ELECTROPHYSIOLOGICAL STUDY
OF BRAIN HYPOXIA

PhD Thesis

Dr. Nikolaos Tsarouchas

UNIVERSITY OF PATRAS
PATRAS, DECEMBER 2009, HELLAS
Διατμηματικό Πρόγραμμα Μεταπτυχιακών Σπουδών στη ΒΙΟΙΑΤΡΙΚΗ ΤΕΧΝΟΛΟΓΙΑ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΕΘΝΙΚΟ ΜΕΤΣΟΒΙΟ ΠΟΛΥΤΕΧΝΕΙΟ
ΤΜΗΜΑ ΗΛΕΚΤΡΟΛΟΓΩΝ ΜΗΧΑΝΙΚΩΝ
ΚΑΙ ΜΗΧΑΝΙΚΩΝ ΥΠΟΛΟΓΙΣΤΩΝ

ΕΘΝΙΚΟ ΜΕΤΣΟΒΙΟ ΠΟΛΥΤΕΧΝΕΙΟ
ΤΜΗΜΑ ΜΗΧΑΝΟΛΟΓΩΝ ΜΗΧΑΝΙΚΩΝ

ΗΛΕΚΤΡΟΦΥΣΙΟΛΟΓΙΚΗ ΜΕΛΕΤΗ
ΤΗΣ ΕΓΚΕΦΑΛΙΚΗΣ ΥΠΟΞΙΑΣ

Διδακτορική Διατριβή

Dr. Νικόλαος Τσαρούχας

Επιχορηγούμενη από το Ελληνικό Ίδρυμα Κρατικών Υποτροφιών (ΙΚΥ)

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
ΠΑΤΡΑ, ΔΕΚΕΜΒΡΙΟΣ 2009
ADVISORY COMMITTEE

Anastasios Bezerianos, Professor, Department of Medical Physics, University of Patras, Hellas
Nikolaos Pallikarakis, Professor, Department of Medical Physics, University of Patras, Hellas
Georgios Kostopoulos, Professor, Department of Physiology, University of Patras, Hellas

EXAMINING COMMITTEE

Anastasios Bezerianos, Professor, Department of Medical Physics, University of Patras, Hellas
Nikolaos Pallikarakis, Professor, Department of Medical Physics, University of Patras, Hellas
Georgios Kostopoulos, Professor, Department of Physiology, University of Patras, Hellas
Panagiotis Papathanasopoulos, Professor, Department of Neurology, University of Patras, Hellas
Georgios Nikiforidis, Professor, Department of Medical Physics, University of Patras, Hellas
Spiros Fotopoulos, Professor, Department of Physics, University of Patras, Hellas
Georgios Oikonomou, Associate Professor, Department of Physics, University of Patras, Hellas
ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

Αναστάσιος Μπεζεριάνος, Καθηγητής, Τμήμα Ιατρικής Φυσικής, Πανεπιστήμιο Πατρών
Νικόλαος Παλληκαράκης, Καθηγητής, Τμήμα Ιατρικής Φυσικής, Πανεπιστήμιο Πατρών
Γεώργιος Κωστόπουλος, Καθηγητής, Τμήμα Φυσιολογίας, Πανεπιστήμιο Πατρών

ΕΞΕΤΑΣΤΙΚΗ ΕΠΤΑΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

Αναστάσιος Μπεζεριάνος, Καθηγητής, Τμήμα Ιατρικής Φυσικής, Πανεπιστήμιο Πατρών
Νικόλαος Παλληκαράκης, Καθηγητής, Τμήμα Ιατρικής Φυσικής, Πανεπιστήμιο Πατρών
Γεώργιος Κωστόπουλος, Καθηγητής, Τμήμα Φυσιολογίας, Πανεπιστήμιο Πατρών
Παναγιώτης Παπαθανασόπουλος, Καθηγητής, Τμήμα Νευρολογίας, Πανεπιστήμιο Πατρών
Γεώργιος Νικηφορίδης, Καθηγητής, Τμήμα Ιατρικής Φυσικής, Πανεπιστήμιο Πατρών
Σπυρίδων Φωτόπουλος, Καθηγητής, Τμήμα Φυσικής, Πανεπιστήμιο Πατρών
Γεώργιος Οικονόμου, Αναπληρωτής Καθηγητής, Τμήμα Φυσικής, Πανεπιστήμιο Πατρών
ACKNOWLEDGMENTS

First of all, I would like to thank my supervisor Professor A. Bezerianos, for all the support and guidance he provided in the realization of this project, and the excellent environment in Patras Biosignal Research Group (including all members of the team), as well as the other members of my advisory committee Professor N. Pallikarakis (Head of the MSc course in Biomedical Engineering) and Professor G. Kostopoulos (Head of the Neurophysiology Unit in Patras).

I would also like to thank Professor G. Benedek for the excellent collaboration we have established with the Department of Physiology (Vision Lab) and the Departments of Neurology & Psychiatry of Szeged University, and the Hungarian Airforce (Aerospace Program).

Finally, the author acknowledges the crucial support of the Greek State Scholarship Foundation (IKY) through a grant awarded to him for the completion of his PhD studies.

Last, but not least, I would like to deeply thank my parents and my family, my wife Elisabeth and my sons, Nikolaos and Konstantinos, for their endless support throughout all these years and all the time I have taken away from them, without which nothing of all this would have been possible.
To my parents
my wife
and my sons
# TABLE OF CONTENTS

**ACKNOWLEDGMENTS**..............................................................................................................ix

**ΠΕΡΙΛΗΨΗ**................................................................................................................................1

**PREFACE**..................................................................................................................................12

## I. CHAPTER 1 - INTRODUCTION

1.1. Brain Hypoxia (Pathophysiology)..........................................................................................14
   1.1.1. Hypobaric Hypoxia
   1.1.2. Pathophysiology of Brain Hypoxia
   1.1.3. Pathophysiology of Hypobaric Hypoxia..............................................................................15
   1.1.4. Effects of Hypobaric Hypoxia on Visual, Cognitive and Motor Functions
   1.1.5. Effects of Hypobaric Hypoxia on Electrophysiological Parameters........................................17

1.2. Ultra-rapid Visual-Cognitive Brain Responses (Electrophysiology)......................................18
   1.2.1. Fast-track categorical discrimination of target (‘animal’) vs. nontarget (‘nonanimal’) images
   1.2.2. Electrophysiological brain responses coupled to visual sensory & cognitive subprocesses
   1.2.3. Visuomotor response integration in single-choice classification/reaction task (production vs. inhibition)....19
   1.2.4. Topography and source localization of early categorical discriminative visual cognitive processes
   1.2.5. A novel tool to diagnose, monitor and study acute or chronic brain pathophysiology.........................20

## II. CHAPTER 2 - MATERIALS

2.1. Materials (Experimental Set-up)............................................................................................21
   2.1.1. Human Subjects – Selection and Ethical Constraints
   2.1.2. Electrophysiological Recordings (EEG Data acquisition)
   2.1.3. Conditions of Hypobaric Hypoxia (Hypobaric Chamber).........................................................22
   2.1.4. Conditions of Hypoxaemia and Hypoxic (Tissue) Hypoxia
   2.1.5. Visuocognitive Stimulation Conditions and Procedures..........................................................24

## III. CHAPTER 3 - METHODS

3.1. Methods of EEG signal processing in the time & frequency domains and statistical analysis........27
   3.1.1. Electroencephalography (EEG) - Event-Related Potentials/Oscillations (ERP/ERO)
   3.1.2. Introduction on Time and Frequency analysis: Wavelet vs. Fourier Transform
   3.1.3. Classical Event-Related Potential Processing and Generation (Time Domain).............................28
   3.1.4. Conventional Event-Related Potential Statistical Analysis (Time Domain)
   3.1.5. The Continuous Wavelet Transform - Multiresolution Time-Frequency Decomposition.................29
   3.1.6. Continuous Wavelet Time-Frequency EEG Signal Transformation - 2D Representation................29
   3.1.7. Amplitude-Phase Analysis of Event-Related Oscillations (Evoked/Phase-Locked and Total/Induced)....32
   3.1.8. Statistical Parametric Time-Frequency Map (SPTFM) Analysis across Categorical Conditions.........34
   3.1.9. Analysis of Variance (3way-ANOVA) across Categorical Conditions and Oxygen Levels............35

## IV. CHAPTER 4 – RESULTS FOR CATEGORICAL TARGET DISCRIMINATION

4.1. Introduction on Visuocognitive Electrophysiological Brain Responses......................................36
   4.1.1. The broadband temporal correlation hypothesis in visual feature binding
   4.1.2. Gamma-band oscillatory responses in visual sensory and cognitive phenomena..........................37
   4.1.3. Broadband oscillatory responses in categorical object representation & discrimination................39
4.2. Electrophysiological Results on Categorical Target Discrimination .................................................. 40
  4.2.1. Event-related potentials (ERP: <20Hz)
  4.2.2. Event-related broadband oscillations (ERO: 1-60Hz) ................................................................. 42
     4.2.2.1. Phase-coherence of broadband oscillations
     4.2.2.2. Evoked (phase-locked) broadband oscillations ................................................................. 45
     4.2.2.3. Total & Induced (non-phase-locked) broadband oscillations ............................................. 49

4.3. Discussion & Conclusions ........................................................................................................... 53
  4.3.1. Interpretation of evoked/phase-locked high-frequency versus total/induced low-frequency oscillations
  4.3.2. Topography and timing: spatiotemporal distribution of broadband oscillations ...................... 54
  4.3.3. Cognitive neurophysiological model of broadband electrical oscillations ............................. 55
  4.3.4. In-depth perspective of high-frequency (γ-band) oscillatory activity ..................................... 56

V. CHAPTER 5 – RESULTS FOR HYPOXIC VERSUS NORMOXIC CONDITIONS

5.1. Electrophysiological markers of functional sensitivity thresholds of visuocognitive processes under hypoxia ........................................................................................................................................... 58

5.2. Psychophysiological results under hypoxic vs. normoxic conditions ........................................ 59
  5.2.1. Physiological Results
  5.2.2. Behavioral Results .......................................................................................................................... 60

5.3. Electrophysiological results under hypoxic versus normoxic conditions ................................ 61
  5.3.1. Statistical Analysis of Event-Related Potentials (ERP) in the Time-Domain
  5.3.2. Statistical Analysis of Event-Related Oscillations (ERO) in the Joint Time-Frequency Domain ... 68
     5.3.2.1. Evoked Event-Related Oscillations (50-250ms poststimulus)
     5.3.2.2. Phase-Coherence of Event-Related Oscillations (50-250ms poststimulus) ....................... 70
     5.3.2.3. Evoked Event-Related Oscillations (300-500ms poststimulus) ........................................ 72
     5.3.2.4. Phase-Coherence of Event-Related Oscillations (300-500ms poststimulus) ................... 74
     5.3.2.5. Total/Induced Event-Related Oscillations (200-600ms poststimulus) ............................ 76

5.4. Discussion - Interpretations & Conclusions ................................................................................. 78
  5.4.1. Conclusions and Interpretations of the ERP statistical results
  5.4.2. Comparisons with previous ERP studies on hypobaric hypoxia .................................................... 80
  5.4.3. Conclusions and Interpretations of the ERO statistical results .................................................. 81
     5.4.3.1. Evoked Event-Related Oscillations (50-250ms poststimulus)
     5.4.3.2. Phase-Coherence of Event-Related Oscillations (50-250ms poststimulus)
     5.4.3.3. Evoked Event-Related Oscillations (300-500ms poststimulus) ........................................ 82
     5.4.3.4. Phase-Coherence of Event-Related Oscillations (300-500ms poststimulus) ................... 83
     5.4.3.5. Total/Induced Event-Related Oscillations (200-600ms poststimulus) ............................ 83
  5.4.4. Comparisons to previous EEG spectral power studies under hypoxia ...................................... 85
  5.4.5. Significance of ERO dynamics and their impact on ERP dynamics under hypoxia
  5.4.6. Effects of brain adaptation and acclimatization to acute hypoxic challenges ....................... 87
  5.4.7. A novel tool for the diagnosis and monitoring of acute and chronic brain disorders ................. 88

BIBLIOGRAPHY ........................................................................................................................................ 89

APPENDIX I ............................................................................................................................................... 98
List of publications as result of the research work performed for the purposes of the present thesis
ΠΕΡΙΛΗΨΗ

ΚΕΦΑΛΑΙΟ 1 – ΕΙΣΑΓΩΓΗ

Η ανθρώπινη οράση αποτελεί ένα από τα πιο πολύπλοκα αντιληπτικά και αναπαραστατικά νοητικά συστήματα που απασχολεί περίπου το 50% ολόκληρης της εγκεφαλικής φλοιϊκής μάζας, με διάφορες οπτικές, αντιληπτικές, ανώτερης τάξης γνωστικές-νοητικές διεργασίες και ολοκληρωμένες οπτικο-γνωστικο-κινητικές λειτουργίες να εμπλέκουν όλους τους λοβούς, φλοιϊκές και υποφλοιϊκές δομές (τον ινιακό, κροταφικό, βρεγματικό και μετωπιαίο λοβό, το θάλαμο, τα βασικά γάγγια, κλπ) και υποκείμενες περιοχές (περισσότερα από 32 περιοχικά εγκεφαλικά κέντρα θεωρούνται ότι εμπλέκονται στο διάφορα στάδια επεξεργασίας της οπτικογνωστικής πληροφορίας).

Η όλη μας προσπάθεια έγκειται στο να αναπτύξουμε εργαλεία Βιοϊατρικής Νευρομηχανικής (Βιοτεχνολογίες) για την σε βάθος λειτουργική μελέτη, ταχεία διάγνωση, συνεχή παρακολούθηση και έγκαιρη αντιμετώπιση και έγκαιρη αντιμετώπιση αξιολόγηση και συνεχή παρακολούθηση και έγκαιρη αντιμετώπιση οξέων και χρόνιων εγκεφαλικών διαταραχών (π.χ. εγκεφαλική υποξία, κρανιοεγκεφαλικές κακώσεις, χωροκατακτητικές εξεργασίες, νόσος Alzheimer, Parkinson, κλπ); επίσης για την λειτουργική αξιολόγηση και συνεχή ελέγχο της προσαρμοστικότητας κατά την εξάσκηση των «ψυχατών» (πιλότοι, αστροναύτες, αναρριχητές, κλπ), ατόμων που ασκούν δραστηριότητες και λειτουργούν μέσα σε περιβάλλοντα αυξημένων οπτικο-γνωστικο-κινητικών απαιτήσεων (πιλότοι, οδηγοί, αθλητές, κλπ), ή ατόμων που υπόκεινται ή πάσχουν από οιαδήποτε μορφή συστηματικής υποξαιμίας (καρδιαγγειακή νόσος, αναπνευστική νόσος, αιμοσφαιρινές πάθεις, κλπ), ή πιο εντοπισμένες εγκεφαλικές υποξίες (αγγειακή εγκεφαλική νόσος, καρδιαγγειακή νόσος, αναπνευστική νόσος, κλπ). Για αυτόν ακριβώς το λόγο αποφασίσαμε να υποβάλλουμε ολόκληρο το οπτικογνωστικό σύστημα, από το στοιχειώδες οπτικοαισθητικό έως το πιο πολύπλοκο νοητικό-κατηγορικό επίπεδο, σε μια πειραματική δοκιμασία κατηγορικής διάκρισης και επιλεκτικής απάντησης στην υπερταχεία διέγερση με οπτικογνωστικά ερεθίσματα και σύγχρονη μέτρηση των προκλητικών πληροφορικών ερεθίσματος του εγκεφάλου σε πεδίο του χρόνου και το συζευγμένο χρονοφασματικό πεδίο. Αυτή η δοκιμασία οπτικογνωστικής κατηγοριοποίησης έλαβε χώρα τόσο σε νορμοξαιμικές όσο και υποξαιμικές συνθήκες (ελεγχόμενη μείωση στον κορεσμό του αίματος σε οξυγόνο από ≥97% γύρω στο 80%), προκειμένου να ελέγξουμε πληροφορικογνωστικά δείκτες (markers) που μπορούν να αντιγράψουν και να συλλάβουν με τον πιο ευαίσθητο και δυναμικό τρόπο ακόμη και πιο βραχύβιες και σχετικά ήπιες μεταβολές της εγκεφαλικής λειτουργίας. Ως τέτοιους δείκτες διερευνήσαμε τα προκλητικά δυναμικά (ERP) και τις ευρυζωνικές δείκτες ταλαντώσεις (ERO) που προέκυψαν στις ινιακο-κροταφικο-βραχυκύκλωτες περιοχές του
εγκεφάλου μέχρι τα υποκείμενα να παράγουν μια κινητική απάντηση στην κατηγοριοποίηση των στόχων (εικόνες ζώων προκαλούσαν παραγωγικές αποκρίσεις), ενώ έπρεπε να την καταστείλουν στην κατηγοριοποίηση των μη-στόχων (εικόνες μη-ζώων προκαλούσαν ανασταλτικές αποκρίσεις).

ΚΕΦΑΛΑΙΟ 2 – ΥΛΙΚΑ/ΑΝΘΡΩΠΟΙ & ΟΡΓΑΝΩΣΗ ΤΟΥ ΠΕΙΡΑΜΑΤΟΣ

Η ηλεκτροψυχιατρική μελέτη της ανθρώπινης εγκεφαλικής υποξίας επιβάλλει σοβαρούς τεχνικούς και ηθικούς περιορισμούς. Ηθικοί περιορισμοί δε μας επιτρέπουν να εκθέσουμε τα ανθρώπινα υποκείμενα ούτε σε εξαιρετικά βαριές συνθήκες υποξαμίας (επίπεδα κορεσμού του αίματος σε οξυγόνο πολύ κάτω του 75%) ούτε για μακρά χρονική διάστημα (πολύ άνω των 15 λεπτών). Οι διαθέσιμες και ασφαλείς συνθήκες πειραματικά επαγόμενης εγκεφαλικής υποξίας περιλάμβαναν έναν υποβαρικό θάλαμο (από το Αεροδιαστημικό Πρόγραμμα της Ουγγρικής Αεροπορίας) μέσα στον οποίο μπορούσαν να δημιουργηθούν συνθήκες χαμηλής ατμοσφαιρικής πίεσης και υποξίας και κατά συνέπεια ελεγχόμενου βαθμού υποξαμίας και ιστική (εγκεφαλική) υποξία με δεδομένους και τους ψυχολογικούς αντιρροπηστικούς μηχανισμούς των υγιών υποκειμένων μας. Ο όρος «υποβαρική υποξία» περιγράφει τις συνθήκες υποξίας λόγω χαμηλών επιπέδων ατμοσφαιρικής πίεσης, όπως φυσικά συμβαίνει σε μεγάλα ύψη, και αποτελεί έναν ασφαλή, κομψό και αποτελεσματικό τρόπο να προκληθεί ελεγχόμενοι βαθμού εγκεφαλική υποξία, προκειμένου να μελετηθούν με ηλεκτροψυχιατρικούς και ψυχομετρικούς όρους οι επιπτώσεις της στις οπτικογνωστικές λειτουργίες του εγκεφάλου.

Για τους πολύ πρακτικούς αυτούς λόγους και σκοπούς, (1) κρατήσαμε τον αριθμό των καναλιών καταγραφής ΗΕΓ στο ελάχιστο (μόνον έπτα), (2) προκαλέσαμε την υπερταχεία διέγερση (για μόλις 66ms) του εγκεφάλου με πολλά πλούσια (ποικίλα κατηγορικού επιπέδου) και διαφορετικά οπτικογνωστικά ερεθίσματα και (3) κάναμε αποδεκτό χρόνο οπτικο-κινητικής ολοκλήρωσης κάτω του ενός δευτερολέπτου από την ερεθίσμα, (4) κατάστησαμε το συνολικό χρόνο καταγραφής ΗΕΓ μόλις στα 15 λεπτά τόσο για τις υποξικές όσο και τις νορμοξικές συνθήκες, (5) φροντίσαμε για τις καλύτερες δυνατές συνθήκες καταγραφής ΗΕΓ στο διάστημα αυτό τουλάχιστον 200 ποιοτικές καταγραφές για κάθε τύπο του δισχιδού κατηγορικού ερεθίσματος, (6) επιλέξαμε ως επίπεδο ατμοσφαιρικής πίεσης στον υποβαρικό θάλαμο το κρίσιμο υψόμετρο των 4500m (15,000ft), μετά το οποίο εμφανίζονται οι πρώτες ελεγχόμενες διαταραχές στις συνθήκες καταγραφής, και (7) συνεπάγοντας την πτώση του κορεσμού της υποξαμίας σε οξυγόνο (SatO2%) κατά μέσο όρο κάτω του 75%, ώστε το επίπεδο υποξαμίας να δύναται να αντιμετωπισθεί από δραστικούς ψυχολογικούς αντιρροπηστικούς μηχανισμούς των υγιών υποκειμένων, ούτως ώστε να ανιχνεύσουμε τις πιο πρόωρες και
μικρότερου βαθμού (σχεδόν ανεπαίσθητες, που τελικά κρίνουν και την ευαισθησία της μεθόδου μας) διαταραχές στις οπτικογνωστικές λειτουργίες και στις αντίστοιχες ηλεκτροφυσιολογικές αποκρίσεις και τέλος (8) επιδιόρθωσαμε σε μια ενδεχομένως ανάλυση των οπτικογνωστικών προκλητών δυναμικών και των προκλητών/επαγόμενων ταλαντώσεων στο πεδίο του χρόνου και το συζευγμένο χρονοφασματικό πεδίο αντίστοιχα για να εξάγουμε όσο το δυνατόν περισσότερη πληροφορία.

ΚΕΦΑΛΑΙΟ 3- ΜΕΘΟΔΟΙ/ΤΕΧΝΙΚΕΣ ΕΠΕΞΕΡΓΑΣΙΑΣ & ΑΝΑΛΥΣΗΣ ΒΙΟΣΗΜΑΤΩΝ

Στο κεφάλαιο 3 (μεθοδολογικό μέρος) αναπτύσσουμε μερικές από τις βασικές αρχές της ηλεκτροφυσιολογίας του ηλεκτρογκεφαλογραφήματος (ΗΕΓ) όπως επίσης και της ηλεκτροφυσιολογίας των οπτικών προκλητών δυναμικών (ΟΠΔ) και ταλαντώσεων (ΟΠΤ). Παρουσιάζουμε τις μεθόδους επεξεργασίας και εξάγωγής των προκλητών δυναμικών και τη συμβατική στατιστική ανάλυσή τους στο πεδίο του χρόνου. Στο πεδίο της συχνότητας αναδεικνύουμε τα μειονεκτήματα και τις ανεπάρκειες του παραδοσιακού μετασχηματισμού Fourier όταν εφαρμόζεται σε βραχέα και μη στάσιμα (σχετιζόμενα με την ταχεία διέγερση και οπτικογνωστική απόκριση) τμήματα του ΗΕΓ.

Μέσα στο πλαίσιο της βελτιστοποιημένης μεθόδου πολυφασματικής αποσύνθεσης του σήματος στο συζευγμένο πεδίο χρόνου-συχνότητας, εισάγουμε το συνεχή μετασχηματισμό του κυματίου που επιτρέπει την πλεονεκτική διαδιάσταση χρονικά-εξελισσόμενη και ευρυζωνική-συχνοτική αναπαράσταση της κατανομής του πλάτους (ενέργειας) και της φάσης του ΗΕΓ σήματος. Η ανάλυση του πλάτους και της φάσης των συχνοτικών συνιστοσών των προκλητών ταλαντώσεων μας επιτρέπει να αποκτήσουμε κρίσιμη συμπληρωματική νέα πληροφορία για την εκλύσιμη (φαινικά-κλειδωμένη) ενέργεια της κατανομής καταγραφών και την ολική, ως επί το πλείστον επαγόμενη (φαινικά μη-κλειδωμένη), ενέργεια της ταλαντωτικής δραστηριότητας.

Επιπλέον αναπτύσσουμε μια νεωτερική μέθοδο στατιστικής παραμετρικής ανάλυσης των χρονοφασματικών πεδίων μεταξύ των συγκρίσεων, η οποία αποκαλύπτει τη στατιστικά σημαντική διαφορική οπτικογνωστική ταλαντωτική δραστηριότητα (που οφείλεται στο δισχιδές κατηγορικό ερέθισμα), την αδρή εγκεφαλική τοπογραφία της και τον πιο ακριβή χρονικό εντοπισμό της μέχρι την έκλυση του μεγαλύτερου όγκου των κινητικών αποκρίσεων.

Τέλος, εφαρμόζουμε τη γενικευμένη στατιστική μέθοδο της ανάλυσης των διακυμάνσεων (N-way ANOVA) για την πιο αξιόπιστη (και στατιστικά πιο ασφαλή, λόγω των πολλαπλών συγκρίσεων) και τεκμηριωμένη ανάλυση των οπτικογνωστικά-συσχετιζόμενων προκλητών.
δυναμικών και ευρυζωνικών προκλητών/επαγόμενων ταλαντώσεων τόσο μεταξύ κατηγορικών ερεθισμάτων όσο και μεταξύ υποξικών και νορμοξικών συνθηκών.

ΚΕΦΑΛΑΙΟ 4 - ΑΠΟΤΕΛΕΣΜΑΤΑ ΤΗΣ ΚΑΤΗΓΟΡΙΚΗΣ ΔΙΑΚΡΙΣΗΣ ΕΡΕΘΙΣΜΑΤΩΝ

Στο κεφάλαιο 4 (ηλεκτροφυσιολογικά αποτελέσματα από τη διάκριση κατηγορικών στόχων έναντι μη-στόχων) παρουσιάζουμε καταρχήν τους λόγους που μας οδηγούν στην ευρυζωνική διερεύνηση των οπτικογνωστικών ταλαντωτικών αποκρίσεων, και ιδιαίτερα της υψίσυχνης ζώνης των γ-ταλαντώσεων (≥20Hz). Αυτές οι ταλαντωτικές αποκρίσεις έχουν κατεξοχήν συνδεθεί με τη δυναμική, ταχεία και ευρυζωνική χωροχρονική συσχέτιση (συγχρονισμό) της ταλαντωτικής δραστηριότητας επιμέρους νευρονικών ομάδων και πληθυσμών που κωδικοποιούν επιμέρους ιδιότητες, γνωρίσματα και χαρακτηριστικά των οπτικών ερεθισμάτων, σε ολοκληρωμένα λειτουργικά συσσωματώματα που κωδικοποιούν τα αντικείμενα αυτά καθαυτά στην ολότητά τους ή τις μεταξύ τους σχέσεις σε όλο και ψηλότερα επίπεδα αναπαράστασης και νοητικές λειτουργίες ύστερα το πιο αφαιρετικό (κατηγορικό) επίπεδο ή ακόμη και ολοκληρωμένες οπτικο-κινητικές λειτουργίες απάντησης στα ερεθίσματα αυτά (συμπεριφορά).

Η στατιστική παραμετρική ανάλυση των προκλητών δυναμικών (<20Hz) ανέδειξε την πιο ουσιαστική διαφορά μεταξύ των κατηγορικών οπτικογνωστικών αποκρίσεων στο έπαρμα P3 (πέραν των 300ms μετά το ερέθισμα) σε όλα σχεδόν τα κανάλια, και ήσσονος σημασίας διαφορές μεταξύ 150-250ms στα ινιακο-κροταφικά (P7/P8) και μεσο-βρεγματικό (Pz) κανάλια, διαφορές που επαναλαμβάνονταν την υπάρχουσα βιβλιογραφία. Αντιθέτως η στατιστική παραμετρική ανάλυση των ευρυζωνικών χρονοφασματικών πεδίων ανέδειξε την πιο ουσιαστική διαφορά στην εκλυόμενη ενέργεια της οπτικογνωστικής ταλαντωτικής δραστηριότητας στην υψίσυχη ζώνη (κυρίως ≥20Hz) κάτω των 250ms μετά το ερέθισμα, σε όλα σχεδόν και κυρίως στα πλάγια ινιακά κανάλια (O1/O2) και ήσσονος σημασίας διαφορές μεταξύ 300-500ms χωρίς κυριαρχική χωροχρονική κατανομή.

Η στατιστική μελέτη της φασικής συνάφειας μεταξύ των μοναδιαίων καταγραφών αποκάλυψε τη σημαντική αύξηση του παράγοντα φασικής συνάφειας στην ίδια ακριβώς υψίσυχη ζώνη (κυρίως ≥20Hz) μεταξύ 50-200ms μετά το ερέθισμα, με την ίδια ακριβώς τοπογραφική κατανομή (ιδίως στα O1/O2), εξηγώντας και μεγάλη βαθμό και την αυξημένη ενέργεια. Αυτό δείχνει ότι η διερεύνηση των διαφορετικών οπτικών αντικειμένων με τα οποία διεξάγεται η εγκεφαλική η κοινή κατηγορικού επιπέδου αναπαράσταση και διάκριση αυτών ως στόχους ή μη-στόχων, συντελείται ήδη μέσα στα πρώτα 200ms (50-150ms), πολύ πριν την πλήρη και λεπτομερή αντίληψη τους. Εξηγεί τις διαφορές που έχουν παρατηρηθεί στις πρόσθετες περιοχές του εγκεφάλου μετά τα πρώτα 150ms, τις ταχείες αποκρίσεις των υποκειμένων μετά τα 300ms (ελάχιστος χρόνος
οπτικο-κινητικής ολοκλήρωσης από 250-350ms), και υποδηλώνει ότι σχετίζεται με ευρείας κλίμακας αυξημένου χωροχρονικού συγχρονισμού φάσης της υψίσυχης (≥20Hz) οπτικογνωστικής ταλαντωτικής δραστηριότητας μεταξύ των μοναδιαίων καταγραφών.

Τέλος, παρόλο που αυξάνεται και στην υψίσυχη ζώνη, η πιο στατιστικά σημαντική διαφορά στην ολική ενέργεια (≥20Hz) αυξάνεται με ευρείας κλίμακας αυξημένου χωροχρονικού συγχρονισμού φάσης της υψίσυχης κλίμακας αυξημένου χωροχρονικού συγχρονισμού φάσης της υψίσυχης (Ki ιμένους (K=20Hz) σχεδόν σε όλα τα κανάλια, χωρίς σαφή χωροχρονικό εντοπισμό. Οι κατηγορικοί στόχοι διαμορφώνουν τις πιο χαμηλές συχνότητες (<10Hz), αυξάνοντας την ολική ενέργεια νωρίτερα (στα πρώτα 400-600ms) και οι μη-κατηγορικοί στόχοι διαμορφώνουν τις πιο υψηλές συχνότητες (10-20Hz) αυξάνοντας την ολική ενέργεια αργότερα (από 200-600ms μετά το ερέθισμα). Αυτό δείχνει ότι η επεξεργασία των κατηγορικών στόχων προηγείται (ή και ολοκληρώνεται νωρίτερα) από των μη-στόχων, ενώ η επεξεργασία των μη-στόχων είναι πιο παρατεταμένη (ή και πιο εργώδης) από τους στόχους καθώς διαμορφώνεται σε υψηλότερη υποζώνη και εξίσου σημαντικά με τους στόχους, σε αντιδιαστολή με το Ρ3 έπαρμα των προκλητών δυναμικών που διαμορφώνεται υψηλότερα μόνο για στόχους. Το γεγονός ότι η ολική ενέργεια διαμορφώνεται κυρίως σε χαμηλές συχνότητες και δεν εμφανίζει συνάφεια φάσης μεταξύ μοναδιαίων καταγραφών υποδηλώνει ότι σχετίζεται με μια δεύτερη πιλότου, αστροναύτες, κλπ.), όσο και κάθε είδους συστηματική παθολογική κατάσταση που μπορεί να οδηγήσει σε αποκορεσμό της αιμοσφαιρίνης σε οξγόνο (καρδιαγγειακή ή αναπνευστική νόσος, αιμοσφαιρινοπάθειες, κλπ) ή και καταστάσεις πιο εντοπισμένης εγκεφαλικής υποξίας (ιστική υποξία, αγγειακή εγκεφαλική νόσος, τοξινώσεις, κλπ). Ως εκ τούτου η μέθοδος μας

ΚΕΦΑΛΑΙΟ 5 - ΑΠΟΤΕΛΕΣΜΑΤΑ ΥΠΟΞΙΚΩΝ ΕΝΑΝΤΙ ΝΟΡΜΟΞΙΚΩΝ ΣΥΝΘΗΚΩΝ

Στο κεφάλαιο 5 (ηλεκτροφυσιολογικά αποτελέσματα για υποξικές έναντι νορμοξικών συνθηκών) παρουσιάζουμε την ανάγκη και χρησιμότητα να διερευνήσουμε και να καθορίσουμε μέσα από ηλεκτροφυσιολογικούς δείκτες (markers) και ψυχομετρικές δοκιμασίες τους ουδούς (thresholds) ευαισθησίας των ανώτερων οπτικογνωστικών λειτουργιών του ανθρώπινου εγκεφάλου στις υποξαιμικές συνθήκες. Αυτό αφορά τόσο τους «ψυβάτες» (πιλότους, αστροναύτες, αναρριχητές, κλπ.), όσο και κάθε είδους συστηματική παθολογική κατάσταση που μπορεί να οδηγήσει σε αποκορεσμό της αιμοσφαιρίνης του αίματος σε οξγόνο (καρδιαγγειακή ή αναπνευστική νόσος, αιμοσφαιρινοπάθειες, κλπ) ή και καταστάσεις πιο εντοπισμένης εγκεφαλικής υποξίας (ιστική υποξία, αγγειακή εγκεφαλική νόσος, τοξινώσεις, κλπ). Ως εκ τούτου η μέθοδος μας
δύναται να αποτελέσει ένα ουσιαστικό εργαλείο και κρίσιμο μέτρο της λειτουργικότητας των ατόμων τόσο μέσα σε εξειδικευμένα περιβάλλοντα αυξημένων οπτικών και νοητικών απαιτήσεων, όσο και στην καθημερινή τους ζωή. Για παράδειγμα, πιλότοι μαχητικών ή πολιτικών αεροσκαφών, αστροναύτες, αναρριχητές, οδηγοί αγωνιστικών ή αυτοκινήτων στην καθημερινή ζωή, ιδίως οι μεγάλης ηλικίας ή έχοντες ιατρικά προβλήματα ιδίως οι οποίοι επιδίδονται σε κάθε είδους δραστηριότητες που απαιτούν ταχείες οπτικο-κινητικές αποκρίσεις, οξείες οπτικο-αντιληπτικές λειτουργίες και ελάχιστους χρόνους αντίδρασης από τις οποίες κρίνονται ανθρώπινες ζωές, θα μπορούν να ασκήσουν ή να συνεχίσουν να ασκούν τέτοιες δραστηριότητες μετά από συνεχή και περιοδικό έλεγχο του οπτικο-γνωστικο-κινητικού τους συστήματος μέσα από τέτοιες πολύπλοκες λειτουργικές δοκιμασίες.

Αυτές οι δοκιμασίες δεν θα διαρκούν περισσότερο από 20 έως 30 λεπτά (μαζί με το χρόνο τοποθέτησης των ηλεκτροδίων, καθώς ο αριθμός τους μπορεί να διατηρηθεί στο ελάχιστο), θα δίνουν μάλιστα σημαντική πλήρως λειτουργική πληροφορία (ηλεκτροφυσιολογική και ψυχομετρική στην κλίμακα των χιλιοστών του δευτερολέπτου) για ολόκληρο το οπτικο-γνωστικο-κινητικό σύστημα, όταν η συνήθης εξέταση με το μαγνητικό τομογράφο (MRI) διαρκεί τουλάχιστον 20-30 λεπτά και δίνει αμιγώς ανατομική πληροφορία για τις δομές του εγκεφάλου. Φυσικά η όλη μας προσέγγιση με το συνδυασμό ενδελεχούς ηλεκτροφυσιολογικής μελέτης και παρακολούθησης (ήλεκτροφυσιολογική και ψυχομετρική στην κλίμακα των χιλιοστών του δευτερολέπτου) για ολόκληρο το οπτικο-γνωστικο-κινητικό σύστημα, όταν η συνήθης εξέταση με το μαγνητικό τομογράφο (MRI) διαρκεί τουλάχιστον 20-30 λεπτά και δίνει αμιγώς ανατομική πληροφορία για τις δομές του εγκεφάλου (αγγειακών εγκεφαλικών, χωροκατακτητικών εξεργασιών, νευροεκφυλιστικών παθήσεων, κλπ.) που επηρεάζουν ή αλλοιώνουν τις οπτικογνωστικές και οπτικοκινητικές λειτουργίες (π.χ. νόσος Alzheimer, νόσος Parkinson, κλπ.). Εν δυνάμει συνιστά κάτι ανάλογο του «στρες τεστ» της καρδιάς, αλλά για τον εγκέφαλο.

Τα ευρήματα μας ήταν εξαιρετικά ενδιαφέροντα. Τα υποκείμενα παρουσίασαν μια εκπληκτικού βαθμού αντιρρόπηση κάτω από αυτές τις υποξαιμικές συνθήκες (σημαντική μείωση του κορεσμού της αιμοσφαιρίνης σε χολόγονο κατά μέσο όρο γύρω στο 80%, καθ’ όλη τη διάρκεια >75% και ανά πάσα στεγή >70%), χωρίς να υποστούν καθόλου οξέα συμβάμα, αισθητή έκπτωση στις οπτικογνωστικές λειτουργίες, οιαδήποτε κάμψη στις οπτικοκινητικές αποκρίσεις ή στο επίπεδο συνειδήσεως. Ωστόσο η αντικειμενική ανάλυση έδειξε κάτω από συνθήκες υποξίας στατιστικά σημαντική μείωση στην επιτυχή αναγνώριση των κατηγορικών μη-στόχων. Αντιθέτως δεν υπήρξε σημαντική μεταβολή (ελαφρά βελτίωση μόνο) στην επιτυχή αναγνώριση των κατηγορικών στόχων και τις αντίστοιχες κινητικές απαντήσεις (χρόνους αντίδρασης), γεγονός που θα μπορούσε να οφείλεται και σε αυξημένη εγρήγορση των υποκειμένων.

Η στατιστική ανάλυση διακόμανσης για τις κορυφές (μέγιστα πλάτη και χρονικές υστερήσεις) των κύριων επαρμάτων των προκλητών οπτικογνωστικών δυναμικών έδειξε στατιστικά σημαντική:
(1) μείωση στο πλάτος μόνο του P1 και παραδο ψης (2) αύξηση στα πλάτη το ν N1 και P3 επαρμάτων, (3) αύξηση της χρονικής υστέρησης της κορυφής του P2, τόσο για στόχους όσο και για μη-στόχους. Τέλος, παρατηρήθηκε (4) αύξηση της χρονικής υστέρησης της κορυφής του P3 μόνο για τους μη-στόχους που συνάδει και με τη σημαντική μείωση στα ποσοστά αναγνώρισης των κατηγορικών μη-στόχων. Τα ανάμικτα αυτά αποτελέσματα τόσο για στόχους όσο και για μη-στόχους φανερώνουν στο επίπεδο των προκλητών δυναμικών τις πρόωρες επιπτώσεις της εγκεφαλικής υποξίας. Δηλαδή το συγκεκριμένο κατασταλτικής δράσης της στις πρώιμες, πιο εγγύς σε οπτικαίς αισθητικοικίας επίπεδο και ενδεχομένως πιο ευαίσθητες στην υποξία λειτουργίες (όπως ανακλώνται στις μεταβολές πλάτους του P1 και υστέρησης του P2 επάρματος) και διεγερτική ή αποανασταλτική δράσης της στις υψηλές όγκες (όπως ανακλώνται στις μεταβολές πλάτους των N1 και P3 επαρμάτων). Οι τελευταίες φαίνεται ότι είναι αποτέλεσμα δυναμικών αντιρροπη στικάκων μηχανισμών διάκρισης ερεθισμάτων σε κατηγορικό επίπεδο, που τελικά αποβιάνουν επαρκώς για την κατηγοριοποίηση των στόχων αλλά ανεπαρκώς για την κατηγοριοποίηση των μη-στόχων (όπως αυτό ανακλάται στις μεταβολές υστέρησης της κορυφής του P3 επάρματος και των ποσοστών επιτυχίας αναγνώρισης για στόχους ύψηλες μη-στόχου). Η στατιστική ανάλυση διακύμανσης των μέσων τιμών πλάτους (ενέργειας) και φασικής συνάφειας των προκλητών ταλαντώσεων για το αντίστοιχο πρώιμο (50-250ms) και ύψηλες (300-500ms) στάδιο οπτικογνωστικών αποκρίσεων αποκάλυψε ακόμη πιο ενδιαφέροντα ευρήματα. Κάτω από υποξαίμης συνθήκες, η μέση τιμή της φασικής συνάφειας (φασικό κλείδωμα) μεταξύ των μοναδιαίων καταγραφών μειώθηκε σημαντικά στις υψηλές (γάμμα) συνιστώσες και ενδεχομένως στις χαμηλές (βήτα, δέκατα, εβδομάδια) συνιστώσες. Αυτό εξηγεί τη σημαντική μείωση της μέσης τιμής της φασικής συνάφειας και της προκλητής ταλαντωτικής ενέργειας για κατηγορικούς και μη-στόχους στη χαμηλή-γάμμα (20-40Hz) και χαμηλή (20-40Hz) και υψηλή (40-60Hz - μόνο για μη-στόχους) συνιστώσες. Στις βαθύσυχες συνιστώσες (<20Hz), η μείωση ήταν στατιστικά αναγνώρισης και απάντηση για κατηγορικούς και μη-στόχους. Και στο όψιμο στάδιο (300-500ms) των οπτικογνωστικών αποκρίσεων κάτω από υποξαίμης συνθήκες, η μέση τιμή της φασικής συνάφειας (φασικό κλείδωμα) μεταξύ των μοναδιαίων καταγραφών μειώθηκε σημαντικά στις υψηλές συνιστώσες και ενδεχομένως στις χαμηλές συνιστώσες. Η μείωση ήταν διαφορική στην υψηλή (28-60Hz) και βήτα (12-20Hz) συνιστώσες. Στις βαθύσυχες (20-28Hz) και χαμηλές (20-28Hz) συνιστώσες, η μείωση ήταν εξ ίσου για στόχους και μη-στόχους.
μη-στόχων σε όλες τις φασματικές ζώνες, ακόμη και σε υποξαιμικές συνθήκες, ιδιαίτερα στη βήτα υποζώνη (12-20Hz). Το γεγονός αυτό μπορεί να συντέλεσε σε μικρό βαθμό στην πιο ευνοϊκή δυναμική των P3 επαρμάτων και των αποκρίσεων για κατηγορικούς στόχους στην υποξία.

Σε πλήρη αντίθεση με αυτή τη σημαντική μείωση του παράγοντα φασικής συνάψεως στο όψιμο (300-500ms) στάδιο των οπτικογνωστικών αποκρίσεων, η μέση τιμή του πλάτους (ενέργειας) των προκλητών ταλαντώσεων κάτω από υποξαιμικές συνθήκες αυξήθηκε σημαντικά σε όλες τις φασματικές ζώνες. Η αύξηση ήταν διαφορική στην υψηλή (28-60Hz - μόνο για μη-στόχους) γάμμα υποζώνης. Ωστόσο η μέση τιμή του πλάτους (ενέργειας) των προκλητών ταλαντώσεων παραμένει κατά κανόνα υψηλότερη για στόχους έναντι μη-στόχου, ακόμη και σε υποξαιμικές συνθήκες. Ιδιαίτερα στην υψηλή γάμμα υποζώνη (28-60Hz) παρατηρήθηκε πολύ ισχυρή αλληλεπίδραση μεταξύ στόχων και υποξίας. Στις βαθύσυχες άλφα και βήτα (8-20Hz) υποζώνες, η διαφορά μεταξύ στόχων και μη-στόχουν κάτω από υποξαιμικές συνθήκες ψάχνει τον πλέον καθοριστικό ρόλο στην έκλυση μεγαλύτερου πλάτους P3 επαρμάτων ίσως και στην ελαφρά βράχυνση της χρονικής υστέρησης των P3 κορυφών, και τελικά στην πιο ευνοϊκή αναγνώριση και απάντηση για κατηγορικούς στόχους.

Η στατιστική ανάλυση διακύμανσης του ολικού πλάτους (ολικής ενέργειας) των επαγόμενων ταλαντώσεων για το αντίστοιχο χρονικό πιο εκτεταμένο όψιμο (200-600ms) στάδιο αποκρίσεων που σχετίζεται με μια άλλη μορφή επεξεργασίας της οπτικογνωστικής πληροφορίας (βλ. κεφάλαιο 4), κάτω από υποξαιμικές συνθήκες έδειξε μια σαφή και σημαντική αύξηση της ταλαντωτικής ενέργειας σε όλες τις φασματικές ζώνες και συχνότητες εξίσου και για τα δύο κατηγορικά ερεθίσματα. Είναι δε χαρακτηριστικό ότι σε αυτό το διάστημα κάτω από νορμοξικές συνθήκες η μέση ολική ταλαντωτική ενέργεια ήταν σημαντικά μεγαλύτερη για μη-στόχους στις υψηλότερες άλφα και βήτα (8-20Hz) υποζώνες, ενώ για στόχους ήταν σημαντικά μεγαλύτερη στις χαμηλότερες θήτα και δέλτα (1-8Hz) υποζώνες. Οι διαφορές αυτές διατηρήθηκαν αναλλοίωτες κατά την αύξηση που προκάλεσαν οι υποξαιμικές συνθήκες. Το τελευταίο υποδηλώνει ότι η επεξεργασία των μη-στόχων είναι τουλάχιστον το ίδιο αν όχι περισσότερο εργώδης από την επεξεργασία των στόχων.

Συμπερασματικά, οι υποξαιμικές μας συνθήκες (Hgb-SatO2%≈80%) προκάλεσαν σημαντικούς βαθμού διαταραχή στο συγχρονισμό φάσης μεταξύ μοναδιαίων καταγραφών στο πιο πρόιμο στάδιο (50-250ms) των οπτικογνωστικών αποκρίσεων που σε υψίστης ζώνης (Hz) σχετίζονται με τη γενική κατηγορική διάκριση των οπτικών ερεθισμάτων σε στόχους ή μη-στόχους και σε βαθύσυχες ζώνες (~20Hz) εξηγούν τη σημαντική μείωση στο πλάτος του P1 επάρματος των προκλητών δυναμικών. Επίσης προκάλεσαν αντιρροπιστικά σημαντική αύξηση της μέσης εκλογέμενης ενέργειας των προκλητών (φασικά-κλειδωμένον) ταλαντώσεων στο πιο ύστερο στάδιο (300-500ms) των οπτικογνωστικών αποκρίσεων που σε υψίστης ζώνης (~20 Hz) σχετίζονται με
εξειδικευμένες κατηγορικές αποκρίσεις συζευγμένες με κινητικές απαντήσεις για στόχους έναντι μη-στόχων και σε βαθύσυχες ζώνες (<20Hz) εξηγούν τη σημαντική αύξηση στο πλάτος του P3 επάρματος των προκλητών δυναμικών. Τέλος, προκάλεσαν αντιρροπητικά σημαντική αύξηση της μέσης επαγόμενης ενέργειας των ολικών (κυρίως μη φασικά-κλειδωμένων) ταλαντώσεων στο πιο εκτεταμένο μετερεθισμικό στάδιο (200-600ms) των οπτικογνωστικών αποκρίσεων που διαμορφώνονται κυρίως σε βαθύσυχες ζώνες (<20Hz) και σχετίζονται με την πιο ποικιλή και λεπτομερή αντικειμενοστραφή επεξεργασία και συναρμογή με κινητικές αποκρίσεις για στόχους ή περαιτέρω διερεύνηση της εικόνας για μη-στόχους.

Αυτά τα ηλεκτροφυσιολογικά και συμπεριφοριστικά αποτελέσματα κάτω από υποξαιμικές συνθήκες μπορούν να ερμηνευθούν σαν μια μορφή άμεσης προσαρμογής ή δραστικού «εγκλιματισμού» του εγκεφάλου σε συνθήκες οξείας υποξικής πρόκλησης. Φαίνεται ότι αποσκοπούν στη μείωση της κατανάλωσης οξυγόνου/ενέργειας και βελτιστοποίηση της ισορροπίας των μεταβολικών και λειτουργικών αναγκών απόκρισης του εγκεφάλου σε περιβαλλοντικά ερεθισμού της ενδιάφερσης ενδιαφέροντος («στόχους») με την ευρύτερη έννοια του όρου). Έτσι ώστε, με τα ελάχιστα οπτικά δεδομένα και την ελάχιστη δαπάνη οξυγόνου/ενέργειας για την επεξεργασία τους, να διατηρούνται αποδοτικές οι οπτικογνωστικές λειτουργίες και λειτουργική η συμπεριφορά των υποκειμένων μέσα στο περιβάλλον τους ακόμη και κάτω από τις πιο αντίξοες συνθήκες. Στη συγκεκριμένη περίπτωση, οι εικόνες στόχου που περιέχουν ζώα απαιτούν την ελάχιστη οπτική πληροφορία και χωρική επεξεργασία ιδιοτήτων-γνωρισμάτων των εικόνων και άρα την μικρότερη κατανάλωση οξυγόνου/ενέργειας για την ανίχνευσή τους σε αντίθεση με τις εικόνες μη-ζώων. Δηλαδή τα υποκείμενα μπορούν να εξάγουν κρίσιμα επιμέρους χαρακτηριστικά γνωρίσματα των αντικειμένων στόχων (ζώων: κεφάλι, μάτια, πόδια, κλπ) που οδηγούν σε υλικοκινητικές ταχείες συζευγμένες με αντικειμένα ταχείες συζευγμένες ταχείες συζευγμένες με αντικειμένα ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες ταχείες συζευγμένες
μέση εκλυόμενη ενέργεια των προκλητών (φασικά-κλειδωμένων) ταλαντώσεων ιδιαίτερα για τους στόχους. Επίσης μπορούν να αυξήσουν αντιρροπηστικά και τη συνολική επαγόμενη ενέργεια (κυρίως μη φασικά-κλειδωμένων) ταλαντώσεων σε χαμηλότερες και διαφορετικές για στόχους έναντι μη-στόχου υποζώνες. Είναι προφανές ότι από το 95% μέχρι κάτω του 50% κορεσμού της αιμοσφαιρίνης σε οξυγόνο (Hgb-SatO2%) ορίζεται μια δυναμική περιοχή αποκρίσεων και συμπεριφοράς του εγκεφάλου. Ολοένα και χαμηλότερα επίπεδα Hgb-SatO2% συνεπάγονται αρχικά πλήρη αντιρρόπηση, στη συνέχεια έναν αμφίρροπο συμβιβασμό μεταξύ κατασταλτικών δράσεων της υποζώσας και αντιρροπηστικών μηχανισμών, προοδευτικά αισθητή κάμψη σε διάφορες λειτουργίες του εγκεφάλου (συμπεριλαμβανομένων και των οπτικογνωστικών) μέχρι πλήρους έκπτωσης αυτών και αιφνιδιαίως από τη συνείδηση. Ολοένα και χαμηλότερα επίπεδα Hgb-SatO2% συνεπάγονται αρχικά πλήρη αντιρρόπηση, στη συνέχεια έναν αμφίρροπο συμβιβασμό μεταξύ κατασταλτικών δράσεων της υποζώσας και αντιρροπηστικών μηχανισμών, προοδευτικά αισθητή κάμψη σε διάφορες λειτουργίες του εγκεφάλου (συμπεριλαμβανομένων και των οπτικογνωστικών) μέχρι πλήρους έκπτωσης αυτών και αιφνιδιαίως από τη συνείδηση.
χαρακτηρισμό, τη διάγνωση και την παρακολούθηση εγκεφαλικών βλαβών ή άλλων οξέων και χρόνιων παθολογικών καταστάσεων του εγκεφάλου (οφειλόμενων ή μη στην υποξία) μέσα από την εξέταση αυτών των αμφίρροπων συμβιβασμών, της κάμψης και των αποθεμάτων αντιρρότησης των οπτικο-αντιληπτικών και ανώτερης τάξης γνωστικών-νοητικών λειτουργιών του εγκεφάλου.
PREFACE

Human vision is one of the most complex perceptual and representational cognitive systems that employs or engages more than 50% of the entire cortical tissue mass, with different visual and higher order cognitive sub-processes involving almost all brain lobes, cortical and subcortical structures (occipital, temporal, parietal, frontal, thalamus, basal ganglia) and major brain regions (more than 32 different brain regions-centers have been implicated in different steps and stages of visual cognitive information processing).

In an endeavor to develop Biomedical (Neuro)Engineering (BME) tools for functionally studying acute and chronic brain disorders (i.e. brain hypoxia), we decided to probe the entire visuocognitive system throughout, from the elementary visual sensory to the complex categorical level by implementing an experimental single-choice reaction classification (‘go/no-go’) task of ultra-rapid visual categorical and discriminative brain stimulation and concurrent measurement of electrophysiological event-related brain responses in the time and the joint time-frequency domains.

In our categorical visuocognitive classification task run under conditions of normoxia vs. hypobaric hypoxia (moderate reduction in blood oxygen saturation levels around ~80%), we investigate the event-related potentials (ERP) and broadband event-related oscillations (ERO) generated at occipitoparietotemporal cortical areas until subjects produce a motor response upon categorization of the targets (‘animal’ images elicited productive behavioral responses), while they suppress it for categorical nontargets (‘nonanimal’ images elicited inhibitory behavioral responses).

The electrophysiological study of human brain hypoxia imposes serious technical and ethical limitations. Ethical constraints did not allow us to expose human subjects into neither too severe hypoxic conditions (blood oxygen saturation levels <75%) nor for too long time periods (>15 minutes). Our available and ethically approved conditions of experimentally induced brain hypoxia comprised a hypobaric chamber (offered by the Hungarian Airforce – Aerospace Program) which could generate conditions of lower hypobaric pressure and equivalent ambient atmospheric hypoxia and consequent moderate degree of blood hypoxia (hypoxaemia) and tissue (e.g. brain) hypoxia given the compensatory physiological mechanisms of our healthy subjects. Therefore the collective term “hypobaric hypoxia” denotes the condition of hypoxia due to low atmospheric pressure levels, as naturally occurs in high-altitudes, and it is a safe, elegant and efficient way of inducing moderate brain hypoxia in order to study in electrophysiological terms its effects on visual and cognitive brain functions.

Our BME methods and techniques are based on the comprehensive time and time-frequency analysis of electrophysiological brain responses, that is, event-related potentials (ERP) and event-
related oscillations (ERO) evoked or induced by complex categorical visuocognitive stimuli. We present the methods of classical ERP processing and conventional statistical analysis in the time domain. In the frequency domain we reveal the disadvantages of the traditional Fourier Transform when applied on short and nonstationary task-relevant EEG segments. Within the frame of the optimized multiresolution joint time-frequency decomposition method, we introduce the continuous wavelet transform which allows for an advantageous 2D time-evolving broadband representation of the amplitude (energy) and phase distribution of the EEG signal.

The amplitude and phase analysis of the event-related broadband oscillations allows us to obtain crucial new complementary information about the evoked/phase-locked energy, the intertrial phase coherence and the total/induced (non-phase-locked) energy of the event-related oscillatory activity. We further develop a novel method of statistical parametric time-frequency map analysis which reveals the statistically significant differential cognitive (categorical) task-relevant broadband oscillatory activity between categorical stimuli across subjects, its topography across scalp sensors and its precise time-localization until the bulk of motor responses is elicited. Finally, we apply the generalized 3-way analysis of variance (3way-ANOVA) for the more reliable and (statistically) safe analysis of the cognitive (categorical) task-relevant event-related potentials and broadband oscillatory activity across categorical stimulus conditions and oxygen-level groups.

Our biosignal processing methods and statistical analysis techniques yielded outstanding results, which open the way for the development of a very promising, both sensitive and practical, neuroengineering tool (brain “stress-test”) that will allow for the functional in-depth study, rapid diagnosis, continuous monitoring and in-time management of acute and chronic brain disorders, such as brain hypoxia.
I. CHAPTER 1 - INTRODUCTION

1.1. Brain Hypoxia (Pathophysiology)

1.1.1. Hypobaric Hypoxia

Hypobaric hypoxia is the condition of hypoxia that results from exposure to low atmospheric pressure levels, with a consequent reduction of the pressure gradient down the respiratory system in the arterial blood partial pressure of oxygen-\( \text{O}_2 \) (\( \text{PaO}_2 \)). Such conditions are present in high-altitudes (mountains, airplanes, space shuttles) and stimulate complex human physiological respiratory (ventilation), circulatory (blood flow) and different tissue adaptation (metabolic) processes to withstand the hypoxic challenge (Guyton AC & Hall JE, 1996; Peacock AJ, 1998). The single best collective index of sufficient atmospheric \( \text{O}_2 \) supply, respiratory uptake and systemic delivery to different tissues (\( \text{O}_2 \)-carrying capacity of blood) is the oxygen saturation level of haemoglobin-Hgb (SatO\(_2\)%), (Fauci AS et al., 1998; Ganong WF, 2005). Normally the SatO\(_2\)% is \( \geq 97\% \) corresponding to a \( \text{PaO}_2 \) of >90mmHg.

1.1.2. Pathophysiology of Brain Hypoxia

The brain is certainly the most sensitive organ to hypoxic insults, whether systemic or local (i.e. cerebral ischemia) (Raichle ME, 1983; Lutz PL et al., 2005). The 75% SatO\(_2\)% level of hemoglobin (that is, on average 3 out of 4 heme groups binding \( \text{O}_2 \)) marks the inflection point in the sigmoidal \( \text{O}_2\)-Hgb dissociation curve, below which rapid decline <40mmHg in \( \text{PaO}_2 \) ensues, and exhausts the arterio-venous \( \text{O}_2 \) gradient (Pa-\( \text{vO}_2 \)) so that brain tissue relies merely upon local metabolic and vasoregulatory (blood flow) circulation mechanisms for extracting any further \( \text{O}_2 \) (Guyton AC & Hall JE, 1996; Fauci AS et al., 1998; Ganong WF, 2005). Severe systemic hypoxaemia (SatO\(_2\)%<50\% \approx \text{PaO}_2<25\text{mmHg}) by means of acutely developing ‘cerebral anoxia’ may result in loss of consciousness within 15-30 seconds and irreversible brain damage after 5-10 minutes (Adams RD et al., 1997; Fauci AS et al., 1998). Less severe systemic hypoxaemia (SatO\(_2\)%= 50-75\% \approx \text{PaO}_2=25-40\text{mmHg}) through excessive or prolonged cerebral hypoxia can cause variable deteriorative effects ranging from subtle cognitive and psychomotor disturbances (Denison DM et al., 1966; Green RG & Morgan DR, 1985; Fowler B et al., 1993; Bartholomew CJ et al., 1999; Li XY et al., 2000) to marked neuropsychological impairment affecting memory, visual spatial
functions, cognition and personality (Regard M et al., 1989 & 1991; Caine D & Watson JD, 2000; Virués-Ortega J et al., 2004 & 2006; Fayed N et al., 2006). In this context, ‘hypoxaemia’ refers to blood hypoxia and constitutes our measurable quantitative experimental variable, whereas ‘hypoxia’ is more general qualitative term that refers either to causative ambient (hypobaric hypoxia) or consequent tissue (including brain tissue hypoxia) lower than normal O₂-tension levels. The level of hypoxia, how rapidly it develops, how long it is sustained, pre-conditioning and subject sensitivity, are all critical factors of the degree of functional compensation versus impairment or reversibility of damage it may be inflicted (Adams RD et al., 1997; Lutz PL et al., 2005).

1.1.3. Pathophysiology of Hypobaric Hypoxia

An individual exposed to hypoxic hypoxia (e.g. as the systemic resultant of hypobaric hypoxia at about 10,000 ft), experiences a reduction in their SatO₂% level from a sea level value of >97% to a value of approximately 90% - 92%. In response to this relatively mild insult, the cardiac and respiratory rates increase slightly. These physiological responses continue as altitude increases. At about 15,000 ft the SatO₂% drops to a value of approximately 80% - 82% and in response to this relatively moderate insult, the cardiac and respiratory rates increase further. Breathing air at 25,000 ft results in a doubling of the heart rate and an increase of 40 to 60% in the respiration rate. For a normally healthy person, these responses provide a measure of protection up to about 13,000 ft for periods of less than 60 minutes or to about 15,000 ft for periods of less than 30 minutes.

1.1.4. Effects of Hypobaric Hypoxia on Visual, Cognitive and Motor Functions

The physiological effects of hypoxia are well understood in terms of gaseous exchange; times of useful consciousness and physical reactions, and excellent summaries are available in the literature (e.g., Ernsting J, Nicholson AN & Rainford DJ, 1999). The full range of accepted visual, general physiological and neuromuscular symptoms induced by hypobaric and consequent hypoxic hypoxia is detailed in Table 1. The altitude at which significant effects of hypoxia occur can be lowered by a number of factors. Physical activity, extremes of temperature, and anxiety all increase the body’s demand for oxygen and hence its susceptibility to hypoxia. Carbon monoxide inhaled in smoking and certain medications can also reduce the oxygen-carrying capacity of the blood and magnify the effects of hypoxia.
Table_1. Physiological and psychological effects on humans exposed to hypoxic hypoxia

<table>
<thead>
<tr>
<th>Visual</th>
<th>General</th>
<th>Neuro-muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in colour perception</td>
<td>Euphoria</td>
<td>Clumsiness</td>
</tr>
<tr>
<td>Decrease in peripheral awareness</td>
<td>Task fixation</td>
<td>Fine tremor</td>
</tr>
<tr>
<td>Decrease in acuity</td>
<td>Personality changes</td>
<td>Slurring of speech</td>
</tr>
<tr>
<td>Dimming</td>
<td>Fuzziness (not dizziness)</td>
<td>Slow movements</td>
</tr>
<tr>
<td></td>
<td>Amnesia</td>
<td>Hypoxic 'flap'</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental confusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity to cold or heat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of self criticism,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>judgement</td>
<td></td>
</tr>
</tbody>
</table>

As altitude increases, the various symptoms are accentuated and the time required for their onset reduces. A summary of specific cognitive effects and their trigger altitudes, as detailed by Ernsting J et al. (1999), is shown in Table 2.

Table_2. Cognitive effects of acute hypoxic hypoxia and the altitudes at which they can be expected to occur

<table>
<thead>
<tr>
<th>Altitude (feet)</th>
<th>Effects of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 5,000</td>
<td>Light sensitivity of the dark-adapted eye affected</td>
</tr>
<tr>
<td>Above 8,000</td>
<td>Short- and long-term memory affected</td>
</tr>
<tr>
<td>Above 10,000</td>
<td>Complex hand-eye co-ordination affected Performance on previously learnt coding and conceptual reasoning tasks affected</td>
</tr>
<tr>
<td>Above 12,000</td>
<td>Performance on pursuit motor tasks affected Choice reaction time on well learned tasks affected</td>
</tr>
<tr>
<td>Above 15,000</td>
<td>Fine hand tremor reduces ability to make precise adjustments</td>
</tr>
<tr>
<td>Above 16,000</td>
<td>Simple reaction time increased</td>
</tr>
</tbody>
</table>

While the effects of unprotected exposure to high altitudes are both rapid and harmful, the research on the effects of hypoxic hypoxia on humans at altitudes up to 15,000 ft is much less precise. Ernsting J et al. (1999) proposed that the failure to find consistent effects of hypoxia on performance, in this area of research, might be due to one or more of the following confounding variables:
1. The use of naive subjects with no previous exposure to hypoxia in a hypobaric chamber where their ignorance creates apprehension.

2. The variability of experimental altitudes achieved utilizing gas mixtures to simulate the reduced partial pressures of oxygen at altitude.

3. Individual variations in the physiological response to hypobaric hypoxia. The critical independent variable should be the 'effective' altitude of the subject, as measured by SatO₂%, rather than their 'nominal' altitude measured by the altimeter. In addition, few experiments have measured individual subject SatO₂%.

4. The use of tasks with little relevance to those performed in the aviation environment. Those that have used tasks such as 2D tracking and monitoring have shown conflicting results.

1.1.5. Effects of Hypobaric Hypoxia on Electrophysiological Parameters

In general, during rapid ascent to high altitudes human cognitive performance deteriorates abruptly, although some people can still successfully perform cognitive tasks even under extreme hypobaric conditions (up to 6000m) (Kida M & Imai A, 1993). The differences in responses may be attributed to different arousal levels, as can be reflected on EEG (Kraaier V et al., 1988), and different short-to-long term adaptation capacities (Hornbein TF & Schoene RB, 2001). Although human EEG studies of systemic hypoxia under hypobaric (Papadelis C et al., 2007) or normobaric (Schellart NA & Reits D, 2001) conditions have demonstrated increased power across all spectral bands, they cannot capture electrophysiological alterations coupled to underlying visual cognitive-behavioral subprocesses.

On the other hand, ‘altinauts’ (pilots, climbers, etc) trained under simulated hypobaric hypoxic conditions to endure with execution of their demanding tasks, need to be assessed in terms of sensitivity thresholds of their brain functions to hypobaric hypoxia. Our approved conditions of moderate hypobaric hypoxia (around 4500m for 15min, subject mean SatO₂%>75%) lie within a powerful and effective compensation range of human physiological and cognitive functions. They may not be sufficient to cause an overt decline in basic visuocognitive functions tested by our stimulus categorization paradigm (ceiling effect), but may still affect some psychometric parameters. The objective of this essay is to probe early alterations in visual categorical and psychomotor functions due to moderate hypobaric hypoxia as reflected on quite sensitive electrophysiological parameters.
1.2. Ultra-rapid Visual-Cognitive Brain Responses (Electrophysiology)

1.2.1. Fast-track categorical discrimination of target (‘animal’) vs. nontarget (‘nonanimal’) images

The human brain demonstrates an astonishing capacity in superordinate level fast-track categorization of complex images containing natural and artificial objects, i.e. animals vs. nonanimals (Thorpe SJ et al, 1996). Ultra-rapid presentation of images merges onset and offset stimulus-elicited cortical responses, prevents contamination of EEG data by image tracking exploratory eye movements, and imposes critical constraints on visual cognitive processes.

1.2.2. Electrophysiological brain responses coupled to visual sensory & cognitive subprocesses

Event-related potentials (ERPs) are generated from averaging across single-trials, enhancing the signal-to-noise ratio of the raw EEG signal. The spatial distribution and temporal latency of the ERP deflections represent the resultant of spatiotemporally summated cortical neuronal responses. Visuocognitive ERPs indicate the time course of visual information processing, including early exogenous components (P1: 80-120ms) sensitive to stimulus luminance, spatial frequency, contrast and low-level cues, as well as late endogenous components (N1: 120-180ms and P3: 300-500ms) modulated by the more complex processes of expectancy, attention, cognition search, categorical discrimination, identification, decision making, response choice and memorization (Licht R & Homberg V, 1990; Luck SJ & Hillyard SA, 2000; Luck SJ, 2005).

The electrophysiological correlates (classic ERP components) of the underlying visuocognitive processes have only recently started to be elucidated (Tanaka JW et al, 1999; VanRullen R & Thorpe SJ, 2001 a): An early process of nonspatial, coarse features extraction (Hillyard SA & Anllo-Vento L, 1998; Hopf JM et al., 2002) and categorical discrimination (VanRullen R & Thorpe SJ, 2001 b, Grill-Spector K & Kanwisher N, 2005) has been associated with modulations in the N1 component for target, meaningful or objects of expertise (Curran T et al, 2002; Proverbio AM et al, 2007; Tanaka JW & Curran T, 2001) and the N170 component for important-to-human faces and animate homomorphic entities (Allison T et al, 1999; Itier RJ & Margot JT, 2004, Rose M et al, 2004). A late process of fine-grain identification (recognition), memory pattern matching (old/new effects) and context updating (targets/non-targets), evaluating stimulus probability and categorical deviance, target expectancy and detection, and incorporating processes of psychomotor response production or inhibition, have all been associated with modulations in the P3 component.
1.2.3. Visuomotor response integration in single-choice classification / reaction task (productive vs. inhibitory responses)

Although P3 is influenced by the probability of an event, for stimuli with a 50/50 probability, the P3 amplitude will be higher for go (targets) than no-go (nontargets) trials in a go/no-go paradigm (Pfefferbaum A et al, 1985). So it has long been argued that stimulus categorization is more important than stimulus probability for the P3 amplitude (Nasman VT et al, 1990; Mecklinger A et al, 1993). In general, P3 amplitude is accepted to reflect the number of neurons allocated to the eliciting task (Wickens C et al., 1983), while P3 latency time to reflect the duration of stimulus evaluation (Kutas M et al., 1977), and can thus be prolonged by task difficulty.

1.2.4. Topography and source localization of early categorical discriminative visual cognitive processes

Topographic analysis of differential ERP waveforms (targets - nontargets) from EEG studies that provide optimal temporal (ms) resolution, evaluated by mass-univariate statistics across different subjects (Thorpe SJ et al, 1996; VanRullen R & Thorpe SJ, 2001 a) and supplemented by source localization attempts (Delorme A et al, 2004; Rousselet GA et al., 2004; Codispoti M et al., 2006), have already demonstrated differential effects across presented complex scenes containing animal vs. nonanimal objects as early as 150ms onwards over lateral occipitotemporal and central parietal/frontal areas, (Thorpe SJ et al, 1996; VanRullen R & Thorpe SJ, 2001 a, Rose M et al, 2004).

PET (Nakamura K et al., 2000) and fMRI studies (Grill-Spector K et al., 2001; Malach R et al., 2002; Grill-Spector K & Malach R, 2004) that provide optimal spatial (mm) resolution have established that early categorical representation and discrimination processes on all visual objects involve the lateral occipital complex (LOC: lateral occipital cortex, inferior temporal gyrus, posterior & mid fusiform gyrus) and are further distributed over category-selective areas down the ventral (fusiform face area, parahippocampal place area, etc) and dorsal (V7, intraparietal sulcus, etc) processing streams (Grill-Spector K & Malach R, 2004). Within the lateral and ventral occipitotemporal cortex, specific categorical modules have been demarcated, showing selective
activation, low-level cue-invariance and perceptual constancy for different kinds of visual objects (e.g. faces, animals vs. nonanimals, houses, scenes, etc).

1.2.5. A novel tool to diagnose, monitor and study acute or chronic brain pathophysiology

In conclusion, visuocognitive electrophysiological brain responses studied with as few as possible sensors at posterior (occipitotemporoparietal) brain sites together with psychometric tests may provide a fairly good index that can objectively quantify the level of sensory and cognitive impairment and/or compensation under hypoxic conditions (and potentially under many other acute or chronic brain insults).
II. CHAPTER 2 - MATERIALS

2.1. Materials (Experimental Set-up)

2.1.1. Human Subjects – Selection and Ethical Constraints

Ten healthy subjects (8 male, 2 female) with a mean age of 29.2 years (ranging from 23 to 37 years) participated in the experiment. The subjects were volunteers from the hospital staff, free of any cardiorespiratory history, neurological and psychiatric disorder or substance abuse. All were right-handed with normal color vision and normal or corrected-to-normal visual acuity. Subjects had history of previous exposure to hypobaric chamber conditions without any signs of fear, anxiety or apprehension. Written consent was obtained from all subjects prior to testing. The entire procedure was approved by the local ethics committee.

2.1.2. Electrophysiological Recordings (EEG Data Acquisition)

EEG activity was continuously recorded in a dark, acoustically and electrically shielded chamber with SynAmps amplifiers (4.1 Neuroscan) with gold cup electrodes (6mm diameter) which were placed with electrode paste at seven occipital-parietal electrode sites (Pz, P3/P4, P7/P8, O1/O2) in accordance with the 10-20 International System, and referred to linked earlobes with a nasal ground. Impedances were kept below 5KΩ. In order to control eye movements/blink, a concurrent electrooculogram (EOG) was recorded. EEG signals were amplified 1000 times, digitized at 1000Hz sampling rate and bandpass-filtered through an analogue (Neurosoft) Butterworth filter at 0.05-200Hz. The default SynAmps notch filters to remove 50Hz or other interferences were avoided.

The continuous EEG data recordings were offline segmented to 1500ms long epochs synchronized to the visual stimuli, from 500ms before picture onset to 1000 ms after onset. Computerized rejection of electrical artifacts was performed before averaging to discard epochs in which eye movements, blinks, excessive muscle potentials, or amplifier blocking occurred. All trials were thoroughly checked for artifacts and discarded using a ≥100µV criterion for EOG and a [-50; +50 µV] criterion over the interval [-300; +800 ms] at all seven occipito-temporo-parietal sensors. Only correct responses were included in the subsequent averages. This left on average ~200 artifact-free and correct-response single-trials to analyze for each one of the four: O2-level
(hypoxia vs. normoxia) x stimulus-condition (targets vs. nontargets) combinations, per channel on every subject.

2.1.3. Conditions of Hypobaric Hypoxia (Hypobaric Chamber)

There was a gradual reduction in the hypobaric chamber pressure from 760mmHg (1Atm or 101.325kPa) to 429mmHg (=0.564Atm or 57.182kPa) within 5 minutes, which is equivalent to rising to 15,000 ft (=4572m) heights. Hypobaric conditions were not manipulated beyond this level, as we were interested in the early subtle changes such moderate hypoxia may induce on evoked categorical visuocognitive responses within effective compensation range and because of ethical constraints, which did not furthermore allow subjects to remain in these conditions longer than max.15min and to desaturate on any occasion below 70% or on average throughout this period below 75%. Vital functions (including Pulse Rate, ECG, Peripheral Arterial Sat%O₂, EEG) were monitored to ensure the safety of the subjects and to alert us in case of an emergency. All ten subjects were measured twice (first for normoxia and then for hypoxia – within subjects design) with no time delay between measurements.

2.1.4. Conditions of Hypoxaemia and Hypoxic (Tissue) Hypoxia

At this point we have to make a useful distinction: hypoxia is a much more general term used to describe lack of oxygen, whether in the atmospheric or ambient environment, or in the body organs, tissues or cells. Hypoxaemia is basically hypoxia in one particular body tissue: the blood tissue (hypox+aemia(=blood)). In our experiment, we manipulated only hypobaric chamber pressure, without affecting the relative partial concentrations of air gases, and we measured the average level of systemic hypoxemia at the peripheral arterial circulation, which correlates fairly well with the O₂ content of the arterial blood, given that the patients are not anemic or have no other Hemoglobin (Hgb) disturbances. By measuring peripheral arterial blood saturation of oxyhaemoglobin (Hgb-SatO₂%), we basically measure the blood O₂ that is chemically bound to hemoglobin, which constitutes the vast majority of O₂ found in the arterial blood, and provides a reasonably good approximate measure of the systemic hypoxaemia on the arterial side of the circulation (due to the peculiarities of the peripheral blood circulation of every individual and the inaccuracies of any peripheral clip oximeter, peripheral Hgb-SatO₂% measurements are not exactly equal but in healthy individuals good approximations of the arterial blood Hgb-SatO₂% levels).
The two terms (hypoxia and hypoxaemia) are not interchangeable and cannot simply replace each other. Therefore from now on, there will be a particular reason and meaning every time we use the one or the other term. In the above defined context, ‘hypoxaemia’ is our measurable quantitative experimental variable, whereas ‘hypoxia’ is a much more general qualitative term that refers either to the causative ambient (hypobaric hypoxia) or the consequent different tissue (including the brain tissue hypoxia) lower than normal O₂-tension (concentration) levels, which by no means were exactly measured in our experimental set-up, but are an inevitable result of hypoxaemia. The following table (Table_3) provides a good description with rough figures of the normal O₂-concentration gradient levels (O₂ partial pressure cascade) from the ambient environment down into the cells and rough number definitions of hypoxaemia and hypoxia:

**Table 3.** Physiological ranges and definitions of hypoxia at different levels of the ambient – respiratory – circulatory – tissue – cellular systems through the key measurable variables of PO₂ (mmHg) and Hgb-SatO₂% in healthy subjects

<table>
<thead>
<tr>
<th>O₂-gradient levels</th>
<th>PO₂ (mmHg)</th>
<th>Hgb-SatO₂%</th>
<th>Hypoxia</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspired air (trachea)</td>
<td>150</td>
<td>99</td>
<td>&lt;140mmHg</td>
<td>Hypobaric Hypoxia</td>
</tr>
<tr>
<td>Alveolar air (lungs)</td>
<td>100-103</td>
<td>99</td>
<td>&lt;90mmHg</td>
<td>Pulmonary Hypoxia</td>
</tr>
<tr>
<td>Arterial blood (systemic circulation)</td>
<td>80-100</td>
<td>95-99</td>
<td>&lt;80mmHg</td>
<td>Arterial Blood Sample OR Pulse Oximetry ►reflects systemic/organ hypoxaemia</td>
</tr>
<tr>
<td>Capillary network (local circulation)</td>
<td>40-50</td>
<td>75-85</td>
<td>&lt;40mmHg</td>
<td>Venous Blood Sample ►reflects indirectly systemic/organ tissue hypoxia</td>
</tr>
<tr>
<td>Interstitial space (extracellular)</td>
<td>20</td>
<td>30-36</td>
<td>&lt;20mmHg</td>
<td>Implant Tissue Electrode ►reflects directly organ tissue hypoxia</td>
</tr>
<tr>
<td>Mitochondria (intracellular)</td>
<td>1-20</td>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We don’t know the exact relationship of hypoxaemia (=in our case, best measured blood hypoxia as peripheral Hgb-SatO₂%) and tissue hypoxia (for example, in our case, brain tissue hypoxia) and the definition of such a relationship is beyond the intentions of our assay. Furthermore, compensatory mechanisms operating at the systemic, organ, tissue and cellular level (with different capacity and adaptability for different individuals) can substantially influence the characteristics of this relationship. Nevertheless, because diffusion from the blood to the tissues primarily drives O₂ transport, when compensatory mechanisms at the systemic (blood circulation) and local (organ/tissue) level (including the extreme-most shifts in the Hgb-O₂ dissociation curve) have been totally exhausted, only then tissue hypoxia tends to almost linearly follow the level of systemic hypoxaemia. This occurs after sufficient time exposure (30 seconds to very few minutes) to extremely low Hgb-SatO₂%≤50% (≤30%) or Pₘ(arterial)O₂≤ 20 mmHg. Normally the Hgb-
SatO₂% is ≥97% corresponding to a PaO₂ (arterial) of >90mmHg. Any PaO₂ < 90mmHg and basically PaO₂ ≤ 80mmHg constitutes hypoxaemia. As one realizes, from a PaO₂ of 80mmHg to a PaO₂ of 20mmHg there is a huge dynamic range over which multiple complex compensatory mechanisms operate to counteract arterial hypoxaemia and buffer tissue hypoxia. A key turning point would be somewhere at SatO₂%≈75% and below (PaO₂≈40mmHg and below) when respiratory mechanisms have been exhausted and cannot generate any more a sufficient O₂-tension (concentration) gradient in the blood (P(a-v)O₂≈0), so that tissue O₂ depends merely upon blood/organ circulation and local/tissue mechanisms for extracting any further O₂.

2.1.5. Visuocognitive Stimulation Conditions and Procedures

The EEG data were collected using categorical stimulus discrimination (classification) in a single-choice reaction task (go/no-go paradigm). The stimulus battery (Antal A et al., 2002) included 500 different digital color photographs of complex natural and urban scenes available from commercial databases. All images were carefully selected and matched for physical stimulus properties and low-level visual cues (image size, average luminance, root-mean-square contrast, color and tone balance, resolution and acutance). At the superordinate categorical level images could be classified as target versus nontarget stimuli. Target images contained different animals of different kinds: mammals, birds, reptiles, sea creatures, insects, etc in their natural and man-made environments. Nontarget images comprised complex scenes from different outdoor and indoor environments, natural scenes with landscapes (mountains, forests, rivers, lakes, seas), geographic environs (rural regions, tropical jungles, savannas, polars, aquatics), plants (trees, flowers, fruits, vegetables), foods, urban scenes with people (human faces, figures), buildings (houses, rooms, offices, shops), infrastructure (roads, streets, parks, stations, ports), vehicles & means-of-transport (cars, trucks, trains, boats, airplanes), artificial & man-made objects (tools, machineries, arts, technologies), etc to mention a few. Images in each category were chosen to be as varied as possible including both general views and close-ups. Subjects could categorize whether images contained an animal or not by eliciting a motor response (pressing a button only in the presence of an animal with their right index finger as accurately and quickly as possible within 1000ms from stimulus onset). A training block was given before the test to ensure that each subject understood the task.

For every subject, 500 different images were presented under normobaric and the same 500 images in totally different order under hypobaric conditions in four separate blocks of 125 trials. Subjects had never seen before and had no a priori information on the type, size, position, view or number of animals and nonanimals. Special care was taken in selecting out the basic (e.g.
mammals, sea creatures, etc vs. plants, landscapes, geographic environs, etc or buildings, infrastructure, vehicles, etc) and subordinate (e.g. apes, bovines, fish, etc vs. trees, green fields, marine places, etc or houses, streets, cars, etc) categorical-level image object compositions as well as the size, position, view or number of animals and nonanimals on every single photograph, so that beyond physical stimulus properties and low-level visual cues matching, images were balanced for categorization task difficulty across superordinate level categories (250 ‘animals’ target images versus 250 ‘nonanimals’ nontarget images). Images were presented in a completely randomized order and no images were presented twice within SatO₂%-levels in order to minimize stimulus-specific practice and learning effects as much as possible.

Categorical priming, practice and cross-learning effects could not be excluded though, because of re-exposure of subjects to a given categorical set of images and because within basic categories there are always interactions across subordinate object categorization processes (no matter how much different apes and bovines are, they still share common higher-order features: head (eyes, nose, mouth) – neck – body – legs – fur – tail). However, the huge number of different images and the immense variability of categorical exemplars used, the ultra-rapid and completely randomized sequence of their presentation can substantially attenuate such effects. For categorical practice and cross-learning effects that may build-up over time the more trials one gets exposed to, the training session also served to saturate and offset them as much as possible.

All stimuli subtended a vertical visual angle of 10 degrees and a horizontal visual angle of 15 degrees from a viewing distance of 100 cm. A small fixation cross was present in the center of the video screen before and after stimulus presentation controlled by a Pentium PC. The luminance of the stimulus area (80 cd/m²) and the background luminance (8 cd/m²) were held constant throughout the experiment. Participants were asked to fixate on the small cross in the center of the screen and avoid eye or body movements. Stimuli of nontargets (nonanimals) and targets (animals) were randomly flashed on the monitor with a 4-frame (4 x 1000/60 = 67ms) duration at a 1:1 probability ratio. The inter-stimulus interval was around ~1.5sec, the stimulus onset asynchrony (i.e. time between the onset of one image and the onset of the next image in a series) was random between 1300ms and 1700ms.

A huge number of 500 different images were presented under normoxia and the same 500 images in completely randomized order under hypobaric hypoxia. The fact that the images were chosen to be as varied as possible in their object compositions, while they were matched for low level physical stimulus properties, allowed so that the only systematic difference that could emerge across the 500 images was only at the superordinate categorical level: 250 target images that contained at least one animal among nonanimal objects (‘animals’) versus 250 nontarget images.
that contained only nonanimal objects (‘nonanimals’). Subjects had to categorize the 500 images at
the superordinate categorical level, that is whether they belonged to the ‘animal’ category (by
pressing the button = productive response) or the ‘nonanimal’ category (by not pressing the button
= inhibitory response). Pressing the button (eliciting a motor response) or not pressing it
(suppressing a motor response) are both forms of behavioral response as a result of categorical
decision-making. A successful behavioral response does not only mean correctly eliciting a motor
response in the presence of an ‘animal’ image but also correctly suppressing a motor response in the
presence of a ‘nonanimal’ image. Conversely, a failed behavioral response does not only mean
incorrectly suppressing a motor response in the presence of an ‘animal’ image but also incorrectly
eliciting a motor response in the presence of a ‘nonanimal’ image. Behavior towards nontargets
(‘nonanimal’ images) is as important to study as behavior towards targets (‘animal’ images).
III. CHAPTER 3 - METHODS

3.1. Methods of EEG signal processing in the time & frequency domains and statistical analysis

3.1.1. Electroencephalography (EEG) - Event-Related Potentials/Oscillations (ERP/ERO)

The scalp surface-projected brain signal (EEG) is a far-field potential resulting from the unique summation in space and time of stimulus/task-relevant and irrelevant oscillatory activities of an orders-of-magnitude higher mass of neuronal oscillators, mixed with additive and stochastic noise, and low-pass filtered through scalp structures (Luck SJ & Hillyard SA, 2000; Makeig S et al, 2004). In this context, event-triggered visuocognitive brain activity can only be extracted in a statistical sense, as a dominant oscillatory pattern of electrical activity emerging from the unique local spatial geometry, temporally synchronous and phase coherent activation of unit cortical domain dipoles that can constructively summate in space and time. Indeed the major EEG contributors are long pyramidal cells with their long axes perpendicularly oriented to the cortical surface and it is their spatiotemporally synchronized oscillatory currents that can generate field-potentials of sufficient magnitude to reach the scalp surface.

Furthermore, only resultant electrical dipolar sources of appropriate magnitude/orientation and phase coherence (locking or resetting) across single trials can yield activity of substantial magnitude to stand out against background EEG noise (high SNR: Signal-to-Noise Ratio) and dominate over task and processing stage-irrelevant, asynchronous or unstructured brain activity. (Makeig S et al., 2002; Delorme A et al, 2002). Therefore, for the “structured” oscillatory pattern of local dominant sources to qualify as stimulus or task-relevant, it must be strictly time-locked to stimulus onset, consistently detected in space (recording loci) in time (across single-trials) and across different subjects (statistical significance) and necessitates to be sufficiently modulated by visual stimulus and/or cognitive task-relevant parameters (Rugg MD & Coles MGH, 1995; Luck SJ, 2005).

3.1.2. Introduction on Time and Frequency analysis: Wavelet vs. Fourier Transform

EEG studies, contrary to fMRI studies that can only probe metabolic brain phenomena (time-scale of seconds), can detect electrical oscillatory brain dynamics distributed over a broad spectral range (time-scale of milliseconds). Traditional ERP analysis based on the amplitudes & latencies of
potential deflections defined on the averaged-out EEG signal allows only for low-frequency (<20Hz) high-amplitude (>3μV) activity to dominate the picture. The extraction of high frequency (≥20Hz) low-amplitude (≤3μV) oscillatory patterns from single-trial visuocognitive task-related EEG segments (events occurring within fractions of a second) by means of the Fourier Transform is obscured by the short-time series, the fixed time-frequency window resolution and the non-stationary nature of the short-lasting task-relevant EEG signal. The Wavelet Transform (WT) comes to the rescue as an advanced signal processing technique that optimizes multiresolution time-frequency (TF) analysis of short EEG segments containing signal transients and non-stationarities and given the appropriate ‘mother wavelet’ (i.e. complex Morlet) allows for a rather advantageous 2D-TF representation of both the energy and phase distributions of the EEG signal (Herrmann CS et al. 2004c).

3.1.3. Classical Event-Related Potential Processing and Generation (Time Domain)

The continuous EEG data recordings were offline segmented to 1500ms long epochs synchronized to the visual stimuli, from 500ms before picture onset to 1000 ms after onset. These concatenated segments were digitally (FIR) high-pass and low-pass filtered at 0.1 and 20Hz respectively. Event-related potentials on each trial epoch were baseline-corrected using the signal during the 300ms that preceded the onset of the stimulus (300ms pre-stimulus baseline). Therefore, for each subject, finally four distinct ERP waveforms per channel were obtained from averaging of these single-trials from -300ms before stimulus onset to +800 ms after stimulus onset. These subject-specific ERPs were used to identify and measure the different ERP components’ peak latencies and amplitudes that entered into further statistical analysis and then were used to produce the grand average waveforms (Figure 2.).

3.1.4. Conventional Event-Related Potential Statistical Analysis (Time Domain)

Grand average and differential waveforms were produced and multiple planned pointwise statistical comparisons on ERP waveforms of targets vs. nontargets were conducted across subjects at an uncorrected predefined 0.05 level (Figure 2.).

The peak amplitudes of the ERP components were extracted over defined time windows around the mean latencies of the major evoked potential peaks: P1 (100ms +/- 50ms), N1 (150ms +/- 50ms), P2 (230ms +/- 50ms), N2 (300ms +/- 50ms) and P3 (400ms +/- 100ms). Our analysis included all seven recording sensors of parietal-central (Pz), parietal (P3/P4), occipito-temporal
(P7/P8) and occipital (O1/O2) spatial distribution (Sensors of Interest: SOIs). During statistical analysis of variance, the five major ERP component peak amplitudes and latencies were treated each with a 3-way replicated measures ANOVA: 2 SatO2%-levels (blood Hgb-O2 saturation level of normoxic vs. hypoxic conditions) x 2 stimulus-conditions (animal target vs. nonanimal nontarget objects) x 7 recording SOIs (Pz, P3/P4, P7/P8, O1/O2).

For post-hoc comparisons, Tukey’s HSD tests were used which provide sufficient protection against multiple comparisons effects for each ERP component tested. Their results are presented as estimates of the mean (M), standard error (SE) and a 95% confidence interval (CI) for the true mean differences; if the CI does not contain 0.0, the difference is significant at the 0.05 level).

If a "global null hypothesis" of no hypoxic effect is tested using all (5x2) ten tests, and the hypothesis is to be rejected if one of the tests shows statistical significance, then a full Bonferroni correction should be applied, adjusting downwards the chance of rejection of each test at 0.05/10=0.005 to keep the overall chance of incorrect rejection at a predefined 0.05 level. However, for multiple time-subsequent electrophysiological variables (ERP deflections) measured all on every single subject mutual correlations must be considered, which require a partial Bonferroni correction for the alpha between 0.05 and 0.005, based on the overall mean correlation among outcome variables. If the “global null hypothesis” gets rejected, the five different ERP components corresponding to underlying visuocognitive subprocesses, can be more safely considered each one on its own merits at an 0.05 level as five predefined individual hypotheses of the hypoxic effect on five distinct subprocesses evaluated by a double (amplitude-latency) test at an 0.05/2=0.025 safe rejection threshold. If targets and nontargets are considered separately across normoxic - hypoxic conditions then this safe rejection threshold should be reduced down to 0.05/4=0.0125.

3.1.5. The Continuous Wavelet Transform - Multiresolution Time-Frequency Decomposition

In order to quantify changes in the broadband event-related oscillatory activity, a multiresolution joint time-frequency (TF) analysis of the data was conducted using a wavelet-based decomposition method (WT) of the processed EEG signal (Mallat S, 1989). This method provides a much better compromise between time and frequency resolution (Tallon-Baundry et al, 1997) than previously proposed methods using short-time Fourier transforms. It provides a time-varying energy of the signal distributed across subsequent frequency bands, leading to a 'continuous' TF representation of the signal. By keeping the number of wavelet cycles constant (or slowly frequency-adjusted at higher frequencies), wavelet TF analysis allows for a rather uniform resolution across different frequency scales (Mallat S, 1998).
The wavelet approach is essentially an adjustable window Fourier spectral analysis with the following general definition:

\[ W(a, b; X, \psi) = |a|^{-1/2} \int_{-\infty}^{\infty} X(t) \psi^* \left( \frac{t - b}{a} \right) \, dt, \]

in which \( \psi^*(\cdot) \) is the basic wavelet function that satisfies certain very general conditions (it must have zero mean and be localized in both time and frequency space), \( a \) is the dilation factor and \( b \) is the translation of the origin. Although time and frequency do not appear explicitly in the transformed result, the variable \( 1/a \) gives the frequency scale and \( b \), the temporal location of an event. An intuitive physical explanation of the above equation is very simple: \( W(a; b; X; \psi) \) is the 'energy' of \( X \) of scale \( a \) at \( t = b \).

Because of this basic form of \( at+b \) involved in the transformation, it is also known as affine wavelet analysis. Generally, \( \psi^*(\cdot) \) is not orthogonal for continuous wavelets for different \( a \). Although one can make the wavelet orthogonal by selecting a discrete set of \( a \), this discrete wavelet analysis will miss physical signals having scale different from the selected discrete set of \( a \). Therefore the nonorthogonal (pseudocontinuous) transform is useful for time series analysis (frequency distribution in time series), where smooth, continuous variations in wavelet amplitude are expected. Whether continuous or discrete, the wavelet analysis is basically a linear analysis. A very appealing feature of the wavelet analysis is that it provides a uniform resolution for all the scales. It is also very useful in analyzing data with gradual frequency changes (nonstationarities).

Since it has an analytic form for the result, it has attracted extensive attention from applied mathematicians. For specific applications, the basic (mother) wavelet function, \( \psi^*(\cdot) \), can be modified and tailored according to our needs. Since the wavelet acts as a correlation template for extracting underlying signal component features, its structure (waveform) should be as similar as possible to the very signal component structure it probes.

The complex Morlet wavelet is defined by a Gaussian enveloped (modulated) complex sinusoidal exponential function. The complex Morlet wavelet returns information about both amplitude and phase, and is better adapted for capturing oscillatory behavior with rather gradual frequency fluctuations. A family of Morlet wavelets is first constructed at specific frequency intervals and within a certain frequency range. Each wavelet has a gaussian distribution both in the time domain (SD_t: \( \sigma_t \)) and in the frequency domain (SD_f: \( \sigma_f \)) around the central frequency \( f_0 \):
\[ w(t, f_0) = (\sigma_t \sqrt{\pi})^{-1/2} \exp(-t^2 / 2\sigma_t^2) \exp(2i\pi f_0 t) \ \text{with} \ \sigma_f = 1/2\pi\sigma_t. \]

Wavelets are normalized so that their total energy is 1, the normalization factor \( A \) being equal to:
\[
A = (\sigma_t \sqrt{\pi})^{-1/2}.
\]

A wavelet family is characterized by a constant ratio \( f_0 / \sigma_f \), which should be chosen in practice between 3 and 8, usually greater than \( \sim 5 \) (Torrence & Compo, 1998). As it is obvious, the time resolution of this method increases with frequency, whereas the frequency resolution decreases.

The time-varying energy \([E(t, f_0)]\) of the recorded signal \((s)\) in a frequency scale or band is the norm of the result of the convolution of the corresponding complex Morlet wavelet \([w(t, f_0)]\) with the signal \([s(t)]\):
\[
E(t, f_0) = |w(t, f_0) \otimes s(t)|^2.
\]

Convolution of the signal by a family of wavelets provides a 2D-TF representation of the signal (Mallat S, 1989).

### 3.1.6. Continuous Wavelet Time-Frequency EEG Signal Transformation - 2D Representation

Time-frequency (TF) analysis of EEG was conducted by means of the continuous wavelet transform (CWT). Convolution of the EEG signal by a family of wavelets provides a 2D-TF representation of the signal. A family of six-cycle complex Morlet wavelets (Gaussian-modulated complex sinusoidal functions) was constructed at 1 Hz frequency steps from 1-60 Hz (broadband responses: BBR).

Each wavelet has a gaussian distribution both in time \((\pm \sigma_t)\) and frequency \((\pm \sigma_f)\) domains around the central frequency \(f_0\):
\[
w(t, f_0) = A \exp(-t^2/2\sigma_t^2) \exp(i2\pi f_0 t) \ \text{with} \ \sigma_t = 1/2\pi\sigma_f. \]

Wavelets are normalized so that their total energy is 1, the normalization factor \( A \) being equal to \((\sigma_t \sqrt{\pi})^{-1/2}\). Our wavelet family is characterized by a constant ratio \(f_0/\sigma_f \approx 2\pi\) so that at every central frequency \(f_0\) the “essential” temporal wavelet duration \((2\sigma_t)\) is \(2\times(1000/f_0)\)ms. At 40Hz this leads to wavelet duration \((2\sigma_t)\) of 50ms and spectral bandwidth \((2\sigma_f)\) of 12.74Hz. Therefore the exact time-frequency resolution of the wavelet depends on the analyzed frequency (Figure 1.).

The time-varying amplitude of the wavelet-transformed single-trial EEG signal in a frequency band around \(f_0\) is the norm of the result of the convolution of the compressed (by scaling factor \(a\)) and shifted in time (by parameter \(b\)) complex wavelet \(\Psi(t) = \exp(-t^2/2) \exp(i2\pi f_0 t)\) with the signal \(\text{eeg}(t)\), as follows:
\[
|w(t, f_0) \circ \text{eeg}(t)| = |A_{\Psi} |\Psi^*((t-b)/a) \cdot \text{eeg}(t)\, dt|,
\]
where \(\Psi^*(t)\) is the conjugate of the complex wavelet.
Figure 1. Complex Morlet wavelet structure, representation and time-frequency resolution characteristics in the Time and Frequency Domains at 20Hz, 30Hz, 40Hz and 50Hz respectively. In the upper panel we present the Time Domain representation of the complex Morlet wavelet, the real part (in red), the imaginary part (in blue) and the modulus or absolute magnitude (in green). In the lower panel we present the equivalent spectral domain characteristics (in blue).

3.1.7. Amplitude-Phase Analysis of Event-Related Oscillations (ERO) (Evoked/Phase-locked and Total/Induced)

The evoked (phase-locked to stimulus onset) broadband oscillatory activity is represented by the demodulated complex average of the wavelet-transformed single-trials (STCA-WT), which is equivalent to the absolute value of the wavelet transform computed on the average of the single-trials, that is, on the ERP (WT-ERP): STCA-WT = |(1/N)∑ Ψ(ψ(t-b)/a)·eeg_i(t)dt| = |AΨ|∫Ψ(ψ((t-b)/a)·eeg_i(t)dt| = WT-ERP, since WT is in essence a linear transform.

The non-phase-locked to stimulus onset (induced, canceled-out in the average) broadband oscillatory activity roughly corresponds to the total activity magnitude irrespective of the phase. To measure the sum of all (evoked and induced) - total broadband activity, at each frequency the moduli (absolute values) of the wavelet-transformed single trials are averaged across: STMA-WT = (1/N)∑ |AΨ|∫Ψ(ψ((t-b)/a)·eeg_i(t)dt|. 
The normalized complex time-varying magnitude of each wavelet-transformed single trial: \( (w(t, f_0) \circ \text{eeg}_i(t, f_0)) / |(w(t, f_0) \circ \text{eeg}_i(t, f_0))| \) averaged across single trials leads to a complex value or a “phase average” describing purely the phase distribution of the time-frequency region around central frequency \( f_0 \) and time sample \( t \). The modulus of this complex value, ranging from 0 (non-phase-locked activity) to 1 (strictly phase-locked activity) evaluates the strength of (amplitude-independent) phase-locking of broadband oscillatory activity across single-trials, termed the phase-locking factor (PLF). It reflects the level of synchronization in the TF phase distribution of cortical broadband oscillatory responses across single-trials.

After calculating all subjects 2D plane TF transforms, the frequency-specific baseline activity in a prestimulus period can be subtracted to yield values that indicate amplitude changes relative to baseline. When wavelet convolutions are computed, the convolution peaks at the same latency as the respective frequency component in the raw data, although the peak width will be smeared. Hence, the baseline was chosen to precede the stimulation by half the width of the wavelet to avoid the temporal smearing of poststimulus activity into the interval directly preceding the stimulus. Therefore, for the gamma frequency range (20-60 Hz) analyzed with a Morlet wavelet with 6 cycles (1000/20 ms x 6 \( \approx \) 300 ms), we used the time interval between -300 and -150 ms before the stimulus to compute the baseline values.

For task-relevant segments of EEG of less than ±500ms peristimulus, that is, for event-related cortical neuroelectrical oscillatory transient events that occur as bursts of activity and need to be precisely localized in time within less than half a second around stimulus onset, the 6-cycle complex Morlet wavelet is mostly optimal for high frequency EEG analysis (ERO optimally equal or above 20Hz and basically above 10Hz). Due to the convolution of the 6-cycle long wavelet (e-folding time) with the EEG signal, for frequencies above 20Hz the first and last 150ms (edge effects) of the signal had to be ignored during analysis (cone of influence). Furthermore, in order to avoid the temporal smearing of post-stimulus activity into the interval preceding the stimulus in the wavelet transform, likewise the first 150ms of the signal prior to stimulus onset have to be ignored. Given the 1400-1600ms long epochs and the roughly \(~500ms \) baseline recorded prior to stimulus onset, that leaves only the -300ms to -150ms prior to stimulus onset as useful/proper baseline reference interval and makes our time-frequency analysis more time-optimal for high-frequency oscillatory events (≥20Hz).

Oscillatory events between 10-20Hz would require statistical analysis of proper poststimulus intervals ≥300ms up to 600ms referenced to effective baseline intervals of at least 300ms length, while below 10Hz statistical analysis is relatively impractical: not only time localization of an event is impossible within so long EEG segments (≥600ms), but visual sensory and cognitive phenomena...
actually take place in much shorter time-scales (<500ms). Even worse, beyond ±300ms peristimulus it is more likely that there is contamination of the EEG signal by inevitable microsaccadic or exploratory eye movements and other EEG artifacts, let alone that merely cognitive activity is hard to separate from concurrent premotor (preparatory, executive or feedback) and motor activity. Therefore, the wavelet-transformed data were referenced on a pre-stimulus -300 to -150ms time-window and time-frequency analysis was considered as more time-optimal at worse for the beta band (>12Hz) and at best for the broad gamma spectral range (≥20Hz up to 60Hz). Nevertheless, the ≤12Hz spectral range (alpha band: 8-12Hz, theta band: 4-8Hz, delta band: 1-4Hz) was still evaluated, in order to gain a more comprehensive understanding on the broadband modulations across all different spectral components and their involvement in the subtle to the most critical underlying event-related oscillatory (ERO) dynamics that contribute to the generation of the classical event-related potential (ERP) components and thus help us improve the interpretation of the major ERP alterations observed under hypoxic conditions.

3.1.8. Statistical Parametric Time-Frequency Map Analysis across Categorical Conditions

We study categorical task-relevant broadband oscillatory activity (1-60Hz) by examining the differential evoked / induced broadband response amplitude (e/iBBR) and phase-locking factor (PLF) for target images (‘animals’) versus nontarget images (‘nonanimals’). In order to extract consistent Regions-of-Interest (ROIs) across all subjects’ TF planes for planned statistical comparisons across categorical stimuli and normoxic-hypoxic conditions thereafter, multiple pointwise statistical comparisons with a conventional parametric statistic (mass univariate T-statistic, uncorrected p<0.05 level) were performed for pairs of conditions on every central frequency component \( f_0 \) on the mean magnitudes of e/iBBR and PLF within a frequency-adjusted (2x1000/\( \sigma_t \) = 2x1000/\( f_0 \) ms) moving time-window centered at every time point \( t \) across subjects’ TF maps. A conventional nonparametric statistic (Wilcoxon signed-rank test) for mass univariate statistical comparisons was also initially employed, but since normality conditions were met and the results were exactly the same as those of the parametric T-statistic, analysis from thereon settled down with the latter one.

ROIs were defined for a central frequency \( f_0 \) and around a specific time point \( t_0 \) if the statistical differences between categorical stimulus conditions in these mean temporal e/iBBR and PLF values were sustained below the fixed p-value threshold (p<0.05) for time duration equal to or greater than \( ±\sigma_t \) (where most of the energy of the wavelet transform is concentrated), that is, two full wavelet cycles at \( f_0 \), equivalent to ≥2x1000/\( f_0 \) ms or time samples centered at time point \( t_0 \).
3.1.9. Analysis of Variance (3way-ANOVA) across Categorical Conditions and Oxygen Levels

Within specific ROIs time windows spanning across multiple adjacent spectral components, statistical analysis was carefully focused on few specific with minimal bandwidth overlap (at least one representative frequency component from each classical spectral range: 1-12Hz=delta/theta/alpha, 12-20=beta, 20-28=low-gamma, 28-60=high-gamma) central frequency components by means of multiple ‘planned’ statistical comparisons, that is, statistically safe post-hoc comparisons (Tukey’s HSD tests instead of simple paired student t-tests) of mean e/iBBR and PLF values within the frame of a 3-way replicated measures ANOVA: 2 SatO₂%-levels (normoxic vs. hypoxic conditions) x 2 stimulus-conditions (animal targets vs. nonanimal nontargets) x 7 recording SOIs (Pz, P3/P4, P7/P8, O1/O2).
IV. CHAPTER - 4
ELECTROPHYSIOLOGICAL RESULTS FOR CATEGORICAL TARGET REPRESENTATION AND DISCRIMINATION

4.1. Introduction on Visuocognitive Electrophysiological Brain Responses

4.1.1. The broadband temporal correlation hypothesis in visual feature binding

For almost two decades now, gamma-band (≥20Hz) oscillatory activity in the visual cortex has been postulated to expand the classical delta/theta/alpha/beta (<20Hz) spectral range to a broadband oscillatory medium for short-to-long range spatiotemporal synchronization of neuronal oscillators, functionally linking them through synchronized high firing rates, while overcoming temporal and spatial connectivity constraints even across disparate neuronal networks. The input (oscillatory postsynaptic) and output (coupled firing) activity patterns of neuronal networks, from individual neurons through population ensembles and columnar modules up to cortical domains can establish flexible dynamical temporal correlations that potentially underlie the hierarchical (bottom-up) binding of visual features into inexhaustible representations of coherent visual objects from simple sensory to complex perceptual levels (Singer W & Gray CM, 1995; Gray CM, 1989 & 1999).

Intracerebral recordings on animals (Rolls ET et al, 1994 & 1997) have demonstrated quite early visual cortical activation in time with a latency of 50-75ms and mean firing rates which can reach as high as 40-60Hz for the most effective stimuli vs. 20-40Hz for the least effective ones. It seems that a rate code is employed at least in the early stages of visual object representation in the striate and early extra striate associative visual cortical areas. A comparison of the latencies of the activation of neurons in different visual cortical areas V1, V2, V4, posterior inferior temporal cortex, and anterior inferior temporal cortex suggests that approximately 10 to 15ms is added by each processing stage, that is, neurons in the next stage of processing start firing soon after (~15ms) neurons in any stage of processing have started to fire. The fact that considerable information is available in short epochs of 20-100ms in the firing of neurons (10-50Hz) provides part of the underlying basis for this rapid sequential activation of connected visual cortical areas. These early high-frequency transient firing rates (>>12Hz up to 60Hz) of neurons in the visual cortical areas seem to play a key role in the rapid and reliable transmission and evaluation of new incoming visual information. The firing of neurons within a cortical area normally continues after the visual stimulus for several hundred milliseconds (another 200-300ms on average), although these late sustained firing rates are usually within a low-frequency range (≤20Hz). This suggests that there
may be a short-term visual memory implemented by the sustained firing of these neurons after a stimulus has disappeared, that may allow more and different modules of the visual system to be engaged through both horizontal (short-range) and vertical (long-range) columnar spatial associations and in a rapid temporal succession, thus establishing what we may call ‘functional spatial assemblies’ in a ‘time-multiplexing fashion’ sustained enough to feed forward to the next processing levels or receive critical feed back from them. In such dynamical systems, the exchange of information required to achieve rapid settling of the network into a final state can be very much faster than might be expected by taking the contribution of each stage as a separate time step. Attentional feedback (top-down) mechanisms from higher order occipito-parieto-temporal associative cortex may modulate (enhance or suppress) early visual cortex neuronal firing rates to selective visual features or global properties for the more effective (target) vs. less effective (nontarget) stimuli.

All these are also consistent with recordings in the inferior temporal cortex (ventral occipitotemporal pathway) in macaques showing that considerable coding information concerning visual object representation and global pattern recognition is available from inferior temporal cortex neurons as early as 100-150msec, even upon a single frame presentation (17ms) of a visual stimulus and with enhanced firing rates initially up to 60 spikes/sec being sustained at lower rates for up to 300msec poststimulus (Kovacs G et al, 1995). Therefore the (bottom-up) processing of animals, faces and non-animal objects down the ventral occipitotemporal stream as early as 100ms shows that global and cue-invariant information about visual objects is conveyed by neurons already in the first 100ms (Sugase Y et al, 1999). Similar latencies of 100-300ms have been postulated for spatial object representation and visuomotor response integration processes down the dorsal occipitoparietal pathway. Attentional processes instead may operate in a (top-down) feedback fashion, comparing incoming information with intrinsic representations and working memory templates, thus modulating bottom-up visual feature binding based on attended qualities and task requirements (Fries P et al., 2001, 1998; Singer W, 1999; Engel AK et al, 2001; Herrmann CS & Knight R, 2004), and resulting in competition of internal representations for reaching perceptual awareness (consciousness) and guiding task-relevant (e.g. visuomotor) behavior.

4.1.2. Gamma-band oscillatory responses in visual sensory and cognitive phenomena

EEG measurements at the scalp surface do not pick up responses from individual neural assemblies, but instead, average responses of a large number of cortical assemblies (orders of magnitude higher). The application of the WT on scalp-surface EEG in the study of different visual-
cognitive processing tasks has led to the detection and characterization of cortical gamma-band oscillatory responses ($\geq$20Hz) involved in many perceptual and cognitive functions such as feature binding (Tallon-Baudry C & Bertrand O, 1999), selective attention (Fries P et al., 2001b), long-term memory (Gruber T et al., 2004; Herrmann CS et al., 2004a) or speech perception (Crone N et al., 2001a,b). Even neurological and psychiatric disorders have been associated with gamma-band abnormalities. (Willoughby C et al., 2003; Gallinat J et al., 2004; Lee KH et al., 2003; Spencer KM et al., 2003 & 2004). However, there is still lurking skepticism about gamma oscillations, because of failures to detect them consistently, reliably or at all (Jürgens E et al., 1995 & 1999) and because of widespread confusion over the functional role of different types of gamma oscillations, notably an early phase-locked gamma response (approximately 100 ms after sensory stimulation) versus a later non-phase-locked or induced gamma response (with a latency around 300 ms or longer).

While most authors used to agree that the late induced gamma response was a correlate of various cognitive processes (Başar-Eroğlu C et al., 1996), recent evidence suggests that it may be the result of microsaccadic eye movements or at least inseparable from their corollary activity (Yuval-Greenberg S et al., 2008; Melloni L et al., 2009). On the other hand, some have argued explicitly that the early evoked gamma response is merely a reflection of early sensory processes (Karakas S and Başar E, 1998), “pure of cognition”. This assumption has been gaining ground until recently, because gamma-band oscillations have been found to depend on physical stimulus parameters similar to those for “exogenous” ERPs. That is, larger gamma-band responses have been obtained for larger stimuli, for central as compared to peripheral stimulation (Busch NA et al., 2004), and for higher spatial frequency (Tzelepi A et al., 2000; Bodis-Wollner I et al., 2001), while the quadrant of stimulation seems to affect the topography of gamma-band responses similar to ERP topography (Tzelepi A et al., 2000). Others have consistently found effects of cognition on induced gamma activity but reported no such effects on evoked gamma activity (e.g. Tallon-Baudry C et al., 1996; Gruber T et al., 2004).

However, various visual cognitive processes have indeed been found capable of modulating this early evoked gamma oscillatory response, such as visual feature-binding (Tallon-Baudry C et al., 1997; Herrmann CS & Mecklinger A, 2000), perception of meaningful or target objects (Keil A et al., 1999; Tallon-Baudry C et al., 1999), attention (Herrmann et al., 1999; Herrmann CS & Knight R, 2001; Debener S et al., 2003; Fell J et al., 2003) and the match-and-utilization model lately proposed by Herrmann et al. (2004a,b). Animal studies advantaged by intracortical recordings have demonstrated that feature-selective attention modulates the sensitivity of feature-selective neurons for orientation (McAdams C & Maunsell J, 1999), contrast (Reynolds J et al., 2000) or color (Motter B, 1994). Furthermore, selective binding, attention and memory, all enhance
oscillatory activity and its synchronization to coherent, meaningful, attended, primed or template stimuli in monkeys (Desimone R & Duncan J, 1995; Fries P et al., 2001) and humans (Tallon-Baudry C et al., 1996, 1997; 1999; Stefanics G et al., 2005; Herrmann CS et al., 2004 a,b). Hence, if cognitive factors do exert an influence on early evoked gamma-band responses, this would most probably result from the early interaction between bottom-up and top-down processes (Busch NA et al, 2006).

4.1.3. Broadband oscillatory responses in categorical object representation & discrimination

The higher the complexity order or the ‘cognitive load’ of the image stimuli, given the short time for visual feature extraction/integration and the broad range of categorical exemplars presented, the more assemblies aggregating through bottom-up processes and subjected to top-down influences will be modulated throughout the visual hierarchy and the more salient the differences between categorical target and nontarget stimuli will emerge at the scalp EEG (Rose M et al., 2004; Busch NA et al, 2006). For this reason, we employed a complex ultra-fast visual-search task on high object-load images (natural and urban scenes containing multiple visual objects and diverse categorical exemplars) subjects never had encountered before (Herrmann CS & Mecklinger A, 2001; Busch NA & Herrmann CS, 2003). Therefore, whatever systematic differences would emerge in cortical responses across the stimulus set could only be attributed to object-invariant superordinate-level categorization processes discriminating between categorical targets and nontargets, beyond the intrinsic variability of subordinate- and basic-level object categories.

The current study aims at examining possible modulations on cortical broadband frequency oscillatory responses (evoked, phase-locked and induced) with respect to the most abstract and complex form of visual stimulus processing: target categorical visual object representation and discrimination of diverse categorical exemplars across two superordinate-level classes (‘animals’ versus ‘nonanimals’). An attempt was made to determine within the posterior occipito (O1/O2)-parieto (P3/Pz/P4)-temporal (P7/P8) brain topography the timing of statistically significant differential effects of these cognitive processes on broadband responses (BBR = 1-60Hz) as compared to traditional event-related potentials (<20Hz) and further examine (in the next Chapter - 5) the effects of moderate brain hypoxia on broadband responses and the possible alterations in the underlying visuocognitive processes that generate them.
4.2. Electrophysiological Results on Categorical Target Discrimination

4.2.1. Event-related potentials (ERP <20Hz)

The grand-average ERP waveforms across all SOIs (Figure 2.) show more or less a comparable pattern, including all the major ERP peaks: P1 – N1 – P2 – N2 – P3. However, there are distinct topographic features across the different scalp sensors: for instance, the P1-N1-P2 wave complex dominates (highest amplitudes) at O1-O2 lateral occipital sensors. After the definite dominance of P1-N1-P2 triphasic complex at O1-O2 sensors, P1 is higher at dorsolateral (P8 > P4 > P3 > P7) and minimal at central (Pz) sensors, while N1 is higher at central (Pz) and minimal at lateral sensors. P2 is higher at occipitotemporal than lateral parietal sensors (P8-P7>P4>>P3) and minimal or nonexistent at central parietal (Pz) sensor. Interestingly, N2 peak is properly defined only at central parietal Pz sensor. Although the P3 component is ubiquitous, however, it is of highest amplitude at parietal areas (Pz>P4>P3) and of lowest amplitude at occipitotemporal sites (P8-P7).

Tracing the dominant ERP peaks (sequential order, amplitude & latency, previous knowledge of underlying sources and functions) across all SOIs one is tempted to roughly conjecture the most dominant scalp origins of the major ERP components: P1 dominates in lateral occipital areas. N1 dominates in lateral occipital areas and probably ventromedial occipitotemporal regions (hence second stronger projection at Pz). P2 dominates in dorsolateral occipitotemporal areas (hence second stronger projection at P8-P7). N2 occurs only at central parietal site and could also be projected from much deeper ventromedial occipitotemporal sites and/or even more anterior central-frontal sites. P3 dominates in central and then lateral parietal areas. Of course, the multiple underlying sources, generators and contributors to all these components cannot be established or excluded by our analysis, because we have made absolutely no attempt of source localization whatsoever. Nevertheless, the gross origins of the triphasic P1-N1-P2 wave complex and the P3 component initially from occipital, and then, ventrally and dorsally spreading, occipitotemporal and occipitoparietal cortical regions are more than obvious.

Statistical parametric analysis (pointwise-applied on the already <20Hz filtered ERP signal and even after application of a 25, 50 and 100ms or equal time samples moving average window for temporal smoothing, a process equivalent to low-pass filtering) across subject ERPs did not yield any significant differences for categorical stimulus conditions before the eminent P3 component from 300ms on poststimulus (Figure 2.). That is, in the low frequency range (<20Hz) of evoked occipital cortical responses (O1-O2 ERP) there was no differentiating effect of event-related
categorical visuocognitive activity but only after 300ms from stimulus onset (P3 component). Simply put, no consistent modulations across single-trials (with different categorical exemplars presented on each trial) and subjects emerged for our categorical task conditions below 20Hz and prior to 300ms. The only statistically significant and very briefly sustainable differentiating effect of event-related categorical visuocognitive activity before 300ms occurred at the occipitotemporal and central parietal sensors (P7-P8 and Pz), that was first higher for targets during the 150-200ms and then higher for nontargets during the 200-250ms time interval.

All these results are very interesting, because they indicate that, as it is consistent with many other studies (Thorpe SJ et al., 1996; VanRullen R & Thorpe SJ, 2001; Delorme A et al., 2004; Codispoti M et al., 2006; Proverbio AM et al., 2007),

i) the visuocognitive information processing spreads down the occipitotemporal and occipitoparietal streams (in retrospect, this justifies the selection of the specific 7 channels out of the 10-20 International System as our sensors-of-interest (SOIs)),

ii) the ‘nonanimals’ elicit differential N1-P2 posterior brain responses as early as 150ms from stimulus onset compared to ‘animals’ at dorsolateral (P7/P8) and ventromedial (Pz) projected occipitotemporal regions (similar findings have been reported for the N2 frontal anterior brain responses (dN150-300, Antal et al., 2002),

iii) the P3 component stands out as the most prominent and ubiquitous ERP component across all our SOIs that fundamentally and absolutely distinguishes among categorical stimulus conditions (targets with productive responses vs. nontargets with inhibitory responses) and

iv) as expected, the elicited P3 component has higher peak amplitudes and earlier peak latencies for targets with productive motor responses compared to nontargets with inhibitory behavioral responses, suggesting that cognitive processing in such a go/no-go paradigm is at least earlier completed and shows higher ERP gain amplification for targets than for nontargets.
Figure 2. Event-related potentials of categorical target (red) and nontarget (blue) stimuli, the major ERP peaks P1, N1, P2, N2 and P3 are indicated based on dominance – Differential waveforms (targets - nontargets) are plotted as the green line and pointwise statistical significant differences are plotted as the black line (significant higher ERP values for targets are indicated as +1.00 while significant higher ERP values for nontargets are indicated as -1.00)

4.2.2. Event-related broadband oscillations (ERO 1-60Hz)

4.2.2.1. Phase-coherence of broadband oscillations

The phase distribution (PLF) in the 2D time-frequency (TF) plane of the continuous wavelet transformed single trials from 1-60Hz were averaged out for every subject across 200 single-trials at every central frequency component $f_0$ and time point $t$. The resulting PLF TF-distributions of each subject were averaged across all subjects to yield so-called grand average PLF TF-distributions for categorical target versus nontarget stimuli at every scalp sensor (SOIs). The magnitude of the grand-average PLF TF-distributions for targets and nontargets was expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as
well as the difference of the two with respect to baseline scaled up from 0-100% (Figure 3). The phase locking factor (PLF) also named as the inter-trial phase coherence (ITPC), evaluates the synchrony in the phase distribution across n single-trials at frequency f and time point t on every scalp sensor (SOI). The inter trial phase coherence is an amplitude-independent measure of evoked (phase-locking or phase-resetting) activity. An ITPC value of one (1) indicates perfect phase coherence in all epochs, while random noise on the average have coherence of 1/sqrt(n) e.g. for 200 single-trials <0.07 (Nunez et al., 1997). Our grand-average PLF TF-distributions at lateral occipital sensor O1 show two peaks across 10 subjects and within the first 200-300ms poststimulus: one between 15-20Hz and one between 5-10Hz, with peak values reaching as high as 0.5 (strong phase-locking), while there was significant phase-locking of much lower value (weak phase-locking range: ≤0.4 for ≥20Hz, ≤0.3 for ≥25Hz, ≤0.2 for ≥30Hz) down to 0.07 for up to 40Hz for nontargets and much higher in magnitude and up to 60Hz for targets.

Nevertheless, at the lateral occipital sensor O1 as the relative (% from baseline changes) grand-average PLF TF-distributions and the pairwise differential (across target vs. nontarget categorical stimuli on every subject) relative grand-average PLF TF-distributions show and intersubject statistical parametric time-frequency map (SPTFM) analysis clearly confirms (Figure 3, bottom right), the statistically most significant and sustainable differential activity for targets vs. nontargets is distributed within this weak phase-locking range (PLF≤0.2 for ≥30Hz ) within the first 200ms poststimulus and then within the 20-30Hz (PLF≤0.4) and 15-20Hz (PLF≥0.4) within the first 300-400ms poststimulus interval.

Interestingly, in the intersubject statistical parametric time-frequency map (SPTFM) analysis, the highest t-scores occurred at 46Hz but from 100ms on and with less than 100ms sustainability. However, the 40Hz classical γ-band frequency component presents the earliest (onset within <100ms poststimulus) and longer lasting sustainability of statistical significance (below the p<0.05 threshold almost throughout the first 200ms poststimulus) and therefore proves to be the most critical time-frequency region (ROI) that distinguishes so early and effectively between categorical targets and nontargets at the occipital sensor O1, when ERP statistical analysis failed to demonstrate such early significant differential effect at any of the 7 channels (SOIs).

The next worthy to note is the 16Hz classical β-band frequency component which defines a ROI in the strong phase-locking lower frequency range (15-20Hz PLF≥0.4) from 50 -250ms poststimulus, again a period during which ERP statistical analysis did not show anything such at the same channel (O1) prior to 300ms poststimulus (onset of classical P3 component). One more thing to note here is that no statistically significant early (<first 300ns) differential effects occurred across targets-nontargets below 16Hz, that is, all the significant ERO modulations in intertrial phase-
locking/resetting occurred in the high frequency range (≥16Hz) and hence none of them could be captured by traditional ERP statistical analysis. Finally, few dispersed and short-lived patches of significant differential effects between targets and nontargets occurred between 300-500ms poststimulus and mostly around 10-30Hz. Significant higher PLF in this TF window may contribute to higher P3 amplitudes or earlier P3 latencies for targets compared to nontargets in the averaged time-domain responses (ERP).

Given these exciting findings at sensor O1, the intersubject statistical parametric time-frequency map (SPTFM) analysis was generalized and applied across all scalp sensors for target vs. nontarget categorical stimuli, in order to reveal the characteristic topographical distribution of broadband ROIs across scalp sensors and identify any possible ROIs of enhanced phase-locking (intertrial phase coherence or synchronization) for targets (red) vs. nontargets (yellow) (Figure 4.). The results indicate that the best and fairly similar such ROIs characteristically emerged at both lateral occipital scalp sensors (O1 and O2) while in no other channels could as early significant and sustainable differential effects be described, implying the lateral occipital complex as the earliest source of such significant differential categorical γ-band and β-band synchronization of oscillatory activity across single trials.
Figure 3. The magnitude of the grand-average PLF TF-distributions for targets and nontargets expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as well as the difference of the two with respect to baseline scaled up from 0-100%. Intersubject statistical parametric time-frequency map (SPTFM) analysis confirms (bottom right), the statistically most significant and sustainable differential activity for targets (>0) vs. nontargets (<0).

Figure 4. The intersubject statistical parametric time-frequency map (SPTFM) analysis, generalized and applied across all scalp sensors for target vs. nontarget categorical stimuli, reveals the characteristic topographical distribution of broadband regions-of-interest (ROIs) across scalp sensors and identifies ROIs of enhanced phase-locking (intertrial phase coherence or synchronization) for targets (red) vs. nontargets (yellow).

4.2.2.2. Evoked (phase-locked) broadband oscillations

The evoked (amplitude-dependent, time and phase-locked to stimulus onset) event-related oscillatory activity (ERO) is represented by the demodulated complex average of the wavelet-transformed single-trials (STCA-WT). The evoked energy distribution in the 2D time-frequency (TF) plane of the continuous wavelet transformed single trials from 1-60Hz were complex-averaged out for every subject across 200 single-trials at every central frequency component $f_0$ and time point
The resulting evoked energy TF-distributions of each subject were averaged across all subjects to yield so-called grand-average evoked TF-distributions for categorical target versus nontarget stimuli at every scalp sensor (SOIs). The magnitude of the grand-average evoked TF-distributions for targets and nontargets was expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as well as the difference of the two with respect to baseline scaled up from 0-100% (Figure 5).

Our grand-average across 10 subjects evoked TF-distributions at lateral occipital sensor O1 demonstrate first of all that they obey the 1/f power law in the broadband EEG and thereafter ERP energy distribution. In terms of absolute amplitudes with respect to our predefined baseline, at 1Hz the amplitudes (energy) reach as high as close to 100μV, by 10Hz they have dropped down around 10μV (this is in the ERP energy range), above 10Hz they move about ≤ 10μV, above 20Hz they move about ≤3μV, while above 30Hz they are well below <1μV, etc. However, as it is obvious from the absolute and relative (% of change) and the differential grand-average evoked energy TF-distributions for targets vs. nontargets referenced to the -150 to -300ms baseline interval (Figure 5.), it is only for frequency components >15Hz that the energy modulation is better time-localized and optimally confined within the 50-250ms poststimulus time interval.

Indeed, as it becomes evident from the intersubject statistical parametric time-frequency map (SPTFM) analysis (Figure 5, bottom right), the statistically most significant and sustainable differential activity for targets vs. nontargets is basically distributed from 15-55Hz within the first 250ms poststimulus. Interestingly, in the intersubject statistical parametric time-frequency map (SPTFM) analysis, the 46Hz classical γ-band frequency component presents the highest t-scores, the earliest onset (at 50ms poststimulus) and longer lasting sustainability of statistically significant (below the p<0.05 threshold throughout 50-200ms poststimulus) higher evoked energy for targets vs. nontargets. Therefore it proves to be the most critical time-frequency region (ROI) that distinguishes so early and effectively between categorical targets vs. nontargets at the occipital sensor O1, when ERP statistical analysis failed to demonstrate such early significant differential effect at any of the 7 channels (SOIs).

The next worthy to note is the 16Hz classical β-band frequency component which defines a ROI in the lower frequency range (15-20Hz evoked energy range 3-8μV) from 50-300ms poststimulus, again a period during which ERP statistical analysis could not show anything such at the same channel (O1) prior to 300ms poststimulus (onset of classical P3 component). Very few dispersed and short-lived patches of significant differential effects between targets and nontargets occurred mostly between 300-500ms poststimulus and around 10-30Hz. Significant higher evoked
energies in this TF window may contribute to higher P3 amplitudes or earlier P3 latencies for targets compared to nontargets in the averaged time-domain responses (ERP).

A very important observation is that all the significant ERO modulations in evoked energy occurred in the high frequency – short time scale (≥16Hz, range 15-55Hz)x(<first 300ns) which absolutely coincides with all the significant ERO modulations in phase-locking (intertrial phase coherence or synchronization) for targets vs. nontargets, implying that the enhanced evoked energy in the (50-250ms) x (15-55Hz) time-frequency region (ROI) is the result of enhanced phase-locking or resetting across single trials (known as well as intertrial phase coherence or synchronization, respectively) for target vs. nontarget categorical stimuli in the resultant oscillatory activity of the underlying cortical domains.

Given these stirring findings at sensor O1, the intersubject statistical parametric time-frequency map (SPTFM) analysis was generalized and applied across all scalp sensors for target vs. nontarget categorical stimuli, in order to reveal the characteristic topographical distribution of broadband ROIs across scalp sensors and identify any possible ROIs of enhanced evoked energy for targets (red) vs. nontargets (yellow) (Figure 6.). The results indicate that the earliest and fairly similar such ROIs characteristically emerged at both lateral occipital scalp sensors (O1 and O2) while in no other channels could as early significant and sustainable differential effects be described, implying the lateral occipital complex as the earliest source of such significant differential categorical γ-band and β-band evoked oscillatory activity.
Figure 5. The magnitude of the grand-average evoked TF-distributions for targets and nontargets was expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as well as the difference of the two with respect to baseline scaled up from 0-100%. Intersubject statistical parametric time-frequency map (SPTFM) analysis confirms (bottom right), the statistically most significant and sustainable differential activity for targets (>0) vs. nontargets (<0).
Figure 6. The intersubject statistical parametric time-frequency map (SPTFM) analysis, generalized and applied across all scalp sensors for target vs. nontarget categorical stimuli, reveals the characteristic topographical distribution of broadband ROIs across scalp sensors and identifies ROIs of enhanced evoked energy for targets (red) vs. nontargets (yellow).

4.2.2.3. Total & Induced (non-phase-locked) broadband oscillations

The non-phase-locked to stimulus onset (induced, largely canceled-out in the complex average) broadband oscillatory activity roughly approximates the total (non-phase-locked and phase-locked) activity magnitude irrespective of the phase. To measure the sum of all (evoked and - comparatively much more - induced) γ-activity at a central frequency \( f_0 \) and time point \( t \), the moduli (absolute values) of the wavelet-transformed single trials are averaged across.

The total energy distributions in the 2D time-frequency (TF) planes of the continuous wavelet-transformed single trials from 1-60Hz were modular-averaged for every subject across 200 single-trials at every central frequency component \( f_0 \) and time point \( t \). The resulting total energy TF-
distributions of each subject were averaged across all subjects to yield so-called grand-average total energy TF-distributions for categorical target versus nontarget stimuli at every scalp sensor (SOIs). The magnitude of the grand-average total TF-distributions for targets and nontargets was expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as well as the differential of the two with respect to the effective baseline interval scaled up from 0-100% (Figure 5).

Our grand-averaged (across 10 subjects) total energy TF-distributions at lateral occipital sensor O1 demonstrate in terms of absolute baseline-corrected amplitudes that the maximal total energy modulations occurred in the 3-9Hz (<10Hz) spectral range with total amplitudes (energies) higher for targets up to 50μV from baseline and in the 10-15Hz (<20Hz) spectral range with total amplitudes (energies) higher for nontargets up to 25μV from baseline. It is interesting that the two spectral ranges are mutually exclusive, that is, where the total energy was maximal for targets it was minimal for nontargets and vice versa. The signal-to-noise ratio (SNR) for the total energy TF-distributions is smaller than the SNR for the evoked energy TF-distributions (almost 50% less) and this obviously comes about because the total energy approach sums-up all energy (phase+non-phase-locked), that is, more noise and task-irrelevant oscillatory activity is also adding-up across single-trials reducing the effective SNR. Unfortunately, the time-localization of event-related oscillations (EROs) in the spectral range below <15Hz is extremely poor, since total energy modulations spread out (diffuse) in long (≥600ms) poststimulus intervals, which makes difficult to establish any relationship to short-lived task-relevant cognitive subprocesses.

The relative (% of change) and the differential grand-average total energy TF-distributions at occipital sensor O1 for targets vs. nontargets referenced to the -150 to -300ms baseline interval (Figure 7.) show that such mutually exclusive differences are also present in the 15-30Hz (low γ-band) spectral range for nontargets and 30-60Hz (high γ-band) spectral range for targets, respectively. However, as it becomes evident from the intersubject statistical parametric time-frequency map (SPTFM) analysis (Figure 7, bottom right), the statistically significant and sustainable differential effects were only distributed well below <20Hz. Specifically, higher total energy was significant for targets only between 4-8Hz within the first 400ms up to 600ms poststimulus, whereas higher total energy was significant for nontargets only between 10-16Hz from 200-600ms poststimulus.

Given these interesting findings at sensor O1, the intersubject statistical parametric time-frequency map (SPTFM) analysis was generalized and applied across all scalp sensors, in order to reveal the topographical distribution of ROIs of enhanced total/induced energy for targets (red) vs. nontargets (yellow) (Figure 8.). Surprisingly, no significant and sustainable differential effects
could be described in induced γ-band responses (iGBR ≥20Hz), instead two ROIs emerged almost across all sensors between 10-20Hz from 200-600ms poststimulus for nontargets and below <10Hz from 0-600ms poststimulus for targets.

**Figure 7.** The magnitude of the grand-average total/induced TF-distributions for targets and nontargets was expressed both in terms of absolute and relative (as % of change) values referenced to a -150ms to -300ms baseline interval, as well as the difference of the two with respect to baseline scaled up from 0-100%. Intersubject statistical parametric time-frequency map (SPTFM) analysis confirms (bottom right), the statistically most significant and sustainable differential activity for targets (>0) vs. nontargets (<0).
Figure 8. The intersubject statistical parametric time-frequency map (SPTFM) analysis, generalized and applied across all scalp sensors for target vs. nontarget categorical stimuli, reveals the characteristic topographical distribution of broadband ROIs across scalp sensors and identifies ROIs of enhanced total/induced energy for targets (red) vs. nontargets (yellow).
4.3. Discussion & Conclusions

4.3.1. Interpretation of evoked/phase-locked high-frequency versus total/induced low-frequency oscillations

Evoked, phase-locked and total/induced broadband event-related oscillatory activities were examined and characteristic phase- and nonphase- locked activity patterns were significantly modulated across our task conditions, showing consistent differential effects across our subjects both in spatial loci (channels O1/O2) and in specific time-frequency windows (evoked/phase-locked: at (50-250)ms x (16-56)Hz and total/induced: at (0-600)ms x (6-16)Hz poststimulus, respectively).

Especially the early evoked component due to intertrial phase-locking is within the spatial (occipital visual cortex) and temporal range (50-250ms time window) of the classical visual occipital gamma-band activity as well as the classical P1 ERP component that have been known to be modulated by sensorial stimulus properties and low-level visual cues (Tzelepi A et al., 2000; Busch NA et al, 2006). It has also been shown that the early evoked gamma component can be modulated by cognitive stimulus-content up to the level of specific visual-object recognition as “target object” after having only just been reencountered in the visual field (Stefanics G et al., 2005) or as coherent patterns and matches to long-term memory templates (Tallon-Baudry C et al., 1996, 1997; 2004; Herrmann CS et al., 2004a,b).

In our study we extend the association of high frequency evoked γ-oscillatory activity (phase-locked component) with higher-order cognitive properties that endow it with the potential to signal detection of a whole target categorical class of visual objects. By this of course we do not mean that all excited neuronal assemblies in the early extrastriate visual cortex already and explicitly code for categorical classes of visual objects. Instead we suggest that rapid and implicit categorical discrimination processes are already initiated in early extrastriate visual cortex (without excluding the feedback driving effect of high-order late visuocognitive cortex) by synchronization of the oscillatory activity of huge numbers of neuronal assemblies (even if these are engaged in lower-level visual feature processing) in the γ-frequency range, an effect probably that propagates throughout the visual hierarchy allowing effective categorical discrimination and visuomotor response integration to be elicited in the end. It is indeed astonishing how rapidly (starting from 300ms onwards, with a mean response latency of \( \approx 460 \text{ms} \pm \text{std} \approx 60\text{ms} \)) and successfully subjects

- 53 -
responded to both target (productive motor response) and nontarget (inhibitory motor response) categorical stimuli.

In terms of total/induced oscillatory energy, a latent critical time-frequency region was defined ≤16Hz x 0-600ms poststimulus, which although largely overlaps with the extended time range (poor phase-locking) and the θ/δ-spectral range of the classical P3 ERP component, it is significantly modulated for targets earlier (0-600ms) and in lower spectral bands (θ/δ) than for nontargets later (200-600ms) and in higher spectral bands (α/β), in a mutually exclusive manner. This may actually signify quite interesting things: i) processing for targets may on average precede and get earlier completed than processing for nontargets, ii) processing for nontargets may be even more laborious and protracted than for targets, iii) the total and induced (nonphase-locked) energy is modulated in a lower frequency range for targets (θ/δ-bands) than for nontargets (α/β-bands).

All three conclusions may help us better understand the underlying dynamics of the P3 component, the alterations it may suffer under a brain hypoxic challenge and further could satisfactorily explain why P3 component manifests on average earlier peak latencies and higher peak/mean amplitudes for targets than for nontargets. Hence, higher P3 amplitudes for targets do not necessarily mean larger number of neurons activated or larger neuronal ‘workload’ allocated to their processing compared to nontargets, but instead they are simply the result of the modulation of event-related oscillations (EROs) that underlie the generation of the P3 component in a lower frequency range or band compared to nontargets. This is something that may get completely missed or misinterpreted in a conventional study of event-related potentials (ERPs), where low-frequency large amplitude waves dominate the entire picture, the analysis and interpretation of the results.

4.3.2. Topography and timing: spatiotemporal distribution of broadband oscillations

fMRI studies have shown that the lateral occipital complex (LOC) is the earliest brain region involved in visual object representation in its most abstract and complex form and hence to initiate effective categorical discrimination among multiple visual object exemplars and/or classes of them.

Electrophysiological (ERP) and psychometric (psychomotor response performance measurement) studies have shown that human brains can effectively engage in multiple (parallel/serial/hierarchical) visual object representations and effectively complete implicit (in conventional psychology terms: subconscious) categorical discriminative processes as early as 150ms after stimulus onset with all that being reflected on differential electrophysiological brain activity (correlating possibly to triggering of appropriate or inhibition of inappropriate behavioral responses) already detected by this time over frontal brain areas. This means that a
substantial/critical portion of categorization and decision-making processes have already been completed by that time (roughly within 150-200ms, typical latency of the N1 component). The earliest primary visual cortical activity (C1 component) allegedly starts around 50ms from stimulus onset (Di Russo F et al., 2001). Therefore the 50-150ms time interval defines the critical time window over which most of the above categorization phenomena as coarse forms of discrimination most likely take place. Based on topography, timing and modulation properties (well localized in space: at O1/O2 channels and time: 50-200ms poststimulus), the elicited high-frequency range differential activity seems most likely to originate from the lateral occipital complex. It is the result of early evoked and phase-locked or phase-synchronized γ-band (≥20Hz) oscillations across single-trials signifying early object-invariant target-selective categorization/discrimination processes.

A latent (poorly localized in space: ubiquitous at all channels and time: 200-600ms poststimulus) total and mostly induced low-frequency range differential activity is the result of β/α/δ-band (<20Hz) non phase-locked oscillations across single-trials. It signifies late object-variant identification/recognition processes, developing within lower frequency sub bands (<10Hz), earlier completed and coupled to variable visuomotor response integration for target-selective stimuli compared to more sustained processing developing within higher frequency sub bands (≥10Hz) and coupled to variable motor inhibitory responses for nontarget-selective stimuli.

4.3.3. Cognitive neurophysiological model of broadband electrical oscillations

Most “cognitive models” assume early (0-250ms) high-frequency (β/γ-band >15Hz) evoked oscillatory responses to constitute the electrophysiological correlate of large-scale dynamically modulated (spatially-distributed and temporally-synchronized) neuronal assemblies, coding for specific coherent patterns or recently formed visual object representations or the result of post-sensorial top-down feedback activity back-projected on early visual cortical areas upon pattern matching with long-term memory templates. We actually go one step further to associate gamma-band responses with object-invariant categorical target discriminative processes encompassing exemplars across diverse classes of visual objects.

Our hypothesized cognitive model assumes that the initial spatial mapping, segmentation and figure-ground object segregation of the visual space, through concurrently running feedback loops among extrastriate and late secondary visual cortical areas, is merged with an early coarse representation of non-spatial and object-invariant categorical features/classes of interest in the visual space (‘targets’ in a broader sense being present in the visual field). Therefore, despite the minimal visual input provided (66ms), ‘animal’ image categorization would require the least
spatial-selective and nonspatial-feature processing versus ‘nonanimal’ images, since subjects may extract and integrate characteristic or salient features of animals (e.g. eyes, wings, legs, hair, etc.) and categorical decisions be made about animal vs. nonanimal images without thorough processing of all available perceptual details, hence by-passing formation of full object representations. The advantage of this strategy for the brain in exploring the visual space from an evolutionary point of view (efficient fight-or-flight survival reactions) is more than obvious.

As the complex visual search and visual processing goes on, higher-order nonspatial visual feature-processing results in formation of fine grain object representations and detailed object identification takes place; this is further coupled to motor response production for images containing the target category versus motor response inhibition and further visual search for images containing nontarget categories. The electrophysiological correlate of these late visuocognitive and premotor processes are the late (200-600ms) low-frequency range (α/θ/δ-band <16Hz) induced oscillatory responses, which imply that the information content as encoded on a large-scale and dynamic rate code (average firing rates of neuronal assemblies) drops substantially after 250msec post-stimulus. That implies that broadly distributed time-locked and phase-locked frequency modulations (FM) may not be an effective coding mechanism any more for information processing; other mechanisms may be employed based on much more localized critical time-synchrony or transient phase modulations (PM) in the activity of unit cortical oscillators which on a large scale sum up in a non coherent, time or phase consistent way. Neuronal oscillators and assemblies thereof may generate late sustained tonic responses at a much lower frequency range, at a lower speed, with higher time and phase variability in their responses and possibly by extracting weak covariances across neurons and neuronal networks (Freeman WJ, 1975; 1994 & 2000).

4.3.4. In-depth perspective of high-frequency (γ-band) oscillatory activity

Multiresolution time-frequency analysis of ERPs conducted with the orthogonal discrete wavelet transform (Quian Quiroga R et al., 2001) has shown that the transient P1-N1 wave complex appearing from 100ms onwards carries more energy in the alpha and theta bands, whereas the marked positive peak around 400ms (P3) upon target stimulation, related with the processes involved in the performance of the task, carries more energy in the delta band (Gurtubay IG et al., 2001). Even if the event-related high-frequency oscillations were nothing more but mere harmonics (spectral copies) (Jürgens E et al., 2001a,b) generated upon modulation on some lower EEG spectral band or basic frequency of ERP components or fundamental ERO activity per se (e.g.
dominant at the alpha-theta & delta spectral range, Quiroga R et al., 2001), it is still worth to study them.

No matter how paradoxical it sounds, sometimes in order to gain more in-depth information about what happens (fine modulations, sharp or gradual fluctuations, signal transients and nonstationarities) in the low basic frequency range we have to look into the high-frequency range! And this is exactly what the wavelet transform furthermore allows us to do: by adopting a family of high-order derivative filters that assess higher-order rates-of-change of basic oscillatory EEG rhythms (induced gamma) and averaged-out ERP components (evoked gamma), they act as magnifying ‘zoom’-lenses that enable us to focus on different-scale structure of EEG/ERP/ERO signals and extract crucial information about modulations that otherwise would have been unobserved on a conventional EEG spectral and ERP peak analysis. Besides, directly studying the low-frequency EEG/ERP/ERO components by means of the WT may not always be as rewarding: because of the poor temporal resolution, the analysis requires extremely large pre- and post-stimulus intervals and it can often be obscured by inevitable eye movements, categorical task-irrelevant activity and other artifacts. Therefore, by the very cognitive nature of the ultra rapid categorical discrimination and fast-track response categorization tasks we ere interested in here, we were forced to look for modulations of EEG/ERP/ERO activity in the broadband spectrum and indeed this turns out to be highly rewarding: early evoked (phase-locked) high-frequency responses (≥16Hz) prove consistent with early target object-invariant categorization processes, whereas late induced (mostly non-phase-locked) low-frequency responses (<16Hz) prove more consistent with latent object-variant identification processes coupled to variably integrated (productive or inhibitory) visuomotor responses.
5.1. Electrophysiological markers of functional sensitivity thresholds of visuocognitive processes under hypoxia

The purpose of the current essay is to determine in electrophysiological terms (markers of) ‘functional’ sensitivity thresholds of visuocognitive processes coupled to productive and inhibitory behavioral responses under hypobaric-hypoxic conditions for ‘altinauts’, for example at the very critical height of 4500m and above. Of course, the same apply to any kind of systemic or local pathological states that can result in brain hypoxia or any other equivalent moderate hypoxic condition (hemoglobin desaturation Hgb-SatO₂%=81.52% ± STD: 2.04%, range: 78-85%, and at least >75% and <90%), such as: cardiovascular or respiratory disease, cerebrovascular disease, intoxication, etc.

The single trial EEG deflections at every time point represent the large-scale organization of spatiotemporally synchronized and geometrically integrated unit oscillators’ activity across different frequency components and spectral bands. The ERP deflections that result from the averaging out across single-trials of these EEG deflections depend at any time point both on the amplitude (energy) and the polarity (phase) of the spatiotemporally summated oscillatory activity across different frequency components and spectral bands, with low frequency high amplitude oscillatory components (<16Hz) that are locked in-phase (evoked) dominating the final ERP waveform.

However, i) total oscillatory activity across different spectral broadband components that is mostly not phase-locked (induced) to stimulus onset, ii) high frequency low amplitude oscillatory components (≥16Hz) that are locked in-phase (evoked), as well as iii) the phase-locking or phase-resetting (a measure of phase synchronization) of different broadband spectral oscillatory components across single-trials are all ignored during this classical ERP approach. This view of brain activity further attributes neurophysiological meaning to the different ERP peaks and troughs without taking into account the evoked amplitude contributions and the induced total oscillatory energy as well as the impact of phase-locking/resetting in the process of their generation across single-trials throughout different broadband spectral components. For this reason, the current essay has undertaken this comprehensive study of broadband evoked and total/induced oscillatory
activity, including a measure (PLF) of inter-trial phase coherence, in order to reveal the event-related oscillatory dynamics that underlie, elucidate and further complement the conventional analysis of classical ERP components.

5.2. Psychophysiological results under hypoxic vs. normoxic conditions

5.2.1. Physiological Results

Peripheral arterial normoxic Sat%O₂ level was at a mean value of 98.65 ± STD: 0.40%, with subject mean Sat%O₂ levels within a 98-99% range, and including all individual time fluctuations within a 97-100% range. After 5min of gradual hypobaric chamber pressure and parallel Hgb-Sat%O₂ level decline, all subjects settled in the same final hypobaric conditions of 0.564Atm (=429mmHg) for 15min. Although each one reacted individually (increased pulse rate, depth and/or rate of ventilation, etc) to compensate for this transient hypoxaemia, during the 15min. hypoxic exposure period all of them were desaturated (end point, p<<0.00001) around an overall peripheral arterial mean Sat%O₂ of 81.52% ± STD: 2.04%, with subject mean Sat%O₂ levels within a 78-85% range, and including all individual time fluctuations within a 74-89% range. There was a statistically significant (paired t-test, p<0.0001) increase in pulse rate (PR) from an overall mean of 79 ± 11 beats/min to 91 ± 12 beats/min (bpm).

To illustrate the moderate hypoxic effect more clearly, let us elucidate these results with some rough figures: our experimental set-up generated an average peripheral SatO₂% level across subjects of 81.52% ± STD: 2.04%, with subject mean (throughout the hypoxic period) Sat%O₂ levels within a 78-85% range. The average SatO₂% level is above 75% and belongs to a powerful compensatory range, when respiratory mechanisms may still be effective and may have a substantial contribution together with systemic cardiovascular and local circulatory mechanisms in counteracting hypoxaemia. The 75% SatO₂% level including from the most extreme-left to the most extreme-right shift in the O₂-Hgb dissociation curve corresponds to a Pₐ (=arterial)O₂ from 32mmHg (in the lungs) up to 52mmHg (in the tissues). As we have already stressed out, the O₂-tension dynamics between blood and tissues/cells are not clear-cut.

The grand-mean SatO₂%-level of: 81.52% (±STD: 2.04% 78-85%, overall range of subjects’ SatO₂%-levels), could at best correspond to a Pₐ (=arterial) O₂ ≥ 58mmHg (=hypoxaemia is defined when <80mmHg) in the arterial tissue-level (this figure although is only a rough approximation, it can confidently be extrapolated from the O₂-Hgb dissociation curve assuming even a right-shift that could be likely at the tissues). Then in a reasonable estimation of the underlying tissue hypoxia in
the case that there would be a roughly linear (diffusion-like) relationship in the O₂-tension
dynamics between blood and tissues/cells, the venous blood O₂-tension would be approximately Pᵥ
(=venous) O₂ ≥ 29 mmHg and on average systemic tissue O₂-tension would still be roughly Pₜ (=tissue) O₂
≥ 14.5 mmHg (=cellular or tissue hypoxia is defined when < 20 mmHg). That certainly does not
mean that the tissues and the cells get very much less amount of O₂ than they would get under
normoxia because there is still a small O₂-gradient and because compensatory mechanisms operate
in the unit of time (capable of generating even an “O₂-debt”), so that an overall increase in blood
flow (circulatory speed-up by increased heart rate and increased flow through resistance drop in
local tissue capillary beds, let alone that brain circulation has its own compensatory peculiarities in
extracting more O₂ and optimizing metabolism and use of O₂ at the tissue and cellular level) could
still deliver obviously lower yet sufficient amounts of O₂ in the unit of time to maintain basic visual
and cognitive brain functions.

5.2.2. Behavioral Results

Generally, subjects maintained a good cognitive status throughout the experiment without any
obvious decline in basic visual cognitive functions. Subjects occasionally reported reduced
attentiveness and ability to concentrate in the execution of their task. Objective analysis of
psychomotor produced response latencies for targets, across normoxic-hypoxic conditions showed
no statistically significant difference (paired t-test, p = 0.3903) in subject mean response time
latencies (from 462.5 ms ± 59.1 ms to 453.0 ms ± 64.8 ms). In terms of successful behavioral
performance rates, correct productive responses to targets and correct inhibitory responses to
nontargets were analyzed: under these hypoxic conditions there was a statistical tendency (paired t-
test, p = 0.0654, a = 0.05) for increase in correct productive response rates for categorizing target
stimuli (‘animal’ images) (overall from 94.64% ± 3.21% to 95.68% ± 2.25%); in contrast, there was
a statistically significant reduction (paired t-test, p = 0.0035, a = 0.05) in correct inhibitory response
rates for categorizing nontarget stimuli (‘nonanimal’ images) (overall from 94.85% ± 1.90% to
91.68% ± 3.56%). Overall during these hypoxic conditions, there was a statistical tendency for
reduction in correct global (averaged-out productive and inhibitory) response rates, (paired t-test,
p = 0.0742, a = 0.05, overall from 94.75% ± 1.96% to 93.68% ± 1.93%).

As it turned out behavioral responses towards ‘animal’ images (94.64% ± 3.21%) were
basically unaffected during moderate hypobaric hypoxia (95.68% ± 2.25%, p = 0.0654), that is,
subjects could as effectively identify and elicit the motor response to the animal category as during
normoxia. However, behavioral responses towards ‘nonanimal’ images (94.85% ± 1.90%) were
impaired during moderate hypobaric hypoxia (91.68% ± 3.56%, p=0.0035), that is, subjects could not as effectively identify and suppress the motor response to the nonanimal category as during normoxia. That is, during moderate hypoxia subjects tended more or less to correctly press the button for ‘animals’, but they also tended to incorrectly press the button more often for ‘nonanimals’ compared to normoxia. It is as if subjects were ‘seeing’ more often animals where they did not really exist or they could not as effectively suppress their inhibitory responses as before (disinhibitory effect of hypoxia). (This is what we refer to as ‘higher bias for targets versus nontargets’).

In order to comprehend this better in behavioral terms, we should bring it in the right context. Let us think of just one such potential and very realistic situation: at 4500m and above or any other equivalent moderate hypoxic condition (hemoglobin desaturation Hgb-SatO2%=81.52% ± STD: 2.04%, range: 78-85%, at least >75% and below <90%) such as: cabin decompression, lack of supplemental oxygen, etc, a pilot is engaged into an air-fight or an air-ground attack. Within seconds or fractions of a second he has to make crucial decisions whether to press a button and fire a missile or not against enemy airplanes (or ground-targets) or ally airplanes (or ground-nontargets). To not press the button (=not fire a missile) in the presence of ally airplanes (or ground-nontargets) is as crucial as to press it in the presence of enemy airplanes (or ground-targets)! This is what we argue for that these particular conditions turned out to result in higher decisional bias in favor of targets (‘animals’ in our case) against nontargets (‘nonanimals’ in our case). The criticality of such ‘functional’ hypobaric-hypoxic sensitivity thresholds for the function of pilots under such extreme conditions is what triggered the undertaking and the support of this project from the Hungarian Aerospace Agency.

5.3. Electrophysiological results under hypoxic versus normoxic conditions

5.3.1. Statistical Analysis of Event-Related Potentials (ERP) in the Time-Domain

The grand average ERP waveforms produced across all subjects for nontarget and target stimuli, comprise characteristic alterations on major ERP peaks across normoxic and hypobaric hypoxic conditions, and are presented for the two most characteristic occipital/parietal scalp sensors in Figure 9.
Figure 9. Event-related potentials of categorical nontargets under normoxia (yellow) and targets under normoxia (green) and categorical nontargets under hypoxia (blue) and targets under hypoxia (red) stimuli, where all the major ERP P1, N1, P2, N2 and P3 component peaks are depicted. Only the traditional early sensory (P1) and late cognitive (P3) ERP components are marked here, not to overload the figure. One can clearly see the modulations across stimulus conditions and oxygen-levels.
The 3-way ANOVA conducted on the major ERP peak amplitudes revealed significant
differences (main effect) between \( \text{SatO}_2\%-\text{levels} \) for most ERP components: \( P1 \) \( [F(1,27) = 20.29, \ p<0.00001] \), \( N1 \) \( [F(1,27) = 15.2, \ p<0.00001] \), \( P2 \) \( [F(1,27) = 4.03, \ p<0.0459] \), \( P3 \) \( [F(1,27) = 12.49, \ p<0.0005] \). Tukey’s HSD tests indicated overall less positive \( P1 \) \( (+3.23\mu V \ vs. \ +4.89\mu V, \ \pm SE:0.26\mu V, \ CI:[0.93, \ 2.37]) \) and \( P2 \) \( (+4.30\mu V \ vs. \ +5.09\mu V, \ \pm SE:0.27 \mu V, \ CI:[0.01, \ 1.54]) \), more negative \( N1 \) \( (-5.27\mu V \ vs. \ -3.63\mu V, \ \pm SE:0.29\mu V, \ CI:[0.81, \ 2.46]) \) and more positive \( P3 \) \( (+5.82\mu V \ vs. \ +4.07\mu V, \ \pm SE:0.35\mu V, \ CI:[-2.72, \ -0.78]) \) component peak amplitudes during hypoxia than normoxia. Mean values and standard deviations of the most characteristic and significantly altered
early sensory \( P1 \) (Figure 10. & Table 4.) and late cognitive \( P3 \) (Figure 11. & Table 5.) component
peak amplitudes are presented for the four distinct \( \text{SatO}_2\%-\text{Levels} \times \text{Stimulus-Conditions} \) across our
seven Sensors of Interest (SOIs). Definitely, peak amplitudes of \( P1 \) component were reduced and
those of \( N1 \) and \( P3 \) components were enhanced under hypoxia across all SOIs and irrespective of
stimulus conditions. Although \( P3 \) component reached its highest peak amplitudes especially for
targets, this interaction was far from showing any statistical significance at all \( [F(1,27) = 1, \ p <
0.3194] \), while \( P2 \) component reduction reached only borderline statistical significance, not
surviving against a Bonferroni corrected threshold \( (p<0.0459, \ corrected \ a=0.025) \).

Main effects of stimulus condition were significant only for peak \( P3 \) \( [F(1,27) = 21.15, \ p <
0.00001] \) component amplitudes. Post hoc comparisons revealed that targets elicited overall and
across \( \text{SatO}_2\%-\text{levels} \) more positive peak \( P3 \) amplitude responses than distractors \( (+6.09\mu V \ vs. \ +3.81 \mu V, \ \pm SE:0.35 \mu V, \ CI:[-3.25, \ -1.30]) \).

Main effects of recordings sites were significant for \( P1 \), \( N1 \), \( P2 \) and \( N2 \) \( [F(6,252) = 5.32, =
11.51, = 25.71, = 18.09, \ all \ p<0.00001] \) ERP components, respectively. Highest amplitudes were
elicited for \( P1 \), \( N1 \) and \( P2 \) components in occipital (O1/O2) and for \( N2 \), \( P3 \) components at central
(Pz) and lateral (P3/P4) parietal channels. After the significant dominance of the \( P1-N1-P2 \) wave
complex in occipital (O1/O2) sensors, \( P1 \) was strongest at occipito-temporal (P7/P8) and weakest at
centro-parietal (Pz) sensors; conversely, \( N1 \) was strongest at (Pz) and weakest at (P7/P8) sensors;
and \( P2 \) was strongest at right occipitotemporal and parietal (P8/P4) and weakest at central and left
parietal (Pz/P3) sensors. The significant occipital-parietal inter-channel variability in the peak
amplitudes of the above ERP components is confirmed throughout our presented Figures
(9.,10.,11.) and Tables (4.,5.).

There were no significant 2- or 3-way interaction effects among recordings sites, stimulus
conditions and \( \text{SatO}_2\%-\text{levels} \).
Figure 10. Mean (thick bars) ± Standard Deviations (thin bars) of P1 peak amplitudes at occipito-temporoparietal sensors for nontargets and targets across normoxic-hypoxic conditions.

Table 4. Mean ± Standard Deviations of P1 peak amplitudes at occipitotemporoparietal sensors

<table>
<thead>
<tr>
<th>P1 peak amplitudes ±standard deviations in microvolts (µVs)</th>
<th>SatO₂%-LEVEL × STIMULUS-CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia Nontargets</td>
</tr>
<tr>
<td>S</td>
<td>P7</td>
</tr>
<tr>
<td>E</td>
<td>P3</td>
</tr>
<tr>
<td>N</td>
<td>Pz</td>
</tr>
<tr>
<td>S</td>
<td>P4</td>
</tr>
<tr>
<td>O</td>
<td>P8</td>
</tr>
<tr>
<td>R</td>
<td>O1</td>
</tr>
<tr>
<td>S</td>
<td>O2</td>
</tr>
</tbody>
</table>
Figure 11. Mean (thick bars) ± Standard Deviations (thin bars) of P3 peak amplitudes at occipito-temporoparietal sensors for nontargets and targets across normoxic-hypoxic conditions.

Table 5. Mean ± Standard Deviations of P3 peak amplitudes at occipitotemporoparietal sensors

<table>
<thead>
<tr>
<th>P3 peak amplitudes ±standard deviations in microvolts (µVs)</th>
<th>SatO₂%-LEVEL × STIMULUS-CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia Nontargets</td>
</tr>
<tr>
<td>SE</td>
<td>P7</td>
</tr>
<tr>
<td>NE</td>
<td>P3</td>
</tr>
<tr>
<td>NS</td>
<td>Pz</td>
</tr>
<tr>
<td>OS</td>
<td>P4</td>
</tr>
<tr>
<td>ST</td>
<td>P8</td>
</tr>
<tr>
<td>OS</td>
<td>O1</td>
</tr>
<tr>
<td>OS</td>
<td>O2</td>
</tr>
</tbody>
</table>
The 3-way ANOVA conducted on the major ERP peak latencies revealed significant differences (main effect) between the SatO\textsubscript{2}-levels only for the P2 [F(1, 27) = 8.22, p<0.0045], while P3 component showed only a statistical tendency [F(1, 27) = 1.89, p<0.1707]. Post-hoc comparisons of hypoxic versus normoxic conditions yielded mean latencies significantly delayed for P2 (242ms vs. 232ms, ±SE:2.5ms, CI:[-16.78, -3.15]) and overall longer but not significant for P3 (399ms vs. 393ms, ±SE:2.4ms, CI:[-11.61, 2.04]).

Main effects of stimulus condition were significant for the N2 [F(1, 27) = 10.08, p<0.0017] and P3 [F(1, 27) = 14.80, p<0.0002] peak latencies. Post-hoc tests showed that across SatO\textsubscript{2}-levels, N2 (304ms vs. 291ms, ±SE:2.8ms, CI:[4.83, 20.44]) and P3 (403ms vs. 389ms, ±SE:2.4ms, CI:[6.57, 20.22]) mean peak responses were significantly more delayed for nontargets than targets.

There was only one significant interaction between SatO\textsubscript{2}-level (hypoxia) and stimulus condition (nontargets) for P3 [F(1, 27) = 6.74, p<0.01] peak latency, which made the P3 responses to nontarget stimuli in hypoxia the most delayed ones (Figure 12. & Table_6.). For target stimuli there was an earlier P3 peak response irrespective of SatO\textsubscript{2}-levels. Based on post-hoc tests overall during hypoxia an insignificant acceleration of P3 peak responses was observed for targets (from 391ms to 387ms, ±SE:3.5ms, CI:[-8.39, 16.91]), whereas a significant slow down of P3 peak responses occurred for nontargets (from 396ms to 410ms, ±SE:3.5ms, CI:[-26.48, -1.17]).

Main effects of recordings sites were significant for P1 [F(6, 252) = 6.34, p<0.00001], N2 [F(6, 252) = 9.55, p<0.00001] and P3 [F(6, 252), p<0.0002] ERP component peak latencies. P1 component peaked earlier in centro–parietal (Pz) and occipital (O1/O2) channels; N2 peaked earlier at centro-parietal (Pz), whereas P3 peaked earlier at occipital sites (O1/O2). For the P3 component, the sequence of mean peak latencies traced through, started from occipital (O1/O2) areas, followed by occipitotemporal (P7/P8) and parietal (P4/Pz/P3) areas, and finished for target stimuli at the left parietal area (P3) (contralateral to the response hand) just prior to motor response activation (Figure 12. & Table_6.).
**Figure 12.** Mean (thick bars) ± Standard Deviations (thin bars) of P3 peak latencies at occipito-temporoparietal sensors for nontargets and targets across normoxic-hypoxic conditions.

**Table 6.** Mean ± Standard Deviations of P3 peak latencies at occipitotemporoparietal sensors

<table>
<thead>
<tr>
<th>P3 peak latencies ±standard deviations in milliseconds (ms)</th>
<th>SatO₂%-LEVEL × STIMULUS-CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia Nontargets</td>
</tr>
<tr>
<td>S</td>
<td>P7</td>
</tr>
<tr>
<td>E</td>
<td>P3</td>
</tr>
<tr>
<td>N</td>
<td>Pz</td>
</tr>
<tr>
<td>S</td>
<td>P4</td>
</tr>
<tr>
<td>O</td>
<td>P8</td>
</tr>
<tr>
<td>R</td>
<td>O1</td>
</tr>
<tr>
<td>S</td>
<td>O2</td>
</tr>
</tbody>
</table>
5.3.2. Statistical Analysis of Event-Related Oscillations (ERO) in the Joint Time-Frequency Domain

5.3.2.1. Evoked Event-Related Oscillations (50-250ms poststimulus)

**Figure 13.** Mean (thick bars) ± Standard Deviations (thin bars) of evoked broadband event-related oscillatory energy (50-250ms poststimulus) for representative frequency components across major spectral bands at occipitotemporoparietal sensors for nontargets and targets between normoxic-hypoxic conditions.

**High Gamma Band**

From 28-60Hz, the mean evoked energy across scalp sensors is significantly decreased under hypoxic conditions but only for targets down to the level of the nontargets, while for nontargets it remained at the same level during hypoxia; a representative example of this is at 34Hz. Because of this substantial decline in mean evoked energy for targets under hypoxia, the oxygen-level x target-stimulus interaction reached high significance $F(1,27) = 8.44$, $p<0.0040$, which also significantly affected the oxygen-level main effect $F(1,27) = 8.52$, $p<0.0038$ and although the mean evoked
energy was the highest for targets versus nontargets under normoxia, this difference was largely neutralized to only a statistical tendency for a stimulus condition main effect $F(1,27) = 2.98$, $p<0.0854$.

**Low Gamma Band**

From 20-28Hz, the mean evoked energy was not substantially changed at all under hypoxic conditions, however, it was significantly higher for targets under either normoxic or hypoxic conditions; a representative example of this is at 24Hz, where the stimulus-condition main effect reached high significance $F(1,27) = 16.94$, $p<0.0001$. There was nothing else remarkable.

**Beta Band**

From 12-20Hz, the mean evoked energy was not significantly altered under hypoxic conditions, however, it was overall significantly higher for targets mainly under normoxic conditions, since there was a decline under hypoxic conditions to the level of nontargets; a representative example of this is at 18Hz, where the stimulus-condition main effect reached borderline statistical significance $F(1,27) = 4.55$, $p<0.0338$. There was nothing else noteworthy.

**Alpha/Theta/Delta Bands**

From $\leq 12$Hz, the mean evoked energy was not significantly altered under hypoxic conditions, neither was significantly modulated for stimulus-conditions (targets vs. nontargets) across either oxygen-conditions (hypoxia vs. normoxia); a representative example of this is at 12Hz.
5.3.2.2. Phase-Coherence of Event-Related Oscillations (50-250ms poststimulus)

\[ \text{Phase-Locking Factor} \]

**High Gamma Band**

From 28-60Hz, the mean phase-locking factor across scalp sensors is higher for targets vs. nontargets under normoxia. Under hypoxic conditions the mean phase-locking across scalp sensors is significantly decreased for targets and nontargets, it declines more for targets than nontargets to come down to about the same hypoxic level; representative example of this is at 34Hz. Because of this substantial decline in mean phase-locking (more for targets) under hypoxia, the oxygen-level main effect reached highest significance \( F(1,27) = 65.59, p << 0.0001 \), while the oxygen-level x target-stimulus interaction reached borderline significance \( F(1,27) = 4.06, p < 0.0451 \) and although the mean phase-locking was substantially higher for targets versus nontargets under normoxia, this difference was largely defused to only a statistical tendency for the stimulus-condition main effect \( F(1,27) = 3.17, p < 0.0761 \).
**Low Gamma Band**

From 20-28Hz, the mean phase-locking factor was significantly higher for targets than nontargets under normoxic conditions and was significantly reduced to the same extent maintaining the considerable difference between targets and nontargets under hypoxic conditions; a representative example of this is at 24Hz. Because of the significantly higher for targets mean PLF under either normoxic or hypoxic conditions the stimulus-condition main effect reached highest significance $F(1,27) = 17.21$, $p<<0.0001$, while the reduction in mean PLF under hypoxia resulted also in significant oxygen-level main effect $F(1,27) = 16.24$, $p<0.0001$.

**Beta Band**

From 12-20Hz, the mean phase-locking factor was considerably higher for targets than nontargets under normoxic conditions and was significantly reduced maintaining a smaller difference between targets and nontargets under hypoxic conditions; a representative example of this is at 18Hz. Because of the significant reduction in mean PLF under hypoxia the oxygen-level main effect reached the highest significance $F(1,27) = 17.69$, $p<<0.0001$, while the higher mean PLF for targets under either normoxic or hypoxic conditions resulted in a moderately significant stimulus-condition main effect $F(1,27) = 5.16$, $p<0.024$.

**Alpha/Theta/Delta Bands**

From $\leq12$Hz, the mean phase-locking factor (PLF) was about the same level under normoxic conditions and was significantly reduced more or less to the same extent under hypoxic conditions for both targets and nontargets, while there was no significant modulation for stimulus-conditions (targets vs. nontargets) across either oxygen-conditions (hypoxia vs. normoxia); a representative example of this is at 12Hz, where the oxygen-level main effect reached highest significance $F(1,27) = 28.94$, $p<<0.0001 \approx 0$. Nil else remarkable.
5.3.2.3. Evoked Event-Related Oscillations (300-500ms poststimulus)

**Figure 15.** Mean (thick bars) ± Standard Deviations (thin bars) of evoked broadband event-related oscillatory energy (300-500ms poststimulus) for representative frequency components across major spectral bands at occipito-temporoparietal sensors for nontargets and targets between normoxic-hypoxic conditions.

**High Gamma Band**

From 28-60Hz, the mean evoked energy across scalp sensors is significantly increased under hypoxic conditions and especially for targets; a representative example of this is at 34Hz, where the oxygen-level main effect was $F(1,27) = 14.30$, $p<0.0002$, while the oxygen-level x target-stimulus interaction reached $F(1,27) = 6.38$, $p<0.0121$. There was only a small statistical tendency for overall higher mean evoked energy for targets vs. nontargets, the stimulus-condition main effect being $F(1,27) = 3.57$, $p<0.0601$. 
**Low Gamma Band**

From 20-28Hz, the mean evoked energy across scalp sensors is significantly increased under hypoxic conditions mostly for nontargets to about the same level as for targets, although the overall across both oxygen conditions mean evoked energy is still higher for targets than nontargets. A representative example of this is at 22Hz, where the oxygen-level main effect is defused by the opposite direction changes for nontargets (increment) and targets (decrement) $F(1,27) = 3.86$, $p<0.0504$, while the oxygen-level x stimulus-condition interaction for the same reason reached high significance $F(1,27) = 14.27$, $p<0.0002$. The stimulus-condition main effect (mean evoked energy higher for targets vs. nontargets) was yet significant $F(1,27) = 8.86$, $p<0.0032$.

**Alpha/Beta Bands**

From 8-20Hz, the mean evoked energy across scalp sensors is definitely increased under hypoxic conditions to the same amount for targets and nontargets although the mean evoked energy is still higher for targets than nontargets for both oxygen-level conditions; a representative example of this is at 10Hz, where the oxygen-level main effect reached $F(1,27) = 29.14$, $p<<0.0001$ In this spectral range there was still a significant stimulus-condition main effect (targets evoked on average higher energy than nontargets) with $F(1,27) = 13.56$, $p<0.0003$.

**Theta/Delta Bands**

From <8Hz, the mean evoked energy across scalp sensors is certainly increased under hypoxic conditions equally for targets and nontargets, no significant difference emerged between targets and nontargets whatsoever; a representative example of this is at 4Hz, where the oxygen main effect was $F(1,27) = 20.34$, $p<<0.0001=0$. 
5.3.2.4. Phase-Coherence of Event-Related Oscillations (300-500ms poststimulus)

Central Frequency: 8Hz +/-SD:1.28 from 300-500ms
P7
P3
Pz
P4
P8
O1
O2
Occipitoparietal Scalp Sensors
Phase-Locking Factor
0.5
0.4
0.3
0.2
0.1
0
normoxia - nontargets
hypoxia - nontargets
normoxia - targets
hypoxia - targets

Central Frequency: 16Hz +/-SD:2.55 from 300-500ms

Central Frequency: 24Hz +/-SD:3.82 from 300-500ms

Central Frequency: 34Hz +/-SD:5.41 from 300-500ms

Figure 16. Mean (thick bars) ± Standard Deviations (thin bars) of phase-locking factor of broadband event-related oscillations (300-500ms poststimulus) for representative frequency components across major spectral bands at occipito-temporoparietal sensors for nontargets and targets between normoxia-hypoxia conditions.

**High Gamma Band**

From 28-60Hz, the mean phase-locking factor (PLF) across scalp sensors is significantly decreased under hypoxic conditions but only for nontargets, while for targets it remained more or less at the same level during hypoxia; a representative example of this is at 34Hz. Because of this substantial decline in mean PLF for nontargets under hypoxia, the oxygen-level x nontarget-stimulus interaction reached highest significance F(1,27) = 22.45, p<<0.0001 which also affected the oxygen-level main effect F(1,27) = 15.58, p<0.0001 and even the stimulus-condition main effect F(1,27) = 6.93, p<0.009.
**Low Gamma Band**

From 20-28Hz, the mean phase-locking factor (PLF) across scalp sensors is significantly decreased under hypoxic conditions but only for targets, although the overall across oxygen conditions mean PLF is still higher for targets than nontargets. A representative example of this is at 24Hz, where the oxygen-level x stimulus-condition interaction for this reason reached the highest significance $F(1,27) = 19.19$, $p<<0.0001$≈0, while the oxygen-level main effect was partly defused by the opposite direction changes for targets (significant decrement) and nontargets (slight increment) $F(1,27) = 6.19$, $p<0.0135$, and the stimulus-condition main effect (overall higher mean PLF for targets vs. nontargets, especially under normoxia) was still significant $F(1,27) = 8.86$, $p<0.0032$.

**Beta Band**

From 12-20Hz, the mean phase-locking factor (PLF) across scalp sensors is significantly and more or less to the same extent reduced under hypoxic conditions for both targets and nontargets although the mean phase-locking factor is overall higher for targets than for nontargets under either normoxia or hypoxia; a representative example of this is at 16Hz, where the stimulus-condition main effect reached the highest significance $F(1,27) = 20.92$, $p<<0.0004$0 (mean PLF for targets was always higher than for nontargets) and the oxygen-level main effect was $F(1,27) = 12.35$, $p<0.0005$.

**Alpha/Theta/Delta Bands**

From <12Hz, the mean phase-locking factor (PLF) across scalp sensors is particularly higher for targets vs. nontargets under normoxia and significantly decreased under hypoxic conditions both for targets (more) and nontargets (less) to come more or less down to the same level; a representative example of this is at 8Hz, where the oxygen-level main effect reached highest significance $F(1,27) = 39.13$, $p<<0.0004$0 and the stimulus -condition main effect reached borderline significance $F(1,27) = 4.40$, $p<0.037$. There was only a statistical tendency for oxygen-level x stimulus-condition interaction $F(1,27) = 3.11$, $p<0.0792$, due to the higher decline in mean PLF for targets under hypoxia.
5.3.2.5. Total/Induced Event-Related Oscillations (200-600ms poststimulus)

Figure 17. Mean (thick bars) ± standard deviations (thin bars) of evoked broadband event-related oscillatory energy (300-500ms post stimulus) for representative frequency components across major spectral bands at occipito-temporoparietal sensors for nontargets and targets between normoxic-hypoxic conditions.

**High Gamma Band**

From 28-60Hz, the mean total/induced energy across scalp sensors is substantially increased under hypoxic conditions equally for targets and nontargets; a representative example of this is at 34Hz, where the oxygen main effect was $F(1,27) = 40.82$, $p<0.0001$. No other significant condition main effect (targets vs. nontargets) or interaction effect (group x condition) could be established.

**Low Gamma Band**

From 20-28Hz, the mean total/induced energy across scalp sensors is absolutely increased under hypoxic conditions equally for targets and nontargets; a representative example of this is at 22Hz, where the oxygen main effect reached $F(1,27) = 102.81$, $p<0.0001$. In this particular one, there
was also a tendency for a main condition effect (nontargets higher than targets) with F(1,27) = 3.21, p<0.0744.

**Alpha/Beta Bands**
From 8-20Hz, the mean total/induced energy across scalp sensors is definitely increased under hypoxic conditions equally for targets and nontargets; a representative example of this is at 10Hz, where the oxygen main effect was F(1,27) = 85.58, p<0.0001\(\approx\)0. In this spectral range, there was also a significant main condition effect (nontargets induced higher mean total energy than targets) with F(1,27) = 5.42, p<0.0207.

**Theta/Delta Bands**
From <8Hz, the mean total/induced energy across scalp sensors is certainly increased under hypoxic conditions equally for targets and nontargets; a representative example of this is at 4Hz, where the oxygen main effect was F(1,27) = 57.00, p<0.0001\(\approx\)0. In this spectral range, there was exactly the opposite significant main condition effect (targets induced higher mean total energy than nontargets) with F(1,27) = 4.80, p<0.0293 compared to the previous spectral range.
5.4. Discussion – Interpretations & Conclusions

5.4.1. Conclusions and Interpretations of the ERP statistical results

The hypobaric conditions employed in our experiment correspond to an altitude of 4572m and belong to the range where a powerful compensation process occurs in experimental subjects. This altitude resulted in a marked decrease of the peripheral arterial oxygen saturation of hemoglobin (Mean SatO₂%: 81.52% ± STD: 2.04%) that was not accompanied by any overt behavioral or psychic alterations. Our results presented above show an astonishing compensation of visual cognitive functions under this level of acute hypoxic exposure. In accordance with us, Schlaepfer at al. (1992) found improved reading speed during an acute, mild hypoxic challenge, which suggests that exposure to such level of hypoxia, does not necessarily result in impairment of mental performance.

Because most conducted studies have revealed deficits in higher order cognitive operations including attention, logical, language, executive functions and memory (Green RG & Morgan DR, 1985; Regard M et al., 1989 & 1991; Bartholomew CJ et al., 1999), it was generally assumed that early visual cortical functions are less altered by hypoxia. However, Forster et al. recorded VEPs in healthy humans at 4300m altitude and reported decreases in VEP peak amplitudes (Forster HV et al., 1975), suggesting already alterations in early visual cortex. Fowler et al. later proposed that prolonged reaction times in visual detection tasks are due to impairment of early visual information processing and there is relatively small or no effect on the identification and response choice stages (Fowler B et al., 1993). The mild and transient hypobaric hypoxic conditions our subjects were exposed to resulted in diverse yet statistically significant effects on ERP component amplitudes: P1 (and to much lesser extent P2) peak amplitudes were attenuated, whereas N1 and P3 peak amplitudes were enhanced. Moreover, there was a significant delay of P2 peak latency for both stimuli, whereas P3 peak latency increased only for nontarget stimuli (significant interaction). The total number of significant ERP component differences significantly exceeded chance expectancy, whereas the fact that some components increased while others decreased means that the findings are not the result of statistical artifact or scalar drift.

A clear reduction in P1 peak amplitude indicates attenuation of the ERP correlate of elementary spatial-selective feature integration in peristriate and early extrastriate visual cortex (Hillyard SA & Anllo-Vento L, 1998; Luck SJ & Hillyard SA, 2000; Di Russo F et al, 2001). Cumulating evidence suggests that primary visual functions (visual acuity, luminance thresholds, color discrimination) and the early visual system (McFarland RA & Halperin MH, 1940; Kobrick J,
1983; Vingrys AJ & Garner LF, 1987; Hornbein TF, 2001; Karakucuk S et al., 2004) are the first to be targeted by hypoxia and may indirectly affect higher order cognitive functions before the last ones get directly compromised (Fowler B et al., 1993; Lindeis AE et al., 1996; Fowler B & Nathoo A, 1997). That is, impairments of the early visual system may propagate further down and act as ‘bottleneck’ to later cognitive processing, raising overall task difficulty. In an effort of the subjects to maintain their task performance intact during the hypoxic challenge, this needs to be counterbalanced by the recruitment of compensatory brain discrimination and recollection processes, or in electrophysiological terms by larger, more widespread and sustained engagement of neuronal ensembles coding for nonspatial and target-selective feature integration and extraction at higher levels of the visuocognitive system. This higher and longer activation of visual categorization and recognition systems (Luck SJ & Hillyard SA, 2000; Curran T et al., 2002; Hopf JM et al., 2002) was reflected in larger N1 peak amplitudes and P2 peak latencies down the occipitotemporal stream and P3 peak amplitudes and latencies (the last ones only for nontargets) at parietal areas, respectively. Our mild transient hypoxemic stress had actually no effect on the final identification and response choice stage for targets (highest P3 peak amplitudes, not affected P3 peak latencies).

In our categorical discrimination task, ‘animal’ images act as target (excitatory or response productive) stimuli as opposed to ‘nonanimal’ images acting as nontarget (response inhibitory) stimuli in complex visuocognitive and (should motor responses be included) visuomotor integration circuits, resulting in differentially augmented amplitudes of P3 peak responses and shortened N2 and P3 peak latencies for targets (Pfefferbaum A et al, 1985). Since there were no physical stimulus and low-level visual cue or other simple systematic differences across ‘animal’ and ‘nonanimal’ images, these differences must be related to some sort of decision-related activation and motor preparatory or inhibitory activity that occurs once the necessary visual processing has been completed. They most likely result from categorical discrimination processes linked to either ‘go’ generated neural activity or inhibitory ‘no-go’ neural activity related to suppression of inappropriate behavioural responses (Thorpe SJ et al., 1996). The P3 peak response latency, that under normoxia reflects the total visuocognitive processing time and speed differences across stimulus conditions (significantly shorter for targets vs. nontargets), seems to be more task-relevant and subjected to deceleration by elevated task difficulty (Kutas M et al., 1977). The alterations it suffered under our hypobaric hypoxia (somewhat accelerated for targets, significantly delayed for nontargets) best reflect changes in the behavioral performance rates (somewhat improved for targets, significantly worsened for nontargets) and slightly shorter overall reaction times for targets. Although on the whole there is an increase in the decisional bias for targets against nontargets, the P3 peak response
amplitudes are amplified under our hypoxic challenge for both stimulus conditions (no significant interactions established), suggesting possible global excitatory and/or disinhibitory effects of mild hypoxia on neuronal circuitry. The P2 response peak latency is instead significantly delayed for both categorical stimuli under this level of hypobaric hypoxia and seems to be the best index of early hypoxic influence on intermediate stages of visuocognitive processing irrespective of stimulus conditions.

5.4.2. Comparisons with previous ERP studies on hypobaric hypoxia

Recent ERP studies (Singh SB et al., 2004 a, b; Thakur L et al., 2005) of the effects of hypobaric hypoxia on humans were conducted under chronic conditions (trials of days up to weeks of exposure, when the time range allows for different adaptation processes to develop), did not use categorical visuocognitive stimuli as in our paradigm and did not find any significant changes in ERP component peak amplitudes, but only in some components’ peak latencies (i.e. N1 and P3). An earlier though ERP study (Kida M & Imai A, 1993) of the effects of acute hypobaric hypoxia on human cognitive processing by means of ERPs in a similar go/no-go reaction time (RT) paradigm indicated abrupt impairment of RTs (lengthened in association with changes in latency and amplitude of the N2-P3 components) at high altitudes, although some subjects did not suffer any changes in RTs up to the extremely high altitude of 6,000m (19,690ft). The P3 component was followed by positive on-going (parietal maximum) slow waves associated with attempts to maintain RTs against the deteriorative effects of hypobaric hypoxia. Similar studies (Takagi M & Watanabe S, 1999) have yielded prolonged reaction times at simulated altitudes of at least 5000m and above.

In contrast, our results have been produced on rapid induction of mild-to-moderate hypobaric hypoxia level (altitude did not exceed 4572m and SatO₂% did not drop below 74%) upon short duration of exposure (max. 15min), with emphasis on brain responses to visual cognitive stimuli that probe complex human categorical functions. Since our experimental conditions were set within effective compensation range, no impairment occurred in RTs and that was also reflected on the unaltered N2-P3 peak latencies at least for target stimuli. However, the strikingly enhanced P3 amplitudes (we maximally detected over parietal sites) are reminiscent of the parietal high amplitude positive on-going slow waves that have been associated with effort of the subjects to sustain their executive performance.
5.4.3. Conclusions and Interpretations of the ERO statistical results

5.4.3.1. Evoked Event-Related Oscillations (50-250ms poststimulus)

As it has already been shown within the frame of the 3-way ANOVA of the conventional analysis of ERP component peaks, as well as in consistence with the results of the novel SPTFM analysis on ERO phase-coherence/evoked energy, in the early 50-250ms post stimulus interval and across scalp sensors there were neither significant modulations (as main effect or interaction with oxygen-level conditions) of the ERP P1-N1-P2 wave complex peaks nor significant modulations of the ERO phase-coherence/evoked energy measures in the low frequency range (below 15Hz) for targets versus nontargets. Although the alpha-spectral band (8-12Hz) contributes most of the energy of the P1-N1-P2 wave complex, it seems that the P1-N1-P2 is mostly modulated in the higher frequency range: therefore across all frequency components in the beta/gamma bands (>15Hz) there was higher mean evoked energy elicited for targets vs. nontargets.

Under hypoxic conditions there was a moderate and of the same degree decline in evoked energy for both targets and nontargets in the beta (12-20Hz) and the low gamma (20-28Hz) bands, while in the high gamma (28-60Hz) band there was a statistically significant decline in the evoked energy only for targets. We clearly see the differential impact of hypoxia on target versus nontarget categorical stimuli in the high gamma range of spectral components (significant group x condition interaction), something that was not even observable on the traditional analysis of evoked potentials (ERPs). Of course, this does not come as a surprise: it is consistent with the fact that the high gamma band is the spectral range where the most statistically significant modulation in evoked energy occurred for categorical target against nontarget stimuli. Therefore it is also likely to suffer the most significant compromise for target stimuli under hypoxic conditions. When it comes to classical ERP statistics, however, this differential effect was rather concealed by the yet higher mean evoked energies under hypoxia for targets versus nontargets in the middle spectral ranges (beta band) which contributes most of the significant modulating energy to the emerging P1-N1-P2 wave-complex components across single-trials.

5.4.3.2. Phase-Coherence of Event-Related Oscillations (50-250ms poststimulus)

When the phase-locking factor (PLF) values are analyzed in the frame of the 3-way ANOVA, there is a significant ubiquitous attenuation in mean phase-locking factors for all frequency components across oxygen conditions (hypoxia vs. normoxia) and significant higher mean phase-
locking factors for targets vs. nontargets in all high range >12Hz spectral bands (beta and low/high gamma), which overlap with and to a large extent explain the similar behavior of the mean evoked energy across oxygen and stimulus conditions. This means that the substantial attenuation of the P1 ERP component under hypoxia is the result of significant reduction in phase synchronization across single-trials throughout all frequency components. This phase-desynchronizing effect results in substantial reduction in evoked energies at least in the high >12Hz range, where most of the evoked energy modulation takes place across stimulus conditions.

5.4.3.3. Evoked Event-Related Oscillations (300-500ms poststimulus)

Across all frequency components there were broadband higher evoked energies for targets versus nontargets, an effect that was sustained even under hypoxic conditions, even in the low gamma band when nontargets significantly increased their evoked energies to about the level of targets. The fact that mean evoked energies for targets were significantly higher than for nontargets across all frequency components for the two oxygen-levels, and especially the significant interaction of hypoxic conditions with target (response productive) stimuli in the high gamma band might explain the much better handling of targets under hypoxia (best behavioral/motor performance accompanied by highest P3 peak amplitudes and shortest P3 peak latencies) compared to nontargets (worst behavioral performance accompanied by smaller P3 peak amplitudes and longest P3 peak latencies).

The lower frequency components (<20Hz) contribute most of the energy to the P3 component and account for most of the difference in P3 between targets and nontargets (8-20Hz) and their distinct behavior under hypoxic conditions. In the higher frequency components (≥20Hz) there was significant enhancement for targets in the high gamma band vs. significant enhancement for nontargets in the low gamma band. Hence, the time-frequency analysis revealed significant oxygen-level x stimulus-condition interactions for targets and nontargets under hypoxic conditions, demonstrating in terms of evoked energies a differential amplification under hypoxia for targets versus nontargets across high/low gamma-frequency bands, something that traditional P3 peak amplitude statistical analysis failed to demonstrate.

5.4.3.4. Phase-Coherence of Event-Related Oscillations (300-500ms poststimulus)

When the phase-locking factor (PLF) values are analyzed in the frame of the 3-way ANOVA, the general trend that stands out across all central frequency components is a substantial attenuation
under hypoxic brain conditions in phase-locking during the time interval that corresponds to the P3 component and defines the P3 component peak (300-500ms poststimulus).

There were broadband-distributed higher mean phase-locking factors (PLF) for targets versus nontargets across all frequency components, an effect that was sustained even under hypoxic conditions, except in the low gamma band when target PLF values significantly decreased to the same level as for nontargets. The fact that mean PLF values for nontargets were significantly lower than for targets across the low range frequency components for both oxygen-levels, as well as the significant interaction of hypoxic conditions with nontarget stimuli (attenuation) in the high gamma band might explain the much worse handling of nontargets under hypoxia (worst behavioral performance accompanied by smaller P3 peak amplitudes and longest P3 peak latencies) compared to targets (best behavioral/motor performance accompanied by highest P3 peak amplitudes and shortest P3 peak latencies).

The phase-locked lower frequency components (<20Hz) contribute most of the energy to the evoked P3 component and account for most of the difference in P3 between targets and nontargets and their distinct behavior under hypoxic conditions. In the phase-locked higher frequency components (>20Hz) there was significant attenuation of phase-locking for nontargets in the high gamma band to a level much below that of targets vs. significant attenuation of phase-locking for targets in the low gamma band to about the same level as that of nontargets. The time-frequency analysis revealed significant oxygen-level x stimulus-condition interactions for targets and nontargets under hypoxic conditions, demonstrating a differential reduction in terms of phase-locking under hypoxia for nontargets versus targets across high/low gamma frequency bands, something that traditional P3 peak amplitude statistical analysis failed to demonstrate.

5.4.3.5. Total/Induced Event-Related Oscillations (200-600ms poststimulus)

The total/induced broadband event-related oscillatory activity was evaluated in the 200-600ms poststimulus time interval because based on the SPTFM analysis results of the previous chapter (IV) concerning the most significant spectral range of modulation of the total/induced energy across categorical stimulus conditions (targets vs. nontargets) the need for better representation of the lower spectral range (<20Hz) emerged. This actually requires extensive time intervals≥400ms of total oscillatory activity to be considered with inevitable poor time localization and they have to be appropriately chosen in order to avoid smearing either of the prestimulus total/induced energy in the poststimulus period or of the poststimulus total/induced energy in the prestimulus effective baseline (reference) period.
The statistical analysis of the total/induced broadband event-related oscillatory activity over the 200-600ms poststimulus interval confirmed: i) the ubiquitous across all frequency components and spectral bands statistically significant enhancement of the mean total/induced energy for both targets and nontargets under hypoxic conditions, ii) the significantly higher mean total/induced energy for nontargets in the alpha/beta spectral range (8-20Hz) with respect to targets and vice versa the significantly higher mean total/induced energy for targets in the theta/delta spectral range (<8Hz) with respect to nontargets.

Moreover, it provides a deeper insight into the event-related induced and broadband perturbed oscillatory brain dynamics (ERSP) beyond the static brain view of the evoked monophasic and low-frequency containing (<20Hz) event-related potentials (ERP). For example, in the midst of the 200-600ms poststimulus interval, the P3 ERP component emerges as a prominent deflection between 300-500ms from averaging across single-trials. In the traditional view of ERPs, the P3 component peak amplitude is accepted to reflect the number of neurons and neuronal groups being allocated to or modular aggregates and clusters - cortical domains being activated during the eliciting task (Wickens C et al., 1983). An oversimplified interpretation of the higher peak P3 amplitudes for targets vs. nontargets would assume that they represent increased amounts of ‘active cortical mass’ or workload for the processing of the task in question. However, as the analysis of the total/induced broadband oscillations shows, nontargets may actually induce higher oscillatory energy across different frequency components and spectral bands (e.g. dominant at alpha/beta/low gamma bands: 8-20Hz) compared to targets (e.g. dominant at theta/delta bands: <8Hz). This in turn explains the higher amplitudes of the oscillations for targets in the lower (<8Hz) spectral range compared to the lower amplitudes of the oscillations for nontargets in the higher (8-20Hz) spectral range, which may further contribute to higher P3 peak amplitudes for targets versus nontargets across single-trials. It further means that the ‘active cortical mass’ or processing workload may not necessarily be lesser for nontargets simply because their smaller oscillatory amplitudes are concealed by the larger oscillatory amplitudes for targets. Instead it may be even higher in amount and modulated across a higher spectral range of low amplitude components, distributed more extensively in space and more sustainable in time compared to targets. For example, during sleep, which is without doubt a less active brain state, low spectral range theta/delta high amplitude waves dominate in the EEG due to widespread spatiotemporal synchronization of unit oscillators activity in that low frequency range, whereas during awake, alerted and more active brain states the high spectral range alpha/beta/gamma low amplitude waves dominate in the EEG due to large-scale spatiotemporal desynchronization of unit oscillators’ activity from the low frequency and likely resynchronization in a much higher frequency range and with a more different spatiotemporal pattern.
5.4.4. Comparisons to previous EEG spectral power studies under hypoxia

Last but not least, our results can be interpreted in the context of many human EEG studies upon rapid induction of systemic hypoxia under either hypobaric (Kraaijer V et al., 1988 a; Ozaki H et al., 1995; Papadelis C et al., 2007) or normobaric (Kraaijer V et al., 1988 b; Schellart NA & Reits D, 2001) conditions, that have already demonstrated significant transient and sustained afterwards increase in total and across all frequency bands spectral power, including alpha, theta and delta frequency bands, that give rise to low frequency high amplitude potentials (occipitoparietal alpha and slow theta and delta EEG activity). Event-related potentials (ERPs) are time-locked to stimulus onset EEG average-filtered (quasi-stationary) signals with low frequency content (<20Hz) (Rugg MD & Coles MGH, 1995; Luck SJ, 2000 & 2005).

Multiresolution time-frequency analysis of ERPs optimized with the Wavelet Transform (Quian Quiroga R et al., 2001) has shown that the transient P1-N1 wave complex appearing from 100ms onwards is correlated with an increase in the alpha and theta bands, whereas the marked positive peak around 400ms (P3) upon target stimulation, related with the processes involved in the performance of the task, is correlated with an increase in the delta band. Therefore the enhancement in N1 and P3 peak amplitudes under hypoxic conditions could be explained by a similarly anticipated spectral energy increment in alpha & theta and delta bands, respectively. However, this universal power enhancement under hypoxic conditions across all spectral bands and frequency components, especially in the low frequency range (<20Hz) which typical ERP components are mostly modulated in, cannot explain the differential alterations observed in the P1 component (significant attenuation in P1). For this reason, it is imperative to investigate the phase coherence and the evoked/induced energy of the event-related oscillatory dynamics across single-trials between normoxic and hypoxic conditions for targets vs. nontargets that underlie and critically determine the corresponding dynamics of the most prominent event-related potential components.

5.4.5. Significance of ERO dynamics and their impact on ERP dynamics under hypoxia

The mean PLF was overall higher in the early 50-250ms poststimulus interval compared to the late 300-500ms poststimulus interval, implying that the early evoked brain responses emerging across single-trials are mostly phase-dependent and signify early target-selective and object-invariant visuocognitive processes of categorical-level representation and discrimination. In simpler terms, the detection/discrimination of a common categorical target across images enhances the mean evoked energy because it enhances the mean phase coherence or synchronization of event-
related oscillations across single trials in the 50-250ms poststimulus time interval. Although the mean PLF significantly declined in the 50-250ms (particularly in the early 50-150ms) poststimulus interval for both targets and nontargets under hypoxic conditions across most spectral bands (differential decline in high/low gamma for targets/nontargets), it still remained overall higher for targets versus nontargets.

At the same time there was a reduction under hypoxic conditions in mean evoked energies for both targets and nontargets across the high (gamma) spectral band. This means that the attenuation that was observed under hypoxia for both targets and nontargets in the P1 ERP component peak amplitudes, as well as the reduction in mean evoked energies across gamma spectral components must be the result of reduced mean phase-locking factor (PLF), a sign of compromise in the early categorical target-selective visual cognitive processes. Even though not observed in the ERP statistical analysis (P1 is significantly reduced under hypoxia for both targets and nontargets, with no significant interactions having been established with either of them), the ERO statistical analysis already reveals: i) that the attenuation of the P1 ERP component is most likely a result of the disturbance in the intertrial phase coherence of the <20Hz ERO components, ii) an advantage for targets having overall higher mean PLF values than nontargets across normoxic-hypoxic conditions, so that despite the significant PLF reduction under hypoxia – this higher intertrial phase coherence for targets could actually facilitate compensatory mechanisms that counteract more effectively any suppressive effects of hypoxia on evoked energy or its phase desynchronizing effect across single-trials.

The mean PLF was overall lower in the 300-500ms poststimulus interval compared to the 50-250ms poststimulus interval, implying that the late evoked brain responses emerging across single-trials are mostly amplitude-dependent and most likely signify late object-variant and response-selective visual cognitive processes of recognition and classification. In simpler terms, the recognition/identification/classification of variable visual objects and their variable matching to a response selection across images enhances the mean evoked energy per se of event-related oscillations but not in a time-consistent and phase-coherent manner across single trials in the particular 300-500ms poststimulus time interval.

Therefore the mean phase-locking (PLF) significantly declined in the 300-500ms post stimulus interval for both targets and nontargets under hypoxic conditions across most spectral bands (differential decline in high/low gamma for nontargets/targets), while it remained overall higher for targets versus nontargets. At the same time there was an enhancement in mean evoked energies under hypoxic conditions more for targets and less for nontargets across most spectral bands. This means that the enhancement that was observed under hypoxia mostly for targets and to a lesser
degree for nontargets in the P3 component peak amplitudes follows the higher mean evoked energies across most spectral components, particularly in the <20Hz evoked ERO components. It is most likely the compensatory reaction to both the already attenuated mean phase-coherence/evoked-energy in the 50-250ms poststimulus time interval (P1 ERP component attenuation) and the attenuated mean phase-locking (PLF values reduction) in the 300-500ms poststimulus interval. Apparently, it is this compensatory reaction with enhanced mean evoked oscillatory energies that yields sharper and earlier P3 responses, higher P3 component peak amplitudes and shorter P3 peak latencies and maintains the difference between targets and nontargets under hypoxia, which could account for the much better behavioral handling and motor performance for targets versus nontargets under the more demanding hypoxic conditions.

5.4.6. Effects of brain adaptation and acclimatization to acute hypoxic challenges

The electrophysiological and behavioral alterations observed may actually constitute an acute ‘acclimatization’ for the brain by cutting down on its O₂ costs, while optimizing its metabolic and functional needs to respond to environmental stimuli of interest (‘targets’ in a broad sense), so that with the minimum visual input and O₂/energy expenditure to process it, efficient output cognitive performance can be maintained under the most extreme conditions (Hochachka PW et al., 1994; Hochachka PW et al., 1999; Hornbein TF & Schoene RB, 2001). ‘Animal’ images would require the least amount of visual input, visual feature and spatial-selective processing, and thus O₂/energy consumption to be detected, since subjects may extract and integrate characteristic or salient features of animals (e.g. eyes, wings, legs, hair etc.) without thorough processing of all available perceptual details. Instead, ‘nonanimal’ images would require longer visual input and more sustained visual feature, spatial-selective and higher order processing until visual-search for animals runs to completion, and thus overall higher metabolic O₂/energy demands to be successfully categorized.

Fize D et al. (2000) in event-related fMRI studies of the same go(animals)/no-go(nonanimals) paradigm have demonstrated an increased regional brain activation corresponding to increased blood flow and O₂-consumption for both stimuli over early occipital visual cortex and differentially longer sustained for ‘nonanimal’ stimuli over late visual extrastriate areas. Hence, it makes sense that ‘nonanimal’ processing is more delayed and earlier affected by our less severe conditions of hypoxaemia and their subsequent cutback on early (more hypoxia-sensitive) visual sensory processes (P1 attenuation) compared to ‘animal’ processing. On the other hand, despite our marked
hypoxaemia, late cognitive processes prove quite hypoxia-resistant providing still effective compensation for ‘animal’ stimuli (unaffected: P3 latencies, response production, reaction times) and exerting powerful gain control (compensatory amplification of N1-P3 ERP components), although compensation is insufficient for the more O₂-demanding ‘nonanimal’ stimuli (delayed P3 latencies, impaired response inhibition).

5.4.7. A novel tool for the diagnosis and monitoring of acute and chronic brain disorders

Visuocognitive evoked/induced brain responses (ERP/EROs), due to the nature of their acquisition, cannot replace EEG or pulse oximetry in the emergency setting. However, when raw EEG demonstrates overt signs of brain hypoxia (onset of progressive theta-delta activity and associated bursts), pulse oximetry most likely shows already a SatO₂% value of ≤50% and the patient is not far from consciousness loss (McCormick PW et al., 1991). Power spectral analysis of EEG though more sensitive to hypoxia levels, cannot provide electrophysiological evidence coupled to underlying sensory and cognitive subprocesses.

Obviously, from 95% to 50% there is a dynamic range over which different SatO₂% levels result in progressive levels initially of compensation, then of compromise and finally of decline in different brain functions until loss of consciousness. The current study explored only one such level of compromise in visuocognitive categorical functions under conditions of moderate hypobaric hypoxia and resultant systemic hypoxaemia, revealing attenuation of early visual sensory versus enhancement of late cognitive processes, sufficient compensation for targets (response production) versus insufficient compensation and impairment for nontargets (response inhibition).

The exploration of these levels of compromise or decline in cognitive brain functions through ERP/EROs over few recording sites is a plausible and practical approach under simulated hypobaric chamber conditions that allows not only to define functional sensitivity thresholds of different brain functions to hypoxia, but also for the continuous assessment, conditioning and training of ‘altinauts’ before their exposure to real such conditions. In the future, the use of visuocognitive evoked responses may spread as a very sensitive tool to functionally characterize brain lesions or other brain pathology (related or not to hypoxia), by examining compromises, impairments and/or compensatory reserves in higher order cognitive functions.
BIBLIOGRAPHY

List of references in alphabetical order used throughout the present thesis


Bodis-Wollner I, Davis J, Tzelepi A, Bezerianos T. Wavelet Transform of the EEG Reveals Differences in Low and High Gamma Responses to Elementary Visual Stimuli. Clinical Electroencephalography 2001;Vol 32(3):139-144

Busch NA & Herrmann CS. Object-load and feature-load modulate EEG in a short-term memory task, Neuroreport (2003), Vol 14 No II:1-4,(DOI:10.1097/01.wnr.0000087727.58565.1b)


Denison DM, Ledwith F, Poulton EC. Complex reaction times at simulated cabin altitudes of 5,000 feet and 8,000 feet. Aerospace Med 1966; 37:1010–1013.


Hornbein TF, Schoene RB. High Altitude: An Exploration of Human Adaptation. eds. New York, NY: Marcel Dekker Inc; 2001 (pp. 343-424).


McFarland RA, Halperin MH. The relation between foveal visual acuity and illumination under reduced oxygen tension. J Gen Physiol 1940; 23(5): 613-630.


Nasman VT, Rosenfeld JP. Parietal P3 response as an indicator of stimulus categorization: increased P3 amplitude to categorically deviant target and nontarget stimuli, Psychophysiology, 1990; 27(3): 338-350


Takagi M, Watanabe S. Two different components of contingent negative variation (CNV) and their relation to changes in reaction time under hypobaric hypoxic conditions. Aviat Space Environ Med 1999 Jan; 70(1): 30-34.


Appendix I

List of publications as result of the research work performed for the purposes of the present thesis

Journal Published/Submitted Papers:


Proceedings in International Conferences with Referees:


