PhD Project Application

1. Full Name of the Applicant: Jorge Emanuel Martins

2. Project Title: The Pursuit of Happiness: State and Trait of Consciousness Saliva's Molecular Biomarkers

3. Supervisor

3.1. Name: Mário Pinto Simões

3.2. Institution: FM-UL

3.3. Curriculum Vitae: add as a supplementary document to the application process.

3.4. Supervisor's Letter: add as a supplementary document to the application process.

4. Co-Supervisor (No Co-Supervisor)

5. Research Institution where the work will be performed: LIMMIT, Faculty of Medicine, University of Lisbon (FM-UL)

6. Starting date: October 2015 (3rd year of the PhD)

Pipeline, pilot study and congress/academic curriculum already concluded between Sept 2014 and Sept 2015, 2nd year of PhD in Neurosciences (FM-UL)

7. Summary (maximum 2000 characters with spaces):

The relationship between consciousness (C) and neural activity, i.e., between mental and brain states, has been widely studied. However, the relation between C and its biochemical markers is still undetermined. Assuming its relevance to neuroscience, medicine and science of C, it is concluded that a common scientific approach is in order.

The assumptions of this study are: (1) An altered state of C (ASC) can be defined as a qualitative alteration of the overall pattern of mental functioning and its associated states and traits of C (STC); (2) Currently there are two types of practices used to achieve a given ASC: natural and induction. The natural correspond of meditation practices (MP), in which the learning process for the achievement of that ASC is usually long. The induction are faster learning techniques, as they always involves a second individual, leading the induction, in addition to the subject of the practice, that induces the desired ASC. (3) The inductions techniques can be seen under the practice of doctor-patient relationship (DPR). (4) These are often used to achieve a subjective state of happiness (SSH). (5) These STC have saliva molecular biomarkers (SMB) and can be correlated with Psychological Assessments (PA).

On the basis of this assumptions, it is proposed a new approach of ASC induction, associated with a SSH, using a specific methodology of inducting and analysis, named The Pursuit of Happiness (TPH) model. The TPH model: (A) Studies the use of an induction technique, named The Way of Happiness (TWH), to achieve STC associated with SSH. (B) Proposes, in parallel, a biomedical analysis named: States and Traits of C: Saliva Molecular Biomarkers (STC.SMB). (C) Correlates

STC.SMB with a PA for ASC and SSH. (D) Develops the TPH Knowledge Discovery Database (TPH.KDD) with data-mining algorithms on ASC, SSH, STC, DPR, SMB, Peak Experiences (PE), Self-Consciousness (SC) and bioinformatics tools in the field neuroscience, medicine and science of C.

8. Technical Description

8.1. Literature Review (maximum 3500 characters with spaces):

C can be defined as the immediate perception that the subject has of what is happening inside or outside of him; the knowledge he has of his thoughts, feelings and actions. C is understood as the momentary reality that the individual experiences according to his perception and SC [1,2] and correlates with the concept of experience described in Nietzsche's philosophy with triple meaning of immediacy, significance and incommensurability [3]. The concept of ASC, defined as 'a qualitative alteration in the overall pattern of mental functioning, such that the experiencer feels his C is radically different from the way it functions ordinarily' [4], may be understood as common ground among neuroscience, medicine and the science of C.

ASC have been used in medicine as an alternative mechanism for the acquisition and integration of knowledge [5]. Both natural and induced ways to reach an ASC have been described. The natural correspond of MP, in which the learning process for the achievement of that ASC is usually long. The induction are faster learning techniques, as they always involves a second individual, leading the induction, in addition to the subject of the practice, that facilitate the achieve of a desired ASC. The inductions techniques can be seen under the practice of DPR.

MP have been linked to the induction of ASC and to neuroplasticity, possibly leading to new brain correlates [6]. MP induce long-term changes in SC, observed both in high and low level cortical representations [7]. The neurophysiological changes induced by MP are of two types: a) occurring during MP practice - state changes and b) accumulating over months or years and persisting even when not on MP - trait changes [7]. Therefore, also ASC can be seen as altered STC. One way of attaining the proposed STC, is inducing mindfulness MP. Mindfulness is described as sustainable awareness aimed at a non-reactive C [8, 9 10]. This promotes physical and mental well-being with positive emotional traits [11], and modulates the limbic-neocortical emotional systems connectivity [12]. Therefore, the need to integrate their principles in medicine [13].

MP and induction techniques, e.g. Clinical Hypnosis (CH), [14,15], as natural and specially as inducing techniques, have been linked to the induction of ASC, leading to neuropsychophysiological and anatomical correlates [16,17,18], are well studied, and have been recognized as an effective clinical tool [19]. These techniques are also a vehicle for inducing PE, associated with SSH [16,20] and described as "flow state" or ASC by [21]. Moreover, induction techniques, are used as first-line therapeutic practices of acute and chronic syndromes [22].

Few findings describe specific biomarkers that can be elicited through ASC, showing some relationship with psychoneuroimmuneendocrine models [19]. Moreover, different ways of reaching, perpetuating and intensifying SSH, through induced ASC, should be scientifically approached, because they have been rarely associated with biochemical markers. In fact, ASC and the induction of SSH and PE, have been only extensively and specifically associated to endogenous dimethyltryptamine pathway [23,24]. At this point it is postulated that these ASC natural or induction techniques may be associated to the sense of SC, and used to promote SSH, and ultimately PE.

On the basis of the previous assumptions, it is proposed a new approach of ASC induction, associated with a SSH, named TPH model, and described in 8.3.

8.2. Objectives (maximum 2000 characters with spaces):

The main objective of this study is the induction of an ASC associated with SSH.

8.2.1. Secondary Objectives

1. Test and validate an induction protocol of ASC applicable to practical clinical, specifically to neuropsychiatric pathology.

2. Open the interest to validate different techniques of induction that, in the future, may be used as tools for the field of biomedical sciences;

3. Understand the metabolic mechanisms involved in ASC;

4. Understand the metabolic mechanisms involved in STC associated with SSH, PE, SC;

5. Identify SMB associated with ASC, and STC associated with SSH, PE and SC;

6. Better develop the technique STC.SMB, patent pending by the author et al., only used for pipeline and pilot study yet;

7. Identify neuroscientific correlates of DPR and PA, and to possibly use them in the medical practice;

8. Better develop the TWA and TPH, and to integrate its results in clinical practice;

9. Generate data-mining algorithms to be used in bioinformatics database, tools and applications, named TPH.KDD.

8.2.1. Implications of the Study

1. Understanding the different clinical aspects of ASC in the body as well as its cognitive and affective processes;

2. Addressing this study, not only in the research field of the science, but also in the philosophy of an DPR;

3. Building stronger evidence-based medicine focused on SSH, and extend its impacts in biomedical sciences, neuroscience and sciences of C.

4. Generating the urgency to endorse the interest of creating a metanalytical study that integrates C, ASC, STC, SMB.STC, SSH, DPR, PE, SC in the field of neuroscience, medicine and science of C;

5. Find pharma and non-pharmacologic opportunities/solutions to the main object of study of sciences of C.

Concluding, this study hopes to contribute to the creation of a uniquely tailored system to address the needs of other patient populations in the future, namely therapeutic paradigms designed to be implemented in clinical groups [25].

8.3. Research Plan, Methods and Task Description (maximum 10000 characters with spaces):

8.3.1. Research Plan

The TPH model, proposed in this PhD, by the author and the research members in this study, is a structured fixed protocol and uses a specific methodology of inducting and analysis, named TPH model. TPH encompasses the different task described in Project Tasks and aims to be a new approach to induce an ASC, specifically a STC associated with a SSH, through a guided MP, similar to mindfulness.

The TPH is composed of:

A. An Induction Technique Protocol, named TWH, a psychotherapeutic tool under the DPR approach of Positive Psychology and CH concepts, described in Task (T) 1.
B. A Biomedical Analysis named: STC.SMB, that identifies non-invasively saliva for molecular biomarkers of ASC and STC of SSH, through proteomic and metabolomics analysis, described in T2.
C. A Phenomenology correlation study between STC.SMB and the PA, described in T3.
D. A Knowledge Discovery Database application, named TPH.KDD and described in T4, to generate:
    a. Data mining interpretations on ASC, SSH, STC, DPR, SMB, PE, SC;
    b. Bioinformatics tools in the field neuroscience, medicine and science of C.

The results obtained in this work aim, in a broad perspective, to enhance our knowledge on the way we process emotional information (e.g. happiness). This work will also demonstrate how a SSH can be induced through ASC, how to explore them under a biomedical analysis, and finally how to generate bioinformatics tools with the hard-data collected. The model proposed might open avenues for new discoveries and new applications, especially in medicine and in the study of SC and DPR.

8.3.2. Research Design

8.3.2.1. Pilot Study

Prior pilot study already completed, by author and research members of this study for:

a) TWP induction method creation, development and optimization, with a sample over 1000 subjects [19,26,27];

b) STC.SMB [28] biomedical analysis pipeline data collection and optimization of protocol, namely:

i.) BioBank (BB) setting and protocol creation (please refer to T2 and T4);

ii.) collection (please refer to T2), processing and analysis of saliva under protocol, with a samplesize of 6 subjects, published [27,29,30] (please refer to T2 for results).

c) PA scales specifically chosen, published [31] and applied to identify executability (please refer to CV);

d) TPH.KDD integration with OralCard [32] and creation of BB Saliva Donors Questionnaire (please refer to T4).

e) Also a book chapter, revising the state of the art in this field, was sent to press [33].

8.3.2.2. Full Sample Study

This study is a randomized controlled trial and multicentered with a two-grouped, different settings pre-posttest design (depending on the sample location).

The PhD study will be done in LIMMIT, as centralizing research unit for all T, and in collaboration with:

i.) IMM, Faculty of Medicine, University of Lisbon (T2 and T4);

ii.) ii.) SalivaTec, Department of Health Sciences, Health Sciences Institute, Portuguese Catholic University (T2 and T4);

iii.) iii.) Biocant, CNC, University of Coimbra (T2); and

iv.) iv.) CENTRIA, ESA and University of Algarve (T4).

The allocation is randomized, the endpoint classification is an efficacy study, the Intervention model is parallel assignment, the masking is single blind (subject, investigator), double blind (outcomes assessor).

For this study 120 healthy volunteers will be recruited and screened to achieve screening percentages of 50% women: screening will continue until the target population is achieved. Following Ethical Board approval, subjects will receive information and informed consent will be signed.

Inclusion criteria include:

- age 20-25 y.o.; Male/Female
- cultural background: university students;
- marital status: married, living common law, widowed, separated, divorced, single;
- normal body mass index; normal blood pressure;
- non-medicated excepting birth control pills.

Exclusion criteria include:

- serious physical illness or uncontrolled disorders of kidney liver, lung, heart, musculoskeletal, rheumatologic, metabolic, neurological or psychiatric;
- severe chronic or terminal disease, which might affect the CNS or PNS;
- pregnant or breast feeding women;

- abuse of alcohol or addictive substances, prior to experience.

The subjects, sampled from different universities of Portugal, concerning the inclusion criteria of the TPH study, will be distributed into two groups with 60 subjects per group for full sample study: 1 Control Groups (no intervention, sham IP) = CG1 = 60 subjects; 1 Experimental Group = EG1 = 60 subjects;

8.3.2.3. Interventions Protocol

The Interventions Protocol (IP), the TPW Induction Protocol, is fully described in T1.

8.3.2.4. Assessments Protocol

The Assessments Protocol (AP) is divided in 3 assessments: the STC.SMB Biomedical Analysis, the PA, and the BB Saliva Donors Questionnaire (TPH.KDD). The AP is fully described in T2, T3 and T4.

8.3.2.5. Schematics of Reserch Design

The TPH is constituted by two groups: EG1 and CG1.

- EG1 (60 subjects); Duration = 40min (IP) + 40min (AP) = 80min.
  T = T1+T2+T3+T4.
- CG1 (60 subjects); Duration = 40min (sham IP) + 40min (AP) = 80min.
  T = shamT1+T2+T3+T4.

8.3.3. Expected Outcomes

It is expected that TWH, the IP, influences the metabolic pathways (SMB), the score of the psychological tests (PA) and the TPH.KDD. Moreover, it is expected that the EG1 will have strong evidence and hard data on: ASC, SSH, STC, DPR, SMB, PE and SC, compared to the CG1. Therefore, T2, T3, T4, T5 will generate stronger scientific evidence on all variables of study in EG1 than in CG1, after the IP (T1).

8.3.4. Project Tasks

The project will be divided into 7 main Ts.

The T will occur simultaneously during the study, starting in T6 and followed by T1,T2,T3,T4,T5 and T7.

8.3.4.1. T1: TWH Induction Protocol [26,27,29,30,33]

Please relate to annexes: A. 8.3.4.1. T1: TWH Induction Protocol for full description.

8.3.4.2. T2: STC.SMB Biomedical Analysis [19,27,28,32,34,35,36,37]

Please relate to annexes: B. 8.3.4.2. T2: STC.SMB Biomedical Analysis for full description.

8.3.4.3. T3: PA [3,38,39,40]

Please relate to annexes: C. 8.3.4.3. T3: PA for full description.

8.3.4.4. T4: TPH.KDD [32]

Please relate to annexes: D. T4_TPH.KDD for full description.

8.3.4.5. T5: Data Acquisition and On-going Data Analysis

This task subtasks: a pilot study (6 subjects, already completed) and a full sample study (120 with 50% pilot subjects).

The first one had the objective of testing and optimizing IP and AP defined in tasks 1 to 4. For that purpose 6 subjects were studied.

The second subtask comprises the full sample study with a total of 120 subjects. Regarding the IP, each subject will be studied in a single session. After the IP, the AP will occur, comprising, immediately the T2 and T3, and afterwards the T4.

8.3.4.6. T6: Recruitment

Select and recruit local students from Portuguese Universities, including post-graduation courses, for the enrollment in the study.

Allocation Sequence Generation: Participants will be randomly assigned to either experimental or comparator arm with a 1:1 allocation as per a computer generated randomization schedule stratified by site and the baseline score using permuted blocks of random sizes. The block sizes will not be disclosed, to ensure concealment.

Implementation: All subjects who give consent for participation and who fulfill the inclusion criteria will be randomized. The experimental setting of the IP will depend on the location of the population of this study, however similar physical environment is mandatory condition.

Blinding (masking): AP protocol will be conducted by an assessor blind to IP allocation. An employee outside the research team will feed data into the computer in separate datasheets so that the researchers can analyze data without having access to information about the allocation. The Investigator is encouraged to maintain the blind as far as possible. Unblinding should not necessarily be a reason for study discontinuation.

8.3.4.7. T7: Project Management

All task will be held by the author.

T1 to T3 concerns to the construction and optimization of the IP, including the pilot study. T5 corresponds to data acquisition and analysis of AP, including the pilot study and a full sample study.

The T7 relates, on the one hand, to the supervision of the research and financial plans, and on the other hand to scientific dissemination. Meetings between all team members are planned to be held every three months or more often if necessary. Reports will be prepared for PhD supervision and team members, as well as for internal management, regarding scientific accomplishments and/or delays and following

courses-of-action; and also about financial execution: in particular efforts will be made in order to follow financial planning, nonetheless changes may be needed when facing particular contingencies.

Finally, T7 also relates to the preparation of reports and scientific dissemination, namely communications and publication of scientific articles in conferences/journals of the specialty and also on the dissemination to the academic public in the form of classes, seminars, workshops and symposiums, maintaining the performance of the 2nd PhD year (see annexed CV). Participation in at least two conferences is expected as well as the publication of 3 peer-review scientific papers. Further dissemination is attained by the establishment of contacts with the scientific/social media.

8.4. Timeline and Milestones (maximum 2000 characters with spaces):

The PhD project proposed is estimated to last for 3 years.

1st year (already completed from September 2014 to September 2015) for Pilot Study as described in 8.3.2.1. 2nd and 3rd years (in development from September 2015 to September 2017) for Full Sample Study as described in 8.3.2.2.

Table 1 summarizes the PhD timeline of events and milestones.

Year	**1st** 9/2014 - 9/2015 Pilot Study			**2nd** 9/2015 - 9/2016 Full Sample Study			**3rd** 9/2016 - 9/2017 Full Sample Study		
Months	4th	8th	12th	16th	20th	24th	28th	32nd	36th
Tasks	**COMPLETED**			**IN DEVELOPMENT**					
T1 TWH Induction Protocol									
T2 STC.SMB Biomedical Analysis									
T3 PA									
T4 TPH.KDD									
T5 1.Data Acquisition									
2.On-going Data Analysis									
T6 Recruitment									
T7 Project Management									
Literature Review									
Paper Redaction and Submission									
PhD Thesis Redaction									

Table 1. PhD Timeline

Milestones: The PhD project planning forecasts the redaction and submission of different academic and scientific content described in 8.3.4.7. T7: Project Management (Please refer to CV).

8.5. Bibliography (up to 40 references):

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9. Annexes

Please refer to the annexes below when conveniently addressed.

NOTE: Numbering restart at annexes, for most convenient use.