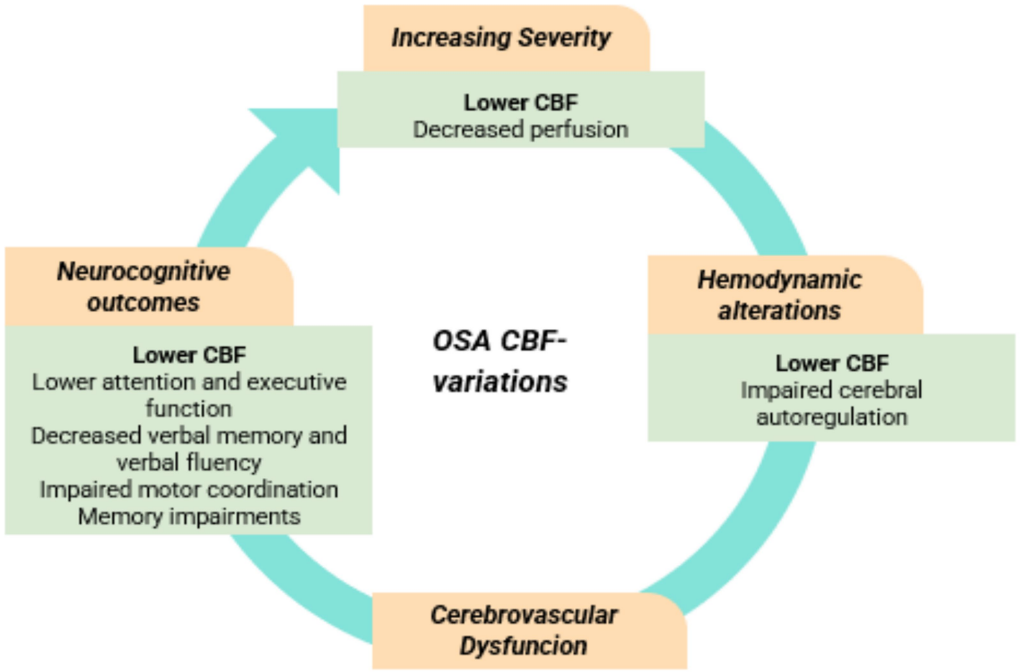


FIGURE 5
Cerebral blood flow (CBF) variations in obstructive sleep apnea (OSA) patients.

dysregulation may compromise the brain's ability to buffer ischemic stress and contribute to the elevated risk of cerebrovascular events such as stroke in this population (Ponsaing et al., 2018).

The neurovascular consequences of OSA extend further to blood–brain barrier dysfunction, which has been identified in patients with otherwise intact large vessel integrity (Palomares et al., 2015). These subtle but pervasive alterations in microvascular and barrier function likely promote chronic neuroinflammation and progressive neural injury (Postrzech-Adamczyk et al., 2019). Finally, OSA is also associated with a greater burden of white matter hyperintensities, further implicating microvascular compromise in its pathophysiology (Li et al., 2023).

In conclusion, the evidence strongly supports a multifaceted impact of OSA on cerebral perfusion, affecting not only sensory-motor and arousal pathways but also higher-order cognitive networks. These perfusion abnormalities, often detectable even before overt structural brain damage, may serve as early neuroimaging biomarkers of neural compromise in OSA (Figure 5). The combination of reduced CBF, impaired CVR, and localized network dysfunction highlights a complex interplay between intermittent hypoxia, vascular dysregulation, and cognitive decline. Longitudinal and interventional studies are needed to determine the reversibility of these deficits and the extent to which therapies such as continuous positive airway pressure therapy can restore cerebral perfusion and preserve neurocognitive function (Buckley et al., 2024). Ultimately, integrating CBF imaging into clinical protocols may offer a valuable tool for the early detection, monitoring, and personalization of treatment in OSA.

Key insights: ASL in hypoxia-induced pathological conditions
• ASL identifies distinct perfusion patterns in pathological hypoxia (e.g., OSA, COPD, CHD), often revealing regional hypoperfusion linked to cognitive and vascular impairments.
• In OSA, altered CBF and CVR patterns persist even during normoxic wakefulness, suggesting long-term neurovascular disruption.
• Pediatric hypoxia shows both global and focal CBF alterations, with implications for neurodevelopment and plasticity.
• Integrating ASL-derived CBF, ATT, and CVR with structural and functional data provides a sensitive approach to monitoring brain vulnerability in clinical hypoxia.

5 Discussion

5.1 Pathophysiological context of hypoxia: cerebrovascular adaptation

Hypoxia, whether acute or chronic, imposes profound challenges on the brain's oxygen-dependent metabolism, triggering a cascade of cerebrovascular responses aimed at preserving neuronal viability. Due to its high metabolic demand and limited oxygen reserves, the brain is particularly susceptible to fluctuations in oxygen availability, from acute insults such as HIE or transient apneic events to sustained exposures like high-altitude residence or OSA (Umbrello et al., 2013). Understanding the balance between adaptive versus maladaptive vascular responses is critical for elucidating hypoxia-induced brain injury and optimizing preventive or therapeutic strategies.

In this context, ASL MRI has emerged as a pivotal neuroimaging tool. Its ability to non-invasively quantify CBF with high regional specificity, without requiring contrast agents, enables researchers and clinicians to monitor cerebrovascular function under hypoxic stress. This offers complementary or superior insights compared to conventional imaging modalities.

5.2 Acute hypoxia and perfusion dynamics

During acute hypoxia, ASL consistently reveals global or region-specific hyperperfusion, predominantly in metabolically demanding and oxygen-sensitive areas such as the prefrontal cortex, motor areas, and deep gray matter. This increased CBF reflects compensatory vasodilation aimed at preserving oxygen delivery despite reduced arterial oxygen content. Simultaneously, ATT often shortens, indicating accelerated blood flow and increased perfusion pressure. However, in severe hypoxia, autoregulatory capacity may be compromised, leading to maladaptive hyperperfusion and increased risk of oxidative stress or microvascular injury, particularly when CBF increases are uncoupled from $CMRO_2$, reflecting a mismatch between oxygen delivery and metabolic demand (Andjelkovic et al., 2020; Fajardo et al., 2022; Auer et al., 2008). These responses show regional and individual variability, influenced by vascular architecture, neurovascular coupling, and developmental or sex-specific factors. For example, in neonatal HIE, early hyperperfusion in the basal ganglia and thalamus has prognostic value for neurodevelopmental outcomes, with evidence of sex-based differences in perfusion vulnerability (Fajardo et al., 2022). These findings highlight the brain's hierarchical strategy of preserving perfusion to essential functional networks during acute hypoxic episodes.

5.3 Chronic hypoxia and vascular remodeling

In contrast, chronic hypoxia, as seen in long-term high-altitude exposure or OSA, elicits more complex and heterogeneous vascular remodeling. While some regions maintain compensatory vasodilation, others, especially within the DMN and hippocampus, exhibit perfusion deficits likely reflecting metabolic downregulation and capillary rarefaction. Regionally specific ATT prolongation may indicate either vascular resistance or maladaptive remodeling processes such as microangiopathy or hypocapnia-induced vasoconstriction. These chronic adaptations are often accompanied by a persistent dissociation between CBF and $CMRO_2$, indicating impaired neurovascular and metabolic coupling (Inoue et al., 2014).

CVR, is frequently blunted in chronic hypoxia and, as detected by ASL, correlates with cognitive impairments in attention, executive function, and memory. Notably, inter-individual variability, as well as ethnic and developmental differences, modulate these responses, with potential implications for personalized risk stratification (Postrzech-Adamczyk et al., 2019).

5.4 Linking advanced ASL metrics to neuropsychological and functional outcomes

While advanced ASL approaches such as multi-delay protocols, VSASL, and vessel-encoded ASL provide detailed characterization of cerebral hemodynamics, relatively few studies have directly linked these parameters to comprehensive neuropsychological or functional assessments. Existing evidence suggests that alterations in CBF, ATT, CVR, and OEF are associated with domain-specific impairments, including reduced attention, executive dysfunction, and memory deficits in conditions such as obstructive sleep apnea, cerebrovascular disease, and chronic hypoxia (Johnson et al., 2025; Dai et al., 2017; Kim et al., 2023). However, the majority of these findings are correlative, with limited mechanistic exploration and sparse longitudinal follow-up. Integrating ASL-derived biomarkers with standardized cognitive batteries and functional measures could enable earlier detection of clinically meaningful changes, improve risk stratification, and guide targeted interventions. Future studies should prioritize multi-center, longitudinal designs that combine advanced ASL with robust neuropsychological profiling, thereby bridging the current gap between cerebral perfusion metrics and functional outcomes.

5.5 Gaps in longitudinal evidence and clinical implementation

These distinct CBF patterns, hyperperfusion in acute hypoxia versus regional hypoperfusion and autoregulatory failure in chronic hypoxia, underscore the dynamic and phase-dependent nature of cerebral adaptation. ASL stands out for its ability to capture these spatiotemporal nuances, advancing our understanding of how the brain transitions from compensation to decompensation under prolonged oxygen stress (Figure 6; Table 3).

Our review did not identify any longitudinal human studies directly linking early perfusion changes to long-term outcomes. Addressing this gap will require prospective cohort designs with repeated ASL measurements, integrated clinical follow-up, and incorporation of multimodal biomarkers. These efforts will be critical to defining the prognostic role of ASL in hypoxia-related brain disorders.

Moreover, the clinical implementation of ASL remains constrained by variability in acquisition protocols, including differences in labeling techniques, PLD settings, and post-processing pipelines, which complicates cross-study comparability. Furthermore, there is currently no universally accepted set of clinical guidelines defining when and how to incorporate ASL, particularly advanced techniques such as multi-delay ASL, into diagnostic workflows. While the ISMRM Perfusion Study Group consensus provides a valuable framework for standardized acquisition (Alsop et al., 2015), additional efforts are required to harmonize protocols across institutions and to validate reproducibility in multi-center settings. Recent works (Wang et al., 2023; Lindner et al., 2023; Paschoal et al., 2024) illustrate progress toward such standardization, yet widespread adoption will depend on establishing clear, evidence-based recommendations for clinical use.

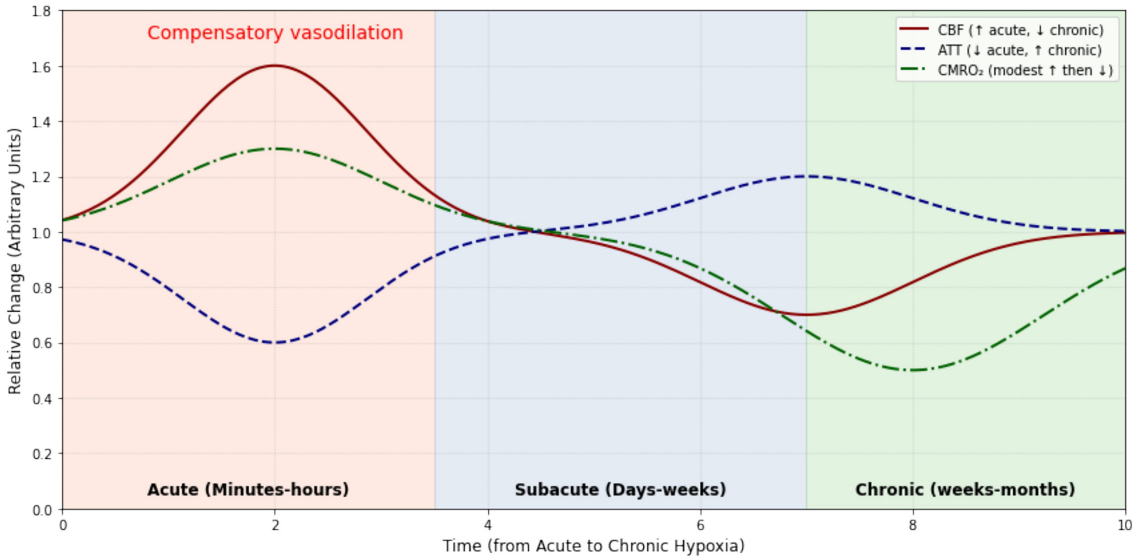


FIGURE 6
Conceptual evolution of CBF, ATT, and $CMRO_2$ across hypoxia phases. CBF, cerebral blood flow; ATT, arterial transit time; $CMRO_2$, cerebral metabolic rate of oxygen.

TABLE 3 Summary of cerebrovascular patterns in acute vs. chronic hypoxia across environmental and pathological contexts.

Dimension	Acute hypoxia	Chronic hypoxia	Context
Temporal onset	Minutes to hours (e.g., sudden altitude ascent, anoxic injury, apnea episodes)	Weeks–years (high-altitude residence, untreated OSA)	Environmental / pathological
CBF response	Global or regional hyperperfusion (sensory, motor, thalamus); compensatory	Variable or reduced CBF (DMN, hippocampus); downregulation, neurovascular uncoupling	ALL
ATT dynamics	Shortened (acute vasodilation and elevated perfusion pressure)	Prolonged or regionally altered (angiogenesis, rarefaction, CO_2 buffering)	ALL
CMRO2 coupling	Mismatch common: increased CBF > $CMRO_2$; risk of oxidative stress	Persistent decoupling in vulnerable regions (hippocampus, cortex)	Especially in OSA
CVR interpretation	May be unreliable (hypoxia ≠ hypercapnia reactivity)	Blunted or altered CVR (variable by ethnicity, disease severity)	Especially in chronic OSA and high-altitude
Functional impact	Transient deficits (reaction time, cognition)	Long-term cognitive decline (memory, executive function)	Pathological> environmental
Physiological mechanisms	No signaling, chemoreflex activation, ROS bursts	Angiogenesis, inflammation, vascular remodeling, blood barrier disruption	Environmental and pathological settings

5.6 Technical limitations, need for standardization and future perspectives

ASL remains sensitive to motion, low signal-to-noise ratio, partial volume effects, and susceptibility artifacts, challenges that are particularly relevant in pediatric, elderly, and clinically impaired populations. Advances such as velocity-selective ASL, multi-band imaging, improved background suppression, and machine learning–based motion and artifact correction are enhancing robustness and reproducibility (Hernandez-Garcia et al., 2022; Lindner et al., 2023). These developments are crucial for translating ASL into routine clinical practice while maintaining high data quality across diverse patient groups.

Emerging ASL techniques such as VSASL and multi-delay protocols provide enhanced sensitivity to OEF and microvascular dynamics, enriching our assessment of neurovascular coupling under hypoxic stress. Integrating ASL with BOLD-fMRI, diffusion imaging, and task-based paradigms can elucidate the functional consequences of perfusion alterations, from sensorimotor deficits to cognitive slowing (Post et al., 2024; Aguirre et al., 2005; Diekhoff et al., 2011; Suzuki et al., 2020; Poorman et al., 2020; Le et al., 2023). Furthermore, combining ASL with machine learning approaches applied to large, multimodal datasets may improve the early detection, classification, and monitoring of hypoxia-related brain pathologies (Hernandez-Garcia et al., 2022; Bhoi et al., 2024).

6 Conclusion

ASL perfusion MRI offers a powerful, non-invasive approach for characterizing the brain's vascular responses to hypoxia. By enabling quantitative, region-specific measurement of CBF and related metrics, ASL provides critical insight into the distinction between adaptive and maladaptive cerebrovascular processes. Its utility spans experimental models, high-altitude studies, and pathological conditions such as HIE and OSA, bridging the gap between basic physiology and translational application. As this review highlights, acute hypoxia predominantly evokes a transient hyperperfusion, aiming to preserve cerebral oxygenation, whereas chronic hypoxia drives heterogeneous remodeling, often culminating in impaired autoregulation and neurovascular uncoupling. These differential patterns underscore the need for dynamic, multimodal imaging strategies. Future work should focus on refining multi-parametric ASL protocols, improving temporal resolution, and integrating computational modeling to more accurately map the trajectory of hypoxia-induced brain changes. Longitudinal studies combining ASL with metabolic, structural, and functional imaging will be instrumental in identifying early biomarkers, predicting cognitive outcomes, and guiding personalized therapeutic interventions for hypoxia-related brain disorders.

Author contributions

ATH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. JM: Writing – original draft. FM: Visualization, Writing – review & editing, Formal analysis, Investigation, Methodology. MN: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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Publications and scientific communication

Publications

Habibi, A. T., Micaux, J., Mauconduit, F., & Noulhiane, M. (In Press). Arterial Spin Labeling Perfusion in Hypoxia: An updated Review of techniques, technical artifacts, and CBF quantification.

Micaux, J., Habibi, A. T., Mauconduit, F., & Noulhiane, M. (In Submission for Human Brain Mapping). Functional connectivity changes during voluntary apnea: Whole-brain dynamics and hippocampal involvement across acute and longitudinal measurements in freedivers.

Micaux, J., Poiret, C., Zhao, J., Hajj, A. E., Tillenon, M., Habibi, A. T., Mauconduit, F., Boumezbeur, F., Chiron, C., & Noulhiane, M. (2025). Does Freediving Lead to Hippocampal Adaptability to Hypoxia and Maintenance of Episodic Memory? *Journal of Integrative Neuroscience*, *24*(7), 36672. https://doi.org/10.31083/JIN36672

Micaux, J., Troudi Habibi, A., Mauconduit, F., & Noulhiane, M. (2025). Hypoxia's Impact on Hippocampal Functional Connectivity: Insights from Resting-State fMRI Studies. *Brain Sciences*, *15*(6), 643. https://doi.org/10.3390/brainsci15060643

Conferences

Micaux J., *et al.*, Spectroscopy, hypoxia and episodic memory. SFRMBM 2023

Micaux J., *et al.*, Does freediving lead to hippocampal adaptability to hypoxia and maintenance of episodic memory? OHBM 2024

Micaux J., *et al.*, Freediving as a natural human model to study hippocampal adaptability to hypoxia and episodic memory. CNS 2025

Micaux J., *et al.*, Freediving as a natural human model to study hippocampal functional connectivity under hypoxia. FENS 2025

Teaching experience

Teaching assistant (chargée de TD): UE PSP1 Introduction to Neuroscience (Year 1) – Boulogne University, Psychology Institute – 2024

Science outreach

- Brain Week: "Discovering different MRI techniques" – NeuroPsi Saclay, 2024
- Brain Week: "Discovering different MRI techniques" – NeuroPsi Saclay, 2025
- Apnea and Brain Newsletters: 2 issues for the French FFESSM. Micaux & Noulhiane.

Certifications

- Using Python for Research – edX (Harvard University) – 2022
- Programming for Everybody (Getting Started with Python) – Coursera (University of Michigan) – 2022
- Research Ethics – MOOC (University of Bordeaux) – 2023
- Scientific Integrity in Research – MOOC (University of Lyon) – 2023
- CENIR Course : Fundamentals of MRI and multimodal MRI – 2023
- Cours Centrale-Supélec : MRI Physics module « Medical Imaging Technologies » – 2023
- Introduction to psychology – Coursera (Yale University) – 2025
- Introduction to abnormal psychology – Coursera (Wesleyan University) – 2025