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Etzel Cardeña and Enrico Facco

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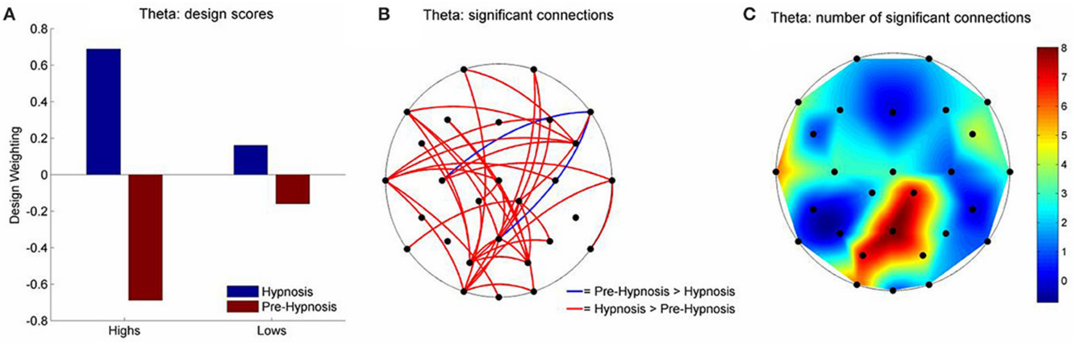
NON-ORDINARY MENTAL EXPRESSIONS

Topic Editors:
Etzel Cardeña, Thorsen Professor in Psychology, Lund University, Sweden
Enrico Facco, Professor in Neurosciences, University of Padova, Italy



Schematic representation of the change in iCOH between the pre-hypnosis and hypnosis states in Theta

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OPINION ARTICLE
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A call for an open, informed study of all aspects of consciousness

Etzel Cardeña *

Department of Psychology, Lund University, Lund, Sweden
**Correspondence: etzel.cardena@psy.lu.se*

Edited by:
Christian Agrillo, University of Padova, Italy

Reviewed by:
Imants Baruss, King's University College at The University of Western Ontario, Canada

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Science thrives when there is an open, informed discussion of all evidence, and recognition that scientific knowledge is provisional and subject to revision. This attitude is in stark contrast with reaching conclusions based solely on a previous set of beliefs or on the assertions of authority figures. Indeed, the search for knowledge wherever it may lead inspired a group of notable scientists and philosophers to found in 1882 the Society for Psychical Research in London. Its purpose was "to investigate that large body of debatable phenomena…without prejudice or prepossession of any kind, and in the same spirit of exact and unimpassioned inquiry which has enabled Science to solve so many problems." Some of the areas in consciousness they investigated such as psychological dissociation, hypnosis, and preconscious cognition are now well integrated into mainstream science. That has not been the case with research on phenomena such as purported telepathy or precognition, which some scientists (a clear minority according to the surveys conducted http://en.wikademia.org/Surveys_of_academic_opinion_regarding_parapsychology) dismiss *a priori* as pseudoscience or illegitimate. Contrary to the negative impression given by some critics, we would like to stress the following:

(1) Research on parapsychological phenomena (psi) is being carried out in various accredited universities and research centers throughout the world by academics in different disciplines trained in the scientific method (e.g., circa 80 Ph.D.s have been awarded in psi-related topics in the UK in recent years). This research has continued for over a century despite the taboo against investigating the topic, almost complete lack of funding, and professional and personal attacks (Cardeña, 2011). The Parapsychological Association has been an affiliate of the AAAS since 1969, and more than 20 Nobel prizewinners and many other eminent scientists have supported the study of psi or even conducted research themselves (Cardeña, 2013).

(2) Despite a negative attitude by some editors and reviewers, results supporting the validity of psi phenomena continue to be published in peer-reviewed, academic journals in relevant fields, from psychology to neuroscience to physics e.g., (Storm et al., 2010; Bem, 2011; Hameroff, 2012; Radin et al., 2012).

(3) Increased experimental controls have not eliminated or even decreased significant support for the existence of psi phenomena, as suggested by various recent meta-analyses (Sherwood and Roe, 2003; Schmidt et al., 2004; Bösch et al., 2006; Radin et al., 2006; Storm et al., 2010, 2012, 2013; Tressoldi, 2011; Mossbridge et al., 2012; Schmidt, 2012).

(4) These meta-analyses and other studies (Blackmore, 1980)suggest that data supportive of psi phenomena cannot reasonably be accounted for by chance or by a "file drawer" effect. Indeed, contrary to most disciplines, parapsychology journals have for decades encouraged publication of null results and of papers critical of a psi explanation (Wiseman et al., 1996; Schönwetter et al., 2011). A psi trial registry has been established to improve research practice http://www.koestler-parapsychology.psy.ed.ac.uk/TrialRegistryDetails.html.

(5) The effect sizes reported in most meta-analyses are relatively small and the phenomena cannot be produced on demand, but this also characterizes various phenomena found in other disciplines that focus on complex human behavior and performance such as psychology and medicine (Utts, 1991; Richard and Bond, 2003).

(6) Although more conclusive explanations for psi phenomena await further theoretical and research developments, they do not *prima facie* violate known laws of nature given modern theories in physics that transcend classical restrictions of time and space, combined with growing evidence for quantum effects in biological systems (Sheehan, 2011; Lambert et al., 2013).

With respect to the proposal that "exceptional claims require exceptional evidence," the original intention of the phrase is typically misunderstood (Truzzi, 1978). Even in its inaccurate interpretation what counts as an "exceptional claim" is far from clear. For instance, many phenomena now accepted in science such as the existence of meteorites, the germ theory of disease, or, more recently, adult neurogenesis, were originally considered so exceptional that evidence for their existence was ignored or dismissed by contemporaneous scientists. It is also far from clear what would count as "exceptional evidence" or who would set that threshold.

Dismissing empirical observations *a priori*, based solely on biases or theoretical assumptions, underlies a distrust of the ability of the scientific process to discuss and evaluate evidence on its own merits. The undersigned differ in the extent to which we are convinced that the case for psi phenomena has already been made, but not in our view of science as a non-dogmatic, open, critical but respectful process that requires thorough consideration of all evidence as well as skepticism toward both the assumptions we already hold and those that challenge them.

Daryl Bem, Professor Emeritus of Psychology, Cornell University, USA

Etzel Cardeña, Thorsen Professor of Psychology, Lund University, Sweden

Bernard Carr, Professor in Mathematics and Astronomy, University of London, UK

C. Robert Cloninger, Renard Professor of Psychiatry, Genetics, and Psychology, Washington University in St. Louis, USA

Robert G. Jahn, Past Dean of Engineering, Princeton University, USA

Brian Josephson, Emeritus Professor of Physics, University of Cambridge, UK (Nobel prizewinner in physics, 1973)

Menas C. Kafatos, Fletcher Jones Endowed Professor of Computational Physics, Chapman University, USA

Irving Kirsch, Professor of Psychology, University of Plymouth, Lecturer in Medicine, Harvard Medical School, USA, UK

Mark Leary, Professor of Psychology and Neuroscience, Duke University, USA

Dean Radin, Chief Scientist, Institute of Noetic Sciences, Adjunct Faculty in Psychology, Sonoma State University, USA

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Charles T. Tart, Professor in Psychology Emeritus, University of California, Davis, USA

Simon Thorpe, Director of Research CNRS (Brain and Cognition), University of Toulouse, France

Patrizio Tressoldi, Researcher in Psychology, Università degli Studi di Padova, Italy

Jessica Utts, Professor and Chair of Statistics, University of California, Irvine, USA

Max Velmans, Professor Emeritus in Psychology, Goldsmiths, University of London, UK

Caroline Watt, Senior Lecturer in Psychology, Edinburgh University, UK

Phil Zimbardo, Professor in Psychology Emeritus, Stanford University, USA

And…

P. Baseilhac, Researcher in Theoretical Physics, University of Tours, France

Eberhard Bauer, Dept. Head, Institute of Border Areas of Psychology and Mental Hygiene, Freiburg, Germany

Julie Beischel, Adjunct Faculty in Psychology and Integrated Inquity, Saybrook University, USA

Hans Bengtsson, Professor of Psychology, Lund University, Sweden

Michael Bloch, Associate Professor of Psychology, University of San Francisco, USA

Stephen Braude, Professor of Philosophy Emeritus, University of Maryland Baltimore County, USA

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Erick Janssen, Adjunct Professor, Department of Psychology, Indiana University, USA

Per Johnsson, Head, Department of Psychology, Lund University, Sweden

Edward F. Kelly, Research Professor in the Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, USA

Emily Williams Kelly, Research Assistant Professor in the Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, USA

Hideyuki Kokubo, Researcher, Institute for Informatics of Consciousness, Meiji University, Japan

Jeffrey J. Kripal, J. Newton Rayzor Professor of Religious Studies, Rice University, USA

Stanley Krippner, Professor of Psychology and Integrated Inquiry, Saybrook University, USA

David Luke, Senior Lecturer, Department of Psychology and Counselling, University of Greenwich, UK

Fatima Regina Machado, Researcher, Universidade de São Paulo, Brasil

Markus Maier, Professor in Psychology, University of Munich, Germany

Gerhard Mayer, Researcher, Institute of Border Areas of Psychology and Mental Hygiene, Freiburg, Germany

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Alexander Moreira-Almeida, Professor of Psychiatry, Universidade Federal de Juiz de Fora, Brasil

Andrew Moskowitz, Professor in Psychology and Behavioral Sciences, Aarhus University, Denmark

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José Miguel Pérez Navarro, Lecturer in Education, International University of La Rioja, Spain

Gerald H. Pollack, Professor in Bioengineering. University of Washington, Seattle, USA

John Poynton, Professor Emeritus in Biology, University of KwaZulu-Natal, South Africa

David Presti, Senior Lecturer, Neurobiology and Cognitive Science, University of California, Berkeley, USA

Thomas Rabeyron, Lecturer in Clinical Psychology, Nantes University, France

Inmaculada Ramos Lerate, Researcher in Physics, Alba Synchrotron Light Source, Barcelona, Spain.

Chris Roe, Professor of Psychology, University of Northampton, UK

Stefan Schmidt, Professor, Europa Universität Viadrina, Germany

Gary E. Schwartz, Professor of Psychology, Medicine, Neurology, Psychiatry, and Surgery, University of Arizona, USA

Daniel P. Sheehan, Professor of Physics, University of San Diego, USA

Simon Sherwood, Senior Lecturer in Psychology, University of Greenwich, UK

Christine Simmonds-Moore, Assistant Professor of Psychology, University of West Georgia, USA

Mário Simões, Professor in Psychiatry. University of Lisbon, Portugal

Huston Smith, Prof. of Philosophy Emeritus, Syracuse University, USA

Jerry Solfvin, Associate Professor in Indic Studies, University of Massachusetts, Dartmouth, USA

Lance Storm, Visiting Research Fellow, University of Adelaide, Australia

Jeffrey Allan Sugar, Assistant Professor of Clinical Psychiatry, University of Southern California, Los Angeles, USA

Neil Theise, Professor of Pathology and Medicine, The Icahn School of Medicine at Mount Sinai, USA

Jim Tucker, Bonner-Lowry Associate Professor of Psychiatry and Neurobehavioral Sciences, University of Virginia, USA

Yulia Ustinova, Associate Professor in History, Ben-Gurion University of the Negev, Israel

Walter von Lucadou, Senior Lecturer at the Furtwangen Technical University, Germany

Maurits van den Noort, Senior Researcher, Free University of Brussels, Belgium

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Helmut Wautischer, Senior Lecturer in Philosophy, Sonoma State University, USA

Donald West, Emeritus Professor of Clinical Criminology, University of Cambridge, UK

N.C. Wickramasinghe, Professor in Astrobiology, Cardiff University, UK

Fred Alan Wolf, formerly Professor in physics at San Diego State University, the Universities of Paris, London, and the Hebrew University of Jerusalem

Robin Wooffitt, Professor of Sociology, University of York, UK

Wellington Zangari, Professor in Psychology, University of Sao Paulo, Brazil

Aldo Zucco, Professor, Dipartimento di Psicologia Generale, Università di Padova, Italy

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Hypnotic induction is followed by state-like changes in the organization of EEG functional connectivity in the theta and beta frequency bands in high-hypnotically susceptible individuals

Graham A. Jamieson[1]* and Adrian P. Burgess[2]

[1] School of Behavioural, Cognitive & Social Sciences, University of New England, Armidale, NSW, Australia
[2] Aston Brain Centre, School of Life & Health Sciences, Aston University, Birmingham, UK

Edited by:
Etzel Cardeña, Lund University, Sweden

Reviewed by:
Devin Terhune, University of Oxford, UK
Andrew A. Fingelkurts, BM-Science - Brain & Mind Technologies Research Centre, Finland

***Correspondence:**
Graham A. Jamieson, School of Behavioural, Cognitive & Social Sciences, University of New England, Psychology Lane, Armidale, NSW 2351, Australia
e-mail: gjamieso@une.edu.au

Altered state theories of hypnosis posit that a qualitatively distinct state of mental processing, which emerges in those with high hypnotic susceptibility following a hypnotic induction, enables the generation of anomalous experiences in response to specific hypnotic suggestions. If so then such a state should be observable as a discrete pattern of changes to functional connectivity (shared information) between brain regions following a hypnotic induction in high but not low hypnotically susceptible participants. Twenty-eight channel EEG was recorded from 12 high susceptible (highs) and 11 low susceptible (lows) participants with their eyes closed prior to and following a standard hypnotic induction. The EEG was used to provide a measure of functional connectivity using both coherence (COH) and the imaginary component of coherence (iCOH), which is insensitive to the effects of volume conduction. COH and iCOH were calculated between all electrode pairs for the frequency bands: delta (0.1–3.9 Hz), theta (4–7.9 Hz) alpha (8–12.9 Hz), beta1 (13–19.9 Hz), beta2 (20–29.9 Hz) and gamma (30–45 Hz). The results showed that there was an increase in theta iCOH from the pre-hypnosis to hypnosis condition in highs but not lows with a large proportion of significant links being focused on a central-parietal hub. There was also a decrease in beta1 iCOH from the pre-hypnosis to hypnosis condition with a focus on a fronto-central and an occipital hub that was greater in high compared to low susceptibles. There were no significant differences for COH or for spectral band amplitude in any frequency band. The results are interpreted as indicating that the hypnotic induction elicited a qualitative change in the organization of specific control systems within the brain for high as compared to low susceptible participants. This change in the functional organization of neural networks is a plausible indicator of the much theorized "hypnotic-state."

Keywords: hypnosis, EEG, theta rhythm, beta rhythm, functional connectivity, coherence, imaginary coherence

INTRODUCTION

Hypnosis here refers to a group of practices in which suggestions are employed to bring about desired changes in behavior, experience and physiology similar to what might be expected if the suggested events were real. These suggestions are preceded by a clearly designated hypnotic induction ritual, which marks them out from mundane reality, and terminated by a hypnotic de-induction, which marks the return of everyday experience. Hypnosis is widely used to control pain and distress in a variety of clinical settings and provides empirically supported treatments for a number of important medical conditions and empirically promising treatments for many more (Mendoza and Capafons, 2009). Hypnotic susceptibility, the ability to respond to hypnotic suggestion, is reliably measured by administration of standardized scales, comprised of specific suggestions tapping a wide range of traditional content areas: ideomotor (involuntary movement) suggestions, various forms of motor paralysis, positive sensory hallucinations, negative hallucinations (blockage of particular experiences such as in hypnotic analgesia), transformations in aspects of the self (e.g., age regression), or post hypnotic amnesia (Woody and Barnier, 2008). Specific test suggestions employ objective response criteria and have well known difficulty levels.

From the inception of scientific investigations into hypnosis (the report of the Royal commission led by Benjamin Franklin in 1784) down to the present day, one central question has divided scientific researchers in the field. That is, are the profound hypnosis-induced changes in experience reported by highly susceptible individuals the result of a similarly profound shift in the operation of the mind-brain system or can they be explained by the operation of mundane psychological processes such as imagination, attention and response expectancies (Kihlstrom, 2002; Lynn and Lilienfeld, 2002)? Recently a variety of specific hypnotic suggestions have been employed in neuroimaging studies making important contributions to the cognitive neuroscience of volition, motor control, attention and pain perception; researchers are now poised to extend these investigations to address the delusions found in a range of clinical neuropsychological conditions (see the comprehensive Nature Neuroscience review by Oakley and Halligan, 2013). While these studies address the role of specific psychological mechanisms in specific suggestions they do not address (or seek to address) the possibility of a fundamental shift in the operation of the mind-brain system in hypnosis. Given that the electroencephalogram (EEG) has been able to show that specific neurophysiological processes are associated with the phenomenologically distinct states of experience (for operationalization of this construct see, Tart, 1975; Pekala, 1991) found in specific states of arousal, attention, epilepsy, sleep stages (Dement and Kleitman, 1957), dreaming (Aserinsky and Kleitman, 1953) and coma (Boccagni et al., 2011) it is not surprising that many researchers have sought to use the EEG to address this issue (Sarbin and Slagle, 1979; Perlini and Spanos, 1991; Fingelkurts and Fingelkurts, 2014).

Many studies have reported spectral band-power changes between pre and post the hypnotic induction, or between high and low susceptibles, or in relation to specific hypnotic suggestions (particularly analgesia) most commonly in the theta (Blais et al., 1990; Sabourin et al., 1990; Crawford, 1994; Graffin et al., 1995), upper alpha (Williams and Gruzelier, 2001; Terhune et al., 2011) and gamma (De Pascalis, 2007) frequency bands. It is not our purpose to review this work here but differences in method, inconsistent findings and the absence of replication prevent any firm conclusion being drawn (Lynn et al., 2007).

However, whereas other phenomenologically distinctive states of consciousness (sleep stages, dreaming, coma etc.) can be recognized from their characteristic EEG profiles, there is no such distinguishing feature for hypnosis and the changes in the EEG reported during hypnosis are well within the range of what is seen during normal non-hypnotic conditions. So, even though these hypnosis-related changes in the EEG might provide important evidence about the nature of the neural mechanisms involved, they do not constitute the sort of qualitatively distinct difference that seems to be required to support the "altered state" interpretation of hypnosis (Hasegawa and Jamieson, 2002; Burgess, 2007). Furthermore, given the large number of studies that have measured EEG during hypnosis, it is reasonable to conclude that, if a hypnosis-specific pattern of EEG band-power had existed, it would have been found long ago.

This is not to suggest that the usefulness of the EEG in this context has been exhausted but that we may have been looking in the wrong place. Phenomenologically distinct states do not seem to be characterized by localized brain activity but by the pattern of interactions between multiple spatially separated neural assemblies (see e.g., Tononi and Edelman, 1998). Conscious experience then, arises from the activity of multiple local cortical sources that interact in a constant flux of mutual influence and informational exchange through cortico-cortical white fiber pathways, through cortico-thalamo-cortical pathways and finally through cortico-striatal-thalamo-cortical pathways in rapidly forming and dissolving networks of functional coalitions (Kelso, 2012; Fingelkurts et al., 2013). The shared information that constitutes these functional neural networks is primarily expressed in the phase or timing relationships between recorded oscillations. It is in this "deep structure" (a form of latent mathematical description) which represents the functional core of the EEG rather than the surface structure expressed in spectral band power/amplitude that the hypnotic state, if it exists, can be expected to be found (Burgess, 2007). It is this aspect of the EEG, functional connectivity, which we address in the current study in order to seek evidence for a possible marker for what may be termed "the hypnotic state."

While there are numerous measures of functional connectivity available to cognitive neuroscience researchers the most widely studied and best understood such measure employed in EEG research is coherence (COH) which provides an index of the frequency specific phase consistency between two time series (typically derived from separate electrodes; Shaw, 1984). Coherence analysis has been employed sporadically in hypnosis research since the 1990's (Sabourin et al., 1990; Kaiser et al., 1997) but across widely divergent paradigms and without consistent findings. Significant decreases in gamma band COH have been reported in high susceptible hypnotized participants; between frontal and somatosensory electrodes in the case of hypnotic analgesia (Trippe et al., 2004). Hypnosis-related decreases in gamma coherence have also been reported and between frontal midline and left fronto-lateral electrodes during the Stroop task suggesting a breakdown in functional connectivity between functionally related locations of the frontal cortex and other regions (Egner et al., 2005).

However, all existing studies of EEG COH and hypnosis share two major problems of interpretation: volume conduction and inflated Type-1 error caused by multiple comparisons. Volume conduction means that electrical activity from a single source may be detected at multiple electrode sites (Fein et al., 1988) which can seriously inflate coherence between the channels. There are a number of functional connectivity measures able to address this issue (see e.g., Stam et al., 2007) but for this study we adopted the imaginary component of coherency (iCOH; Nolte et al., 2004—see Materials and Methods for details). The second problem, that of an inflated Type-1 error arises because for n EEG channels, there are $n(n-1)/2$ possible channel pairings requiring multiple statistical comparisons and some appropriate method of Type-1 error control. In this study, we used a multivariate method of analysis, Partial Least Squares (PLS) (Lobaugh et al., 2001; McIntosh and Lobaugh, 2004), that not only controlled the overall Type-1 error rate but also allowed us to identify the "deep structure" of the differences in functional connectivity between the hypnotic and pre-hypnotic states.

As understood here a "hypnotic state" corresponds to a qualitative restructuring of the operational framework in which psychological processes take place and accounts for the distinctive phenomenology of the hypnotized person (Pekala and Kumar, 2007; Cardeña et al., 2013). This state is hypothesized to be initiated, in those susceptible to hypnosis, by the hypnotic induction and facilitates, if not enables, the operation of distinct psychological processes which implement responses to specific hypnotic suggestions such as amnesia, age regression or hypnotic analgesia

(Mazzoni et al., 2013). If hypnosis brings about a change in mental functioning that enables or facilitates the operation of the processes which underlie the response to specific types of hypnotic suggestion then we would expect to see evidence of this as a change in the organization of functional connectivity in the hypnotic condition following a hypnotic induction but prior to the administration of specific hypnotic suggestions. However, as first articulated by the late Ken Bowers, no response, whether behavioral, experiential or physiological, elicited by a hypnotic procedure may legitimately be termed hypnotic unless it is associated in some way with the participants' measured level of hypnotic susceptibility (Woody, 1997).

The aim of the present study was to investigate EEG functional connectivity recorded during eyes closed resting before and after a standard hypnotic induction procedure in groups of high and low susceptible participants respectively. Functional connectivity was measured using COH and iCOH and PLS was employed to identify any components (deep structure) with a significant relationship to the interaction of state (pre-hypnosis vs. hypnotized) and trait (high vs. low susceptible) conditions of the experimental design.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited from students at Imperial College London who were pre-screened using the Harvard Group Scale of Hypnotic Susceptibility: Form A (HGSHSA) (Shor and Orne, 1962). A subset of high (HGSHSA score ≥9) and low (HGSHSA score ≤3) scorers were invited to individual screening using the Stanford Hypnotic Susceptibility Scale Form C (SHSSC) (Weitzenhoffer and Hilgard, 1962) to confirm their hypnotic susceptibility. Those who continued to score ≥9 on the SHSSC were identified as high susceptibles and those who continued to score ≤3 on the SHSSC were identified as low susceptibles. The final sample consisted of 12 high susceptible participants (age range 20–24, 2 men) and 11 low susceptible participants (age range 20–24, 3 men). All participants were healthy and right handed. Written informed consent was obtained from all participants and the experiment was conducted as approved by the Riverside Research Ethics Committee and followed the principles expressed in the Declaration of Helsinki and data were analyzed anonymously.

PROCEDURE

The procedure of the experiment is outlined in **Figure 1**. EEG was recorded from participants as they sat with their eyes closed (4 min) followed by a continuous recognition memory test for words and faces (15 min). This period will be referred to as the "pre-hypnosis" state. They then underwent the standard hypnotic induction procedure from the SHSSC (fixation on a visual target followed by eyelid heaviness and involuntary eye closure) and sat with their eyes closed for a further 4 min followed by a second memory test. This period will be referred to as the "hypnosis" state. The data to be reported in this paper refer to the EEG recorded during the resting state with the eyes closed in the pre-hypnosis and hypnosis conditions. Analysis of the recognition memory paradigm will not be reported here.

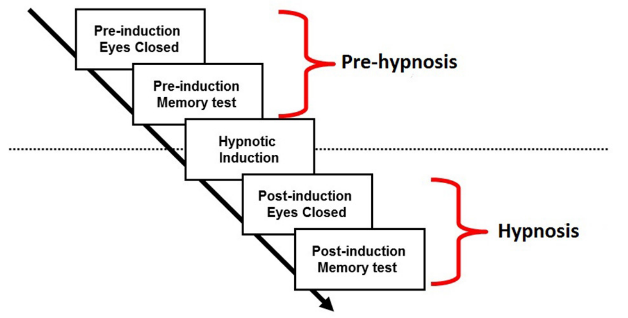

FIGURE 1 | Procedure.

MATERIALS AND EQUIPMENT

EEG was recorded using a 32 channel Neuroscan Synamps amplifier. Signal bandpass was 0.1–100 Hz and the digital sampling frequency was 500 Hz. Twenty-eight electrodes were positioned on the scalp using an ECI electrode cap with electrodes placed according to the International 10–20 system with an additional nine electrodes: Oz, FC5/6, CP1/2, CP5/6, and PO1/2. Electrode impedances were all under 5 kΩ. Reference was to the left ear and converted to average reference offline.

SIGNAL PREPARATION

EEG was divided into consecutive segments of 2048 ms and detrended. Any epochs including values outside of range −100 μV to +100 μV range were excluded from further analysis. The acceptance rate for epochs was high across all participants and in the worst case was 83%. All analysis was performed on these epochs which, with duration of 2048 ms and a sampling rate of 500 Hz, gave frequency resolution of 0.488 Hz.

EEG power spectrum

The power spectrum of the EEG at each channel was estimated in the 0.488–44.921 Hz frequency range using FFT following Welch's method with a Hamming window. Power values were converted to amplitude values by taking the square root of the power as amplitude follows an approximately normal distribution.

EEG functional connectivity

Functional connectivity between all 28 channels was measured using coherence (COH) (Shaw, 1984) and imaginary coherence (iCOH) (Nolte et al., 2004). COH is a widely used measure of functional connectivity in EEG research and is a normalized measure of the phase consistency between two signals that ranges from 0 to 1. However, COH provides an inflated estimate of the true functional connectivity because it is susceptible to the effects of volume conduction. Volume conduction means that electrical activity from a single source may be detected at two spatially separate recording sites and, unfortunately, COH is unable to distinguish between the case of a single common source and functional connectivity between two or more distinct sources.

Fortunately, there are several simple measures of functional connectivity that are insensitive to the effects of volume conduction and we chose one of those recommended by Stam et al. (2007), iCOH. COH is the absolute value of coherency (COHy), which is a complex number (made up of a real and an imaginary component: rCOHy and iCOHy) that represents the normalized cross-spectrum of the two signals of interest. The real component, rCOHy, represents that part of the co-variation between the signals that is zero-phase lagged (i.e., instantaneous) whereas the imaginary component, iCOHy, represents the part that is phase-lagged. As the effects of volume conduction are always instantaneous (i.e., zero-phased), iCOHy provides an index of functional connectivity that is insensitive to the effects of volume conduction. However, zero-lagged connectivity may not all be due to the effects of volume conduction, excluding rCOHy means that some real connectivity will be excluded also meaning that iCOHy will provide an underestimate of the true connectivity. For convenience, instead of using iCOHy, we used the absolute value which is imaginary coherence, iCOH. Like COH, iCOH is a normalized measure of connectivity that ranges from 0 to 1. In short, we used two estimates of functional connectivity: COH, which overestimates the "true" connectivity as it includes the effects of volume conduction and iCOH, which is insensitive to the effects of volume conduction but which underestimates the "true" connectivity because it will exclude any real zero-lagged effects.

COH and iCOH were estimated following Welch's method with a Hamming window and averaged across frequency bands: delta (0.1–3.9 Hz), theta (4–7.9 Hz) alpha (8–12.9 Hz), beta1 (13–19.9 Hz), beta2 (20–29.9 Hz), and gamma (30–45 Hz) frequency ranges. With 28 channels this gave a total of 378 electrode pairs.

STATISTICAL ANALYSIS

EEG power spectrum

FFT amplitude spectrum data (0.488 to Hz 44.921 in steps of 0.488 Hz) from the high and low susceptible groups for the pre-hypnosis and hypnosis conditions were compared using PLS analysis(Lobaugh et al., 2001). The PLS analysis was performed in MatLab using a software package available from http://www.rotman-baycrest.on.ca/. PLS is a method for determining whether the values of a multivariate dataset are systematically affected by the experimental manipulation, in this case, STATE (i.e., Hypnosis vs. Pre-hypnosis) and/or GROUP membership (High vs. Low susceptible). PLS extracts a series of latent variables (LV) that maximally differentiates the covariances in the data according to the experimental design and group membership. This is done by singular value decomposition of the crossblock covariance matrix (i.e., the cross-product of the design matrix and the data matrix). The relative importance of each LV is indicated by the percentage of the crossblock covariance matrix that it can account for and the statistical significance of each LV is determined by permutation testing. In this case, with two experimental conditions and two groups, a total of four LVs will be extracted but only the first two will be meaningful. The meaning of each LV can be determined by examination of the Design Scores which indicate the relative weighting of each on the four conditions (Pre-hypnosis & High-susceptible, Hypnosis & High-Susceptible, Pre-hypnosis & Low-susceptible and Hypnosis & Low-Susceptible). PLS also produces "saliences" which indicate the extent to which each element of the multivariate dataset contributes to the LV. In the case of PLS for the FFT amplitude spectrum, the permutation test, indicated whether one or more of the LVs was statistically significant, the Design Scores indicated whether this was a main effect of STATE, GROUP or an interaction between the two, and the saliences indicated the frequencies and electrode channels where the effects were seen.

As a secondary analysis, FFT amplitudes were compared using a mixed design ANOVA with STATE (Hypnosis vs. Pre-hypnosis) and REGION (Region Left Frontal, Left Central, Left Posterior, Right Frontal, Right Central and Right Posterior) as within-subject measures and GROUP (High susceptibles vs. Low susceptibles) as a between subject measure. For REGION, FFT amplitude values were averaged as follows (Left Frontal: FP1, F7, F3, FC5; Right Frontal FP2, F8, F4, FC6; Left Central: T7, C3 CP5, CP1; Right Central: T8, C4, CP6 CP2; Left Posterior: P7, P3, PO1, O1; Right Posterior: P8, P4, PO2, O2).

EEG functional connectivity

The COH and iCOH data for all 378 electrode pairs for each STATE (Hypnosis vs. Pre-hypnosis) and GROUP (High susceptibles vs. Low susceptibles) were analyzed using PLS. Separate analyses were conducted for each frequency band (Delta, Theta, Alpha, Beta1, Beta2, and Gamma). In the case of PLS for the COH and iCOH, the permutation test, indicated whether one or more of the LVs were statistically significant, the Design Scores indicated whether this was a main effect of STATE, GROUP or an interaction between the two, and the saliences indicated the electrode pairs where the effects were seen.

For all PLS analyses, the statistical significance was determined using permutation testing with 1000 permutations, and the reliability of the saliences (i.e., where and weighting of the Latent Variable was significantly greater than zero) was established using bootstrapping with 1000 re-samplings.

RESULTS

There were no significant differences in the EEG amplitude spectrum between the pre-hypnosis and hypnosis conditions or between the high and low susceptible groups (PLS: LV1, 76.71% of the crossblock covariance, $p < 0.303$; LV2 23.29%, $p < 0.985$). This was confirmed by the ANOVA (**Table 1**) which showed that there were no significant effects of STATE, GROUP or interaction between STATE, GROUP, and REGION in any frequency band. In short, there was no evidence of any change in EEG amplitude between the pre-hypnosis and hypnosis conditions.

There were also no differences in functional connectivity results between the pre-hypnosis and hypnosis conditions or between the high and low susceptible groups using COH in any frequency band (**Table 2**). Only in the Theta frequency band was a trend toward statistical significance for the first latent variable (PLS: LV1, 65.99% of the crossblock covariance, $p < 0.071$) and examination of the Design Scores showed that this was a LV that contrasted the pre-hypnosis and hypnosis conditions in both groups. That is, there was a non-significant trend toward theta coherence being higher in the hypnosis state than in the pre-hypnosis state for both groups of participants.

Table 1 | Results of the ANOVA on the EEG amplitude by STATE, GROUP, and REGION.

	State	Group	State × Group	State × Region	State × Region × Group
Delta	$F_{(1,\ 21)} = 0.040$, $p < 0.843$	$F_{(1,\ 21)} = 2.189$, $p < 0.154$	$F_{(1,\ 21)} = 0.071$, $p < 0.793$	$F_{(5,\ 17)} = 0.727$, $p < 0.612$	$F_{(5,\ 17)} = 1.397$, $p < 0.275$
Theta	$F_{(1,\ 21)} = 0.377$, $p < 0.546$	$F_{(1,\ 21)} = 2.828$, $p < 0.107$	$F_{(1,\ 21)} = 0.255$, $p < 0.619$	$F_{(5,\ 17)} = 1.091$, $p < 0.401$	$F_{(5,\ 17)} = 0.850$, $p < 0.533$
Alpha	$F_{(1,\ 21)} = 0.060$, $p < 0.808$	$F_{(1,\ 21)} = 2.220$, $p < 0.151$	$F_{(1,\ 21)} = 0.029$, $p < 0.867$	$F_{(5,\ 17)} = 0.847$, $p < 0.535$	$F_{(5,\ 17)} = 1.367$, $p < 0.285$
Beta1	$F_{(1,\ 21)} = 0.0000$, $p < 1.000$	$F_{(1,\ 21)} = 1.287$, $p < 0.269$	$F_{(1,\ 21)} = 0.603$, $p < 0.446$	$F_{(5,\ 17)} = 2.230$, $p < 0.099$	$F_{(5,\ 17)} = 0.176$, $p < 0.968$
Beta2	$F_{(1,\ 21)} = 0.816$, $p < 0.377$	$F_{(1,\ 21)} = 1.670$, $p < 0.210$	$F_{(1,\ 21)} = 1.844$, $p < 0.189$	$F_{(5,\ 17)} = 2.341$, $p < 0.086$	$F_{(5,\ 17)} = 0.632$, $p < 0.678$
Gamma	$F_{(1,\ 21)} = 0.629$, $p < 0.437$	$F_{(1,\ 21)} = 0.854$, $p < 0.366$	$F_{(1,\ 21)} = 0.689$, $p < 0.416$	$F_{(5,\ 17)} = 1.420$, $p < 0.267$	$F_{(5,\ 17)} = 0.299$, $p < 0.907$

State: Hypnosis vs. Pre-hypnosis; Group: High susceptibles vs. Low susceptibles, Region Left Frontal, Left Central, Left Posterior, Right Frontal, Right Central and Right Posterior.

Table 2 | Results of the Partial Least Squares Analysis of Coherence/Imaginary Coherence by state (Hypnosis vs. Pre-hypnosis) and group ("High Susceptibles" vs. "Low Susceptibles").

	Coherence (% crossblock variance, permutation test *p*-value)		Imaginary Coherence (% crossblock variance, permutation test *p*-value)	
	1st Latent variable	2nd Latent variable	1st Latent variable	2nd Latent variable
Delta	56.51%, $p < 0.358$	43.49%, $p < 0.736$	55.74%, $p < 0.439$	44.26%, $p < 0.904$
Theta	65.99%, $p < 0.071$	34.01%, $p < 0.832$	**63.17%, $p < 0.013$**[a]	36.83%, $p < 0.880$
Alpha	50.98%, $p < 0.661$	49.02%, $p < 0.687$	60.48%, $p < 0.343$	39.52%, $p < 0.962$
Beta1	59.14%, $p < 0.390$	40.86%, $p < 0.886$	**61.57%, $p < 0.043$**[b]	38.43%, $p < 0.865$
Beta2	54.71%, $p < 0.347$	45.29%, $p < 0.640$	57.85%, $p < 0.071$	42.15%, $p < 0.681$
Gamma	52.86%, $p < 0.529$	47.14%, $p < 0.728$	67.99%, $p < 0.230$	32.01%, $p < 0.931$

[a] *See (**Figure 2A**) to show the Design Scores associated with this result.*

[b] *See (**Figure 3A**) to show the Design Scores associated with this result.*

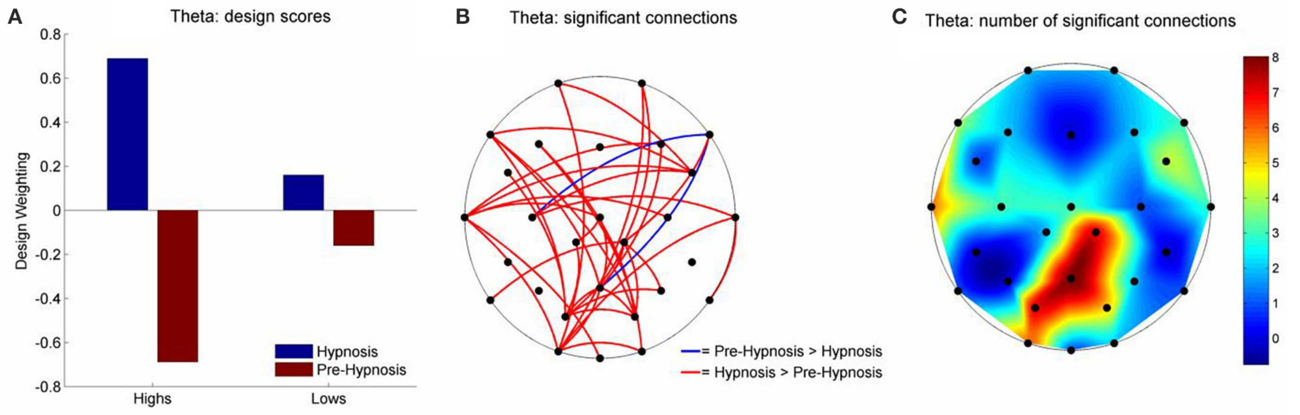

FIGURE 2 | Schematic representation of the change in iCOH between the pre-hypnosis and hypnosis states in Theta. (A) Shows the Design Scores for the significant LV which was a contrast between the pre-hypnosis and hypnosis states predominantly for the high susceptible participants. **(B)** Shows those connections that significantly loaded on the LV, red lines showing a positive loading and blue lines showing a negative loading. Given the Design Scores, the red lines indicate those connections where there was an increase in iCOH from the pre-hypnosis state to the hypnosis state in the high susceptible participants; Blue lines indicate those connections where there was a decrease. **(C)** Shows the number of significant changes in iCOH associated with each electrode site. In this case, there was a hub of connections focused on the central-parietal region that was maximal at Pz.

There were, however, significant differences in the theta and beta1 frequency bands for iCOH (**Table 2**). For theta, LV1 was significant (63.15% of the crossblock covariance, $p < 0.013$) and the Design Scores (**Figure 2A**) showed that this effect was a contrast between the pre-hypnosis and hypnosis conditions for the high susceptibles only. Those functional connections where there was a significant difference in iCOH between the Hypnosis and Pre-hypnosis conditions are shown in (**Figure 2B**).

The changes were predominantly an increase in iCOH in the hypnosis condition compared with the pre-hypnosis condition that clustered at central posterior sites with a maximum at Pz (**Figure 2C**).

For beta1, LV1 was significant (61.57% of the crossblock covariance, $p < 0.043$) and the Design Scores (**Figure 3A**) showed that this effect, like that for theta, was a contrast between the pre-hypnosis and hypnosis conditions. Again, the contrast was strongest for the high susceptibles but, the weightings of the low susceptibles were somewhat stronger than for theta. Those functional connections where there was a significant difference in iCOH between the Hypnosis and Pre-hypnosis conditions are shown in (**Figure 3B**). The changes were predominantly a decrease in iCOH in the hypnosis condition compared with the pre-hypnosis condition that clustered at fronto-central and occipital sites (**Figure 3C**).

The mean change in iCOH for those connections that differed significantly on the PLS analysis are shown in (**Figure 4A**) shows that iCOH for the low susceptible participants did not differ between the pre-hypnosis and hypnosis conditions. Both groups of participants showed similar levels of iCOH during the pre-hypnosis condition but the high susceptible participants showed a significant increase in iCOH during hypnosis. **Figure 4B** shows the iCOH for beta1. Both groups show slightly lower iCOH

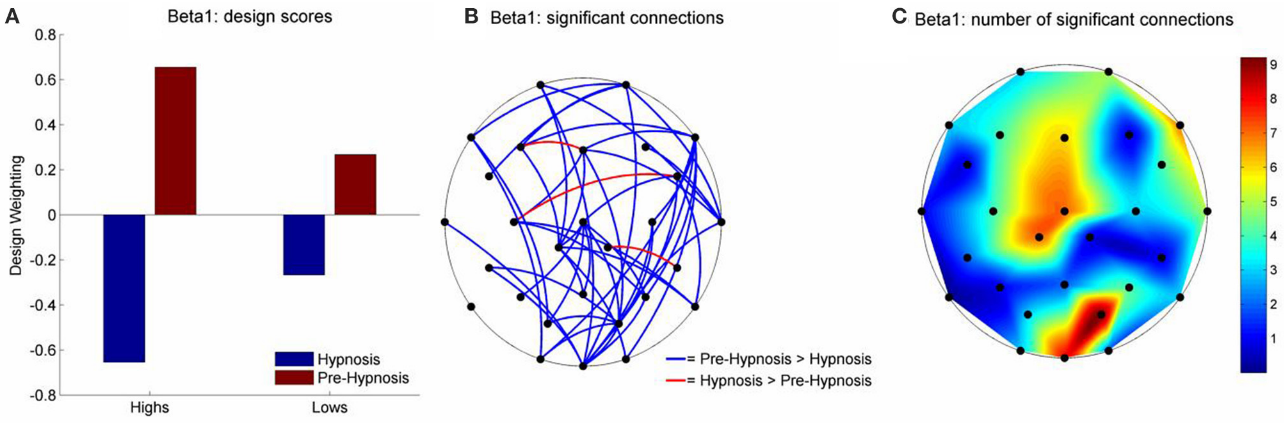

FIGURE 3 | Schematic Representation of the change in iCOH between the pre-hypnosis and hypnosis states in Beta1. (A) Shows the Design Scores for the significant LV which was a contrast between the pre-hypnosis and hypnosis states. The loadings were greater for the high susceptible than for the low susceptible participants but the relative difference was less strong than was seen in Theta (**Figure 2A**). **(B)** Shows those connections that significantly loaded on the LV, red lines showing a positive loading and blue lines showing a negative loading. Given the Design Scores, the blue lines indicate those connections where there was a decrease in iCOH from the pre-hypnosis state to the hypnosis state and red lines indicate an increase in iCOH. The differences were most pronounced in the high susceptible participants. **(C)** Shows the number of significant connections at each electrode site. In this case, there were two clusters of connections; one centered on the vertex (maximal at Cz), and one focused at posterior electrodes (maximal at PO2).

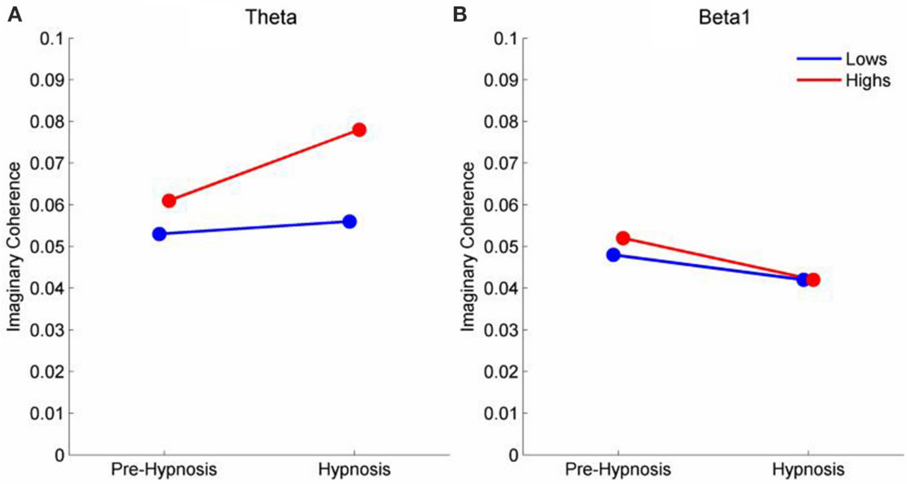

FIGURE 4 | Mean iCOH in the Hypnosis and Pre-hypnosis conditions for high and low susceptible participants in the (A) theta and (B) beta frequency ranges.

during the hypnosis condition but the change was marginally greater for the high susceptible participants.

DISCUSSION

The present study has identified two candidate neurophysiological markers, for the presence of a hypnotic state. Each marker takes the form of a changed pattern of functional connectivity from a pre-hypnosis baseline to the period immediately following the hypnotic induction. The first (and stronger finding) was for increased theta band functional connectivity following hypnotic induction in high but not low susceptible participants organized around a central-parietal hub. The second was for decreased functional connectivity in the beta1 band following hypnosis stronger in the high than the low susceptible participants around fronto-central and occipital hubs.

Several other functional connectivity studies of EEG changes during a resting hypnotized condition have been published in recent years (Fingelkurts et al., 2007; Terhune et al., 2011; Cardeña et al., 2013). Each of these studies features the use of a unique functional connectivity measure seeking, as does the present study, to avoid the well-known problems of volume conduction and multiple comparisons associated with traditional coherence analysis. Using their own structural synchrony measure (Fingelkurts et al., 2007), found an increase in the number of functional connections for the theta frequency band and decrease of functional connectivity for the beta frequency band during hypnosis, however they also report significant results across all of the traditional frequency bands. Terhune et al. (2011) reported a significant decrease in high susceptibles in hypnosis in the Phase Lag Index between frontal and parietal electrode groupings in the upper alpha band whilst Cardeña et al. (2013) found topographic variability in beta and gamma band to be related to hypnotic depth reports amongst high susceptibles.

In the present study candidate markers were identified by PLS analysis of iCOH but not ordinary COH data confirming the importance of removing the effects of volume conduction in order to make functional interpretations of EEG coherence analyses. Another important feature of the present analysis was the use of PLS to identify and extract the deep structure of the EEG data specifically related to the experimental manipulations which were the necessary focus of this investigation. Given equivalent sensory and behavioral processing demands in the pre and post hypnotic induction conditions we did not expect to find any significant differences in spectral band amplitude measures between pre and post hypnotic induction, high or low susceptibles or the interaction of these factors and we did not. Therefore, changes in band amplitude do not represent a plausible alternative explanation of the present findings (Florian et al., 1998).

The possible finding of a neurophysiological marker of the hypnotic state is of the utmost importance for the development of the state vs. non-state debate in hypnosis research and for the cognitive neuroscience of hypnosis and related conditions (Hasegawa and Jamieson, 2002; Kallio and Revonsuo, 2003; Jamieson and Woody, 2007). A successful state marker will be observable whenever a hypnotic state is present and absent when it is not present making it possible for researchers to distinguish between hypnotic and non-hypnotic responses to the same suggestion. Another very important application, with potential clinical significance, is the identification of the operation of a hypnotic state, and hypnotic processes, in conditions outside of formal hypnosis where it has been hypothesized to operate, such as post-traumatic dissociation, trance or possession states, or some psychological and medical conditions. The role of hypnosis in these conditions is highly controversial. If proven a biomarker of the hypnotic state could provide a final resolution of these important issues.

At this point such applications must await future development. The first task is to robustly replicate and quasi-replicate the present results if they are not to join the graveyard of the many specific and interesting cognitive neuroscience findings in the area of hypnosis that have been reported with excitement and then neither replicated nor built upon. Mature science is not built upon individual experiments but upon programs of research where multiple experiments build upon, criticize, and feed into each other. It is a troubling feature of contemporary cognitive neuroscience research into hypnosis that this is not currently happening. In the case of the findings reported here, this issue can be readily and easily addressed. Numerous laboratories around the world have archives of pre- and post—hypnotic induction multichannel EEG data from high, low hypnotically susceptible participants and such datasets can be readily reanalyzed using the methods employed here to establish the robustness of the present results.

In particular existing coherence analyses in the domain of hypnosis could be revisited with the present techniques. Recent EEG studies of hypnosis employing alternative functional connectivity measures (e.g., Fingelkurts et al., 2007; Terhune et al., 2011; Cardeña et al., 2013) may also test the robustness of these findings by applying the present methods to their data sets while the current dataset could be similarly reanalyzed with those alternative measures to determine if similar results are obtained. This would require active cooperation across many laboratories and the sharing of raw data sets. Such a development would greatly facilitate both the replication and the testing of network related hypotheses in this area and might usefully lead to the establishment of a repository of hypnosis neuroscience datasets (EEG, MEG, fMRI, PET, etc.) of past and present studies, updated as new datasets (of both published and unpublished studies) become available. We believe this should be a priority task for the future.

Beyond the necessity of replication it remains essential to further understand the nature of the functional neurophysiological system/s which underlies the present results. Are there two independent function networks involved, one corresponding to the theta findings and the other corresponding to the beta 1 findings? Or do they interact? Or are they rather both expressions of a deeper underlying process? Although these two candidate markers occur in different frequency bands, they might reasonably be considered to reflect complementary features of a single process. Indeed, the re-configuration of cortical oscillations across conventional frequency boundaries may be much more common (and necessary) than once thought (Canolty and Knight, 2010) and it has recently been proposed as a potential mechanism to account for both induced and evoked changes in the EEG (see the Firefly model Burgess, 2012). However, at this point we simply do not know, but we will need to know if the concept of a hypnotic state is to acquire further scientific understanding. A useful step to explore in this direction may be to take the analysis of these resting state functional connectivity changes from sensor space (in this case recording electrodes) to source space (estimated reconstruction of oscillatory activity at cortical gray matter sources) and to examine changes in connectivity between the estimated sources.

FUNCTIONAL ROLES OF THETA AND BETA1 NETWORKS

While there are few direct parallels between the present findings and recent cognitive neuroscience studies of hypnosis there may be some points of contact that give a clue to the possible functional meaning of the current results. Looking first at the LV1 results for theta we see that the iCOH *increases* in hypnosis appear to be organized around a central-parietal hub (see **Figure 2C**). Functional connectivity in the theta band has been closely linked to the coordination of transient functional coupling (exchange of information) between distant cortical regions (Von Stein and Sarnthein, 2000; Schack et al., 2005). The repeatedly observed phenomena of gamma-theta nesting (Burgess and Ali, 2002) provides a mechanism allowing long range theta synchronization to coordinate bottom-up processing activity in widely separated local networks at the specific time points as required by controlled cognitive processing (Womelsdorf et al., 2010).

Synchronized theta oscillations have been shown to play a key role in active cognitive processes including episodic memory (Burgess and Gruzelier, 1997, 2000; Nyhus and Curran, 2010), working memory (Sauseng et al., 2010), error detection (Cohen, 2011) and semantic processing (Sauseng et al., 2005). Each of these cognitive operations is associated with the experience of deliberate effortful control, the very antithesis of the experience reported by high susceptibles when responding to hypnotic suggestion (Polito et al., 2013). Theta elicited in these contexts is characterized by a topography known as frontal midline theta and is closely associated with the operation of top down attentional processes of cognitive control (Mitchell et al., 2008). For this reason evidence of attentional modulation by hypnotic suggestion (Egner and Raz, 2007) and sporadic reports of enhanced theta activity in high susceptibles, in hypnosis or both (not found in the present study) is widely interpreted as evidence that the engagement of executive attentional control lies at the heart of hypnotic phenomena. By contrast, contemporary dissociation theories of hypnosis (Jamieson and Woody, 2007; Sadler and Woody, 2010) point to evidence for a breakdown in the coordination of frontal executive control in hypnosis (Jamieson and Sheehan, 2004; Egner et al., 2005) as indicating that a fundamental reorganization of higher level control processes is being implemented in the hypnotized brain.

It is apparent that the hypnosis-related increases in theta connectivity shown by the high susceptibles in our study did not show the fronto-central hub associated with frontal midline theta and executive attention control (see **Figure 2**). This finding may be reflected in the fMRI study of resting hypnosis by McGeown et al. (2009) who report a deactivation in the rostral division of the ACC in high susceptibles following hypnotic induction. Rather the theta connectivity increases in the present study clustered around a central-parietal hub. This aspect of the current findings may also be reflected in a previous fMRI study of responses to a hypnotic paralysis suggestion for the left hand (Cojan et al., 2009). When required to respond subjects showed increased activity in the right motor cortex (despite paralysis) indicating a preparatory motor intention to respond. Coincident with this activation increased in the precuneus (central-parietal cortex) as did functional connectivity with right motor cortex. Cojan et al. (2009) suggest that their findings may indicate the role of (hypnotically suggested) high level self-representations operating through a parietal attention mechanism in orchestrating and coordinating the behavioral response to this suggestion.

Looking next at the LV1 results for beta 1 we see that the topography of iCOH *decreases* in hypnosis appear to be organized around a fronto-central hub followed by an occipital hub (see **Figure 3C**). While great caution must be applied to any inference from sensor (electrode) space to cortical source space this first hub overlies motor and premotor cortex and supplementary motor areas. Intracortical recording studies from homologous regions in awake monkeys have uncovered the major role played by beta oscillations in maintaining motor activity throughout large scale motor networks (Brovelli et al., 2004). In addition (Bosman et al., 2012) have shown that cortical beta primarily originates from the same deep cortical layers from which feedback projections arise (while fast frequency gamma sources lie primarily in shallow layers from which feed-forward projections arise). Blakemore et al. (2003) have provided compelling evidence to support the theory that the perceived involuntariness of responses to hypnotic ideomotor suggestions are due to a failure of the premotor cortex to generate "efference copies" of motor commands leading to inaccurate forward models of self-generated actions which in turn has been shown to underlie the experience of involuntariness found in hypnotic ideomotor suggestions (Blakemore et al., 2003). In a recent fMRI study (Deeley et al., 2013) found that loss of perceived control of movement by high susceptibles responding to hypnotic suggestion was directly related to decreased functional connectivity between the supplementary motor area and components of the wider motor system (including the occipital/visual cortex). The possibility of a relationship between the current beta1 iCOH findings and these studies is entirely speculative but one may reasonably suggest that, if future research is conducted into similar hypnotic suggestions from an electrophysiological perspective, then the investigators should consider examining the role of beta1 band functional connectivity.

LIMITATIONS OF THIS STUDY

An important limitation of the current study is that the design does not counterbalance the order hypnotic and non-hypnotic testing conditions and therefore it cannot rule out the possibility of order effects unrelated to the administration of the hypnotic induction causing the observed iCOH changes between pre and post hypnotic induction eyes closed resting EEG recordings. Cardeña et al. (2013) sought to control for this possibility by using repeated testing at intervals within the hypnosis condition while Williams and Gruzelier (2001) and Jamieson et al. (2005) utilized an ABA design conducting non-hypnotic testing in both pre and post hypnotic testing periods. The latter two studies found separate effects in the pre hypnosis vs. hypnosis conditions to those in the hypnosis vs. post hypnosis conditions and we suspect such temporal order (but genuine) hypnosis effects are an intrinsic feature of hypnosis itself. Order effects, as an alternative explanation, do not identify a specific cause of results but rather describe a feature of an unknown causal mechanism. Two features of the current results make a non-hypnosis related order effect an unlikely explanation for the pre-post hypnotic induction effects observed. The first is that these differences are systematically related to hypnotic susceptibility. As noted previously the major criterion for designation the effect of a suggestion administered in hypnosis (and the hypnotic induction may be considered as the first such suggestion) as "hypnotic" is that it is systematically related to hypnotic susceptibility. The second, though related to the first, is that these effects are larger in those with high hypnotic susceptibility than those with low susceptibility. Plausible non-hypnotic time related psychological processes such as boredom, distraction and random thought processes might plausibly be expected to be greater in low than high susceptible participants so that if anything time related differences related to these processes would be greater in the low susceptible group. However, we consider it prudent for future research to systematically manipulate testing order to confirm or eliminate the presence of treatment (hypnotic induction) unrelated order dependent effects. We note that the common practice of collapsing results across order counterbalanced conditions at best smears the effect of any treatment unrelated order effect and at worst mixes two independent asymmetric order related non treatment mechanisms and so does not provide an adequate control for such order effects (Jamieson et al., 2005).

Future evaluation of the present findings must take into account the potential role of specific suggestions included in different hypnotic induction procedures (although present data were derived from a period following the induction rather than during the induction itself). While we have taken the important step of identifying a candidate neurophysiological marker for the hypnotic state the neural foundations of such a state (which may or may not be the same thing as a neural marker for the state, although they must at the very least be related) will play a direct role in accounting for key features of the changed phenomenology which has hitherto been the primary basis for attributing the existence of such a state. This has not yet been demonstrated in the present study and must await the application of appropriate phenomenological measures and analysis in conjunction with quantification of the currently proposed hypnotic state markers in future studies (Pekala and Kumar, 2000, 2007; Pekala, 2002; Deeley et al., 2012; Cardeña et al., 2013).

As cogently noted by McGeown et al. (2009) altered state theories of hypnosis do not merely posit that an altered state is one of the outcomes of hypnosis but that the nature of the altered state plays at the very least an enabling role in the emergence of those responses to specific hypnotic suggestions that may truly be called hypnotic. It must be acknowledged that at most the present work demonstrates that hypnosis is accompanied by an altered state of neural network organization and not that this state plays a role in responding to the different types of hypnotic suggestion (ideomotor, motor-inhibition, perceptual-cognitive and amnesia) that are increasingly the focus of cognitive neuroscience studies (Oakley and Halligan, 2013). However, it is a priori most implausible that such a major functional reorganization of interactions between and within neural networks will have no implications for ongoing cognitive processes. Having a reliable marker for hypnotic state, as we have proposed here, is a crucial first step. Once it can be determined that we have found such a marker the causal dynamics of the hypnotic state can begin to be unraveled.

AUTHOR CONTRIBUTIONS

Adrian P. Burgess and Helen J. Crawford designed the study and collected the data. All the hypnotic inductions and the assessments of hypnotic susceptibility were conducted by Helen J. Crawford. Adrian P. Burgess and Graham A. Jamieson analyzed the data and wrote the paper.

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"Reality" of near-death-experience memories: evidence from a psychodynamic and electrophysiological integrated study

Arianna Palmieri[1]*, Vincenzo Calvo[1], Johann R. Kleinbub[1], Federica Meconi[2], Matteo Marangoni[1], Paolo Barilaro[1], Alice Broggio[1], Marco Sambin[1] and Paola Sessa[2,3]

[1] Department of Philosophy, Sociology, Pedagogy and Applied Psychology (FISPPA), University of Padova, Padova, Italy
[2] Department of Developmental Psychology and Socialization (DPSS), University of Padova, Padova, Italy
[3] Centre for Cognitive Neuroscience, University of Padova, Padova, Italy

Edited by:
Enrico Facco, University of Padova, Italy

Reviewed by:
Sara L. Gonzalez Andino, Hôpitaux Universitaires de Genève, Switzerland
Bruce Greyson, University of Virginia Health System, USA

***Correspondence:**
Arianna Palmieri, Department of Philosophy, Sociology, Pedagogy and Applied Psychology (FISPPA), University of Padova, via Venezia 8, Padova 35131, Italy
e-mail: arianna.palmieri@unipd.it

The nature of near-death-experiences (NDEs) is largely unknown but recent evidence suggests the intriguing possibility that NDEs may refer to actually "perceived," and stored, experiences (although not necessarily in relation to the external physical world). We adopted an integrated approach involving a hypnosis-based clinical protocol to improve recall and decrease memory inaccuracy together with electroencephalography (EEG) recording in order to investigate the characteristics of NDE memories and their neural markers compared to memories of both real and imagined events. We included 10 participants with NDEs, defined by the Greyson NDE scale, and 10 control subjects without NDE. Memories were assessed using the Memory Characteristics Questionnaire. Our hypnosis-based protocol increased the amount of details in the recall of all kind of memories considered (NDE, real, and imagined events). Findings showed that NDE memories were similar to real memories in terms of detail richness, self-referential, and emotional information. Moreover, NDE memories were significantly different from memories of imagined events. The pattern of EEG results indicated that real memory recall was positively associated with two memory-related frequency bands, i.e., high alpha and gamma. NDE memories were linked with theta band, a well-known marker of episodic memory. The recall of NDE memories was also related to delta band, which indexes processes such as the recollection of the past, as well as trance states, hallucinations, and other related portals to transpersonal experience. It is notable that the EEG pattern of correlations for NDE memory recall differed from the pattern for memories of imagined events. In conclusion, our findings suggest that, at a phenomenological level, NDE memories cannot be considered equivalent to imagined memories, and at a neural level, NDE memories are stored as episodic memories of events experienced in a peculiar state of consciousness.

Keywords: NDE, near-death-experience, hypnosis, memory, EEG, integrative effort, clinical psychology, psychophysiology

INTRODUCTION

Near-death-experience (NDE) is classically described as an intense psychological experience of debated nature, characterized by an atypical state of consciousness occurring during an episode of apparent unconsciousness and usually in life-threatening conditions (Moody, 1975; Greyson and Stevenson, 1980). The interest in this phenomenon is well-founded when considering its incidence, ranging from 10% (Greyson, 2003) to about 35% (Zingrone and Alvarado, 2009) in individuals who have been close to death—and its across-the-board nature such that NDE reports in different cultures are substantially similar independently of sociological, demographic, and psychological variables (Kellehear, 2009). It is notable that there is evidence of NDEs in very young children as well (Sutherland, 2009).

In a referential review, Agrillo (2011) outlined the most recurring features reported in the literature that characterize NDEs, namely (a) awareness of being dead; (b) increase of mood in terms of euphoria, happiness, and well-being; (c) out-of-body experience; (d) entering a tunnel-like structure; (e) perception of a light; (f) perception of heavenly or hellish landscape; (g) encounter with deceased relatives, religious figures, or beings of light; (h) experience of a life review; (i) different temporal perception; and (j) perception of sounds or music. These features are included in the NDE scale (Greyson, 1983) currently considered the gold standard to identify veridical NDEs.

An additional facet of this phenomenon, that needs to be mentioned, is that even if a NDE usually occurs in circumstances of closeness to death, the literature describes many reports of individuals that have had a NDE without being physically in danger. A NDE can also be experienced during depression, isolation, meditation (Owens et al., 1990; van Lommel, 2010, 2011), psychological critical life events (Facco and Agrillo, 2012), or it may occur in healthy individuals present during a close relative's death (Moody and Perry, 2010).

Moody's first modern report about NDE, which contains 150 narratives, is entitled "Life after life" (Moody, 1975). This title is illustrative of the challenge, from both scientific and philosophical points of view, represented by NDE as one of the most fascinating issues in cognitive neuroscience research (Agrillo, 2011). In this context, two theoretical frameworks are aimed at interpreting this phenomenon: the so-called "biological/psychological" and the "survivalist" hypotheses (Braithwaite, 2008). The former theory suggests that NDEs are a consequence of brain functional changes that usually, but not always, occurs during the dying process and/or a psychological response to the perceived threat of death, such as cerebral hypoxia (Blackmore and Troscianko, 1988), cerebral anoxia (Lempert et al., 1994), hypercarbia (Klemenc-Ketis et al., 2010), serotonin (Morse et al., 1989) or noradrenaline (Mobbs and Watt, 2011) release alteration, massive liberation of glutamate (Jansen, 1989) or endorphins (Sotelo et al., 1995). In this vein, a referential article by Blanke et al. (2004) reported, for instance, that a typical feature of NDE, i.e., the out-of-body experience, is underpinned by a neural dysfunction, and can occur in neurological patients where the occurrence of a disintegration between personal (vestibular) space and extrapersonal (visual) space is conceivable. The latter theory advances suppositions toward a separation between mind and body, postulating a persistence of some sort of "soul" after the body's death. Among the survivalist interpretations, the theory of continuity proposes that memories, self-identity, and cognition, with emotions, continue to function independently from the unconscious body (van Lommel, 2011; Bókkon et al., 2013).

The numerous reports of NDEs in the absence of life-threatening conditions encourage an extensive, large-scale effort in NDE rendering, that goes beyond the reductionist interpretation that consider NDEs as consequences of dying brain biological mechanisms. One of the most critical aspects that could lead to a further step in understanding such a complex phenomenon is related to NDE's mnesic encoding, storage, and recall. In his review, van Lommel (2011) highlighted some core issues arising from NDE, including "why is the experience of the self during NDE so real? How is it possible to experience enhanced consciousness with the possibility of veridical perception independently of the lifeless body?" (p. 20). NDE memories are characterized by a sense of "phenomenological certainty" of the experience, typical of the perception during daily life (Dell'Olio, 2010). In this vein, Potts (2002) reported that NDEs have been described by individuals as perceived as "real" or even "realer than real."

In a recent study, Thonnard et al. (2013) examined this aspect of NDEs in depth. The authors specifically investigated NDE memories with the Memory Characteristics Questionnaire (MCQ; Johnson et al., 1988), built to evaluate peculiar characteristics of real and imagined event memories (Johnson et al., 1988). They compared memories of real and imagined past events in three groups of individuals that survived from the coma, one of which was characterized as having had NDEs and a control group. In summary, Thonnard et al. (2013) reported that NDE memories have more features than any kind of memory of real and imagined events, or memories related to a period of totally unconscious state such as coma. According to their interpretation, these findings demonstrate that NDEs cannot be considered as imagined events at all. Moreover, the authors highlighted that NDE memories seem to be *unique* and *unrivaled*.

Given the theoretical relevance of these premises, we were inspired by Thonnard et al. (2013)'s study. Our purpose was to investigate the features of NDE memories both at psychological and electrophysiological levels, in a group of NDE experiencers (NDErs), compared to a matched control group of individuals who never experienced a NDE. In contrast to the study of Thonnard et al. (2013), to achieve our aims we used a hypnotic-based protocol devised to facilitate the richness and thoroughness of the recalls. Such a method, rooted in psychodynamic tradition, is considered an excellent aid to facilitate and to focus on the recall of any kind of memory, both real and imagined (Erdelyi, 1994; Orne et al., 1996; Scoboria et al., 2002; Wagstaff et al., 2004). Particularly worthwhile for our purposes, hypnosis has already been successfully used in clinical practice, as reported in the literature, to evoke memories of NDEs that have happened previously. It was reported that some individuals were able to remember their NDEs only under hypnosis (Schroeter-Kunhardt, 1993; Facco, 2012).

From a psychological perspective, our first objective was to further characterize the NDE memories at the phenomenological level. We analyzed and compared NDE memories with memories of real and imagined events, in a group of NDErs and in a control group. Memory characteristics were assessed using MCQ before (to obtain a common baseline) and after the hypnotic procedure. In accordance with Thonnard et al. (2013), we expected that NDE memories would show similar features to those of real events, and different to those of imagined events.

From an electrophysiological perspective, our hypnosis-based recall approach was implemented by recording the electroencephalographic signals of participants. Electroencephalography (EEG) was chosen as an eligible means to measure neural activity associated with the nature and/or distinctiveness of the NDE memories, when compared to both real and imagined memories. Among the number of advantages that it brings, EEG offered the possibility to explore the neural correlates in a non-invasive way. It permitted a setting where the hypnotist could remain beside the participant during the administration of the hypnotic protocol.

We were particularly interested in examining whether the subjectively perceived peculiarity/vividness of NDE memories had a neural counterpart. Moreover, we were interested in uncovering a specific marker of NDE memories, in line with NDErs' peculiar phenomenological reports. We expected to observe more commonalities between real and NDE memories compared to memories of imagined events. Of particular interest for the present investigation, were those EEG frequency bands labeled theta, alpha (principally the faster frequencies within this band, i.e., high alpha or upper alpha), and gamma, because several EEG studies linked them, among other cognitive processes, to mnesic operations (Bastiaansen and Hagoort, 2003; Jensen et al., 2007; Klimesch, 2012). Cortical theta band oscillations, in the range of 4–7 Hz, observed at frontal, temporal and posterior regions of the scalp have been linked to retrieval in memory paradigms (Burgess and Gruzelier, 2000; Klimesch et al., 2001). Alpha band oscillations, in the range of 7.5–13 Hz, represent the dominant frequency at rest and they mostly originate from the occipital lobe. Klimesch (2012) argued that high alpha band desynchronization primarily reflects controlled access to/retrieval from the knowledge system, including not only long-term memory but also procedural and implicit-perceptual knowledge. Within this theoretical framework, it was suggested that the retrieval of semantically well-integrated information elicits more cortical excitation (i.e., alpha-band desynchronization or decrement of alpha power) than less integrated information. In conclusion, gamma band oscillations (above 30 Hz) also seem related to memory processes. In paradigms exploring long-term memory, it has been shown that gamma activity at the encoding predicts successful memory performance (Sederberg et al., 2003) and at retrieval, gamma activity was stronger for familiar words correctly recognized as having been previously presented than for new words that were correctly rejected as not having been previously presented (Osipova et al., 2006). It is notably that Sederberg et al. (2003) proposed that gamma activity may represent a marker of true memories; thus, during memory recall enhanced "gamma activity" may reflect the reactivation of "synaptically encoded representations" (Jensen et al., 2007) or, in other terms, the reactivation of the neural circuit originally recruited during encoding (Slotnick and Schacter, 2004).

Studies investigating EEG markers of hypnosis have produced mixed results so far (Oakley, 2008; Cardeña et al., 2013), indicating high alpha (MacLeod-Morgan and Lack, 1982), theta (Graffin et al., 1995), and gamma (Cardeña et al., 2013) as potential indices of hypnosis or hypnotic susceptibility. Because our purpose was not to focus on exploring the nature of hypnosis in itself and its neural correlates and because all the critical comparisons we were interested in were between types of memory (retrieved under hypnosis), we decided to focus our analyses on EEG recorded during hypnosis.

In the light of such premises, we expected that silent free recall of (at least) real memories would have been associated with theta, high alpha and/or gamma band power.

We also hypothesized a relationship between the amounts of additional memory details reported after hypnosis and the power of these frequencies. As discussed above, because high alpha band desyncronization is linked to memory processing, we expected to observe a negative correlation between high alpha band power and the difference score in the amount of detail of the real memories after hypnosis. In contrast, a positive correlation was predicted between theta and gamma band power and the difference score for these memories, as suggested by existing evidence. The most intriguing question, however, was whether a similar relation would have been observed also for NDE memories in the experimental group as well. If these memories have characteristics similar to those of real memories and involve the same storage systems, an analogous relationship between theta, high alpha, and/or gamma power and the difference score of NDE memories after hypnosis should be observed. The most appealing issue here was to uncover whether the subjectively perceived *uniqueness* of NDE memories (Thonnard et al., 2013) is associated with qualitatively comparable but eventually enhanced neural processing or rather they are qualitatively different from real memories, and more similar to imagined memories. To better explore this matter we extended our analyses to the other known EEG band frequencies.

According to our knowledge, neural activation in NDErs has been described only in two previous studies, one performed during sleep state (Britton and Bootzin, 2004) and the other in a meditative state/control condition (Beauregard et al., 2009). Therefore, this is the first systematic study that investigates neural activation during NDE recall and, more in general, the first that integrates psychodynamic and electrophysiological techniques.

MATERIALS AND METHODS

PARTICIPANTS

Ten individuals who had self-reported NDEs participated in the research. These NDErs were reached by using the referral sampling method, often employed in hidden populations which are difficult for researchers to access (Schroeter-Kunhardt, 1993). They were recruited through a national association composed of individuals who had had NDEs or were just interested in the NDE topic. An advertisement of our research purposes addressed to those who had experienced a NDE was made available by means of a social network, where all the association members were included. Ten of them were reached by phone in order to participate in the study. They were seven females and three males and their mean age was 49.0 years ($SD = 6.8$).

Their NDE was experienced in four of them by a traumatic injury followed by loss of consciousness; three of them reached NDE during a coma state caused by severe medical condition (for example sepsis); two of them had a NDE without any threatening condition (i.e., isolation or existential crisis). NDErs were compared with a 10-subjects control group without NDE.

The control group included 10 volunteer healthy subjects (seven females, mean age = 48.2 years, $SD = 6.9$), matched by gender, age, and educational level with the experimental group.

The first exclusion criterion for all participants was to not report the history of psychiatric, neurological, or substance use disorders and to not take any psychotropic drug at the time of the experimental procedure. The second exclusion criterion was the absence of personality disorders. All participants underwent two in-depth clinical interviews, far-between 1 week. In the first clinical interview, an experienced clinical psychologist administered the Structured Clinical Interview for DSM-IV Axis II Disorder (SCID-II; First et al., 1997) to both groups of participants in order to exclude individuals with personality disorders from the research. In the second clinical interview, two expert psychotherapists investigated through a non-structured interview the presence of personality disorders in order to exclude particularly, subclinical psychotic/schyzotypical traits or dissociative aspects. The only inclusion criterion was related to the experimental group of NDErs. They completed the NDE Scale, a self-rated, 16-item, multiple-choice questionnaire developed to assess these experiences (Greyson, 1983). All of them obtained a score of seven or above, which is generally used as a criterion for considering an experience to be a NDE (Greyson, 1983). The mean NDE score was 16.5 ($SD = 5.7$, range = 7–24). In general, all of the participants met the aforementioned criteria to be considered as eligible to participate in the research. Overall, our study included the participation of 20 subjects, divided into two groups, NDErs and their matched controls.

The study was approved by the Ethics Committee of Padova University (protocol No. 1321). Written informed consent was obtained from all individuals who participated in the study.

MEASURES

Characteristics of memories

To assess the participants' characteristics of memories, we used the MCQ (Johnson et al., 1988), in a modified version adapted by D'Argembeau and Van der Linden (2008) and used by Thonnard et al. (2013). This MCQ version included 15 items assessing several memory characteristics such as sensory details, memory clarity, self-referential and emotional information, reactivation frequency, and confidence in their own memory (Thonnard et al., 2013). An MCQ total score was derived summing all the 15 items (each on a 1–7 points Likert scale).

EEG acquisition and analyses

When populations of neurons simultaneously fire (i.e., synchronization), their rhythmic input is reflected in the extracellular field potential as brain oscillations. Spectral analyses allow decomposing the recorded EEG data by Fast Fourier transform (FFT) into component frequencies. It is largely established that power estimates of each component frequency reflect the number of neural units synchronously active.

EEG activity was continuously recorded under hypnosis during silent free recall of memory conditions. All participants were comfortably seated with their eyes closed. The EEG was recorded from 32 active electrodes placed on an elastic Acti-Cap positioned over the scalp in accordance with an extension of the international 10/20 system and referenced to the left earlobe. Horizontal EOG (HEOG) was bipolarly recorded from electrodes laterally positioned on the outer canthi of both eyes. Vertical EOG (VEOG) was recorded bipolarly from two electrodes, one above (Fp1) and one below the left eye. The impedance was kept less than 10 KΩ. EEG, HEOG, and VEOG activities were amplified (pass band 0.1–100 Hz) and digitized at a sampling rate of 1000 Hz.

EEG was analyzed offline using the Brain Vision Analyzer Software (version 2.0, Brain Products, Munich, Germany). EEG was digitally bandpass filtered (0.5–44 Hz, slope: 24 dB/octave) and re-referenced offline to the average of the left and right earlobes. The filtered and re-referenced EEG was further processed by using an independent component analysis (ICA). We used an ICA-based artifact correction in order to separate and remove VEOG and HEOG artifacts from EEG data by linear decomposition. Components contaminated with eye movements were corrected. EEG was further visually scanned by two independent observers to identify other artifact contamination including muscle artifacts and rejected. Following this procedure data from three participants (two from the experimental group and one from the control group) were excluded from successive analyses because of excessive muscle artifacts. The EEG was segmented into 2000 ms epochs.

For each participant, the artifact-free EEG was then subjected to FFT by averaging over each 2-s epoch using a Hanning window to normalize the spectrum analysis. Spectral power was computed for the following frequency bands: delta (2–3 Hz), theta (3.5–6 Hz), low alpha (7.5–9.45 Hz), mid alpha (9.5–10.45 Hz), high alpha (10.5–12 Hz), beta (14–25 Hz), and gamma (32–44 Hz).

PROCEDURE

A week before the experimental procedure, all the participants underwent a clinical interview with an experienced clinical psychologist who administered the SCID-II (First et al., 1997) and NDE participants also completed the NDE scale (Greyson, 1983). These measures were collected to exclude the participants with a score on the NDE scale of lower than seven (Greyson, 1983) or those on which, due to physical or mental health issues, hypnosis could have been potentially harmful. Furthermore, following Holden and MacHovec (1993)'s guidelines, the interview was aimed at excluding participants with negative and/or stressful NDE experiences. None of the participants were excluded by these means.

Right before the experimental procedure, we exhaustively described the research methodology, carefully avoiding to explicate the researcher's hypotheses or expectations, and all participants confirmed their agreement. Two trained psychotherapists interviewed participants according to a psychodynamic-oriented approach to confirm their psychological well-being and, mainly, to exclude the presence of psychotic symptoms or high state anxiety levels, according to Holden and MacHovec (1993)'s guidelines. Moreover, the interview was finalized to build a favorable alliance between participants and researchers.

During the experimental procedure we asked participants to recall two distinct memory conditions, in two subsequent sessions, in turn divided in two phases.

The two memories conditions were real events memories and target memories. In detail, in the real events memories condition, participants were asked to recall and narrate the most positive emotionally salient real event memory. In the target memories condition, the NDE group was asked to recall their NDE memory and the control group an imagined event memory (i.e., past dreams, fantasy, or unfulfilled intentions). Participants were invited to match emotional value and personal importance of real memories with target memories.

The first session of the experimental procedure began with a "pre-hypnotic" phase, where subjects were asked to recall the real memory event in a wakeful state, and then to describe it with as much detail as possible. In the second phase, labeled "post-hypnotic" phase, participants were asked to recall the same event after a hypnotic session aimed to enhance richness and thoroughness of memories (Erdelyi, 1994; Scoboria et al., 2002; Wagstaff et al., 2004). At the end of each phase, both "pre-hypnotic" and "post-hypnotic" memories were assessed with MCQ (Jensen et al., 2007; Thonnard et al., 2013).

After the first session, participants were invited to rest for about 15 min and then they were asked to complete an easy visuospatial task, in order to divert their own attention.

Subsequently, in the second session, we repeated the same sequence of "pre-hypnotic" and "post-hypnotic" phases, asking participants to recall target memories.

Real and target memories order was counterbalanced within subjects and between NDE and control groups.

The hypnotic protocol had the same structure in both sessions and was inspired by the protocol used by Palmieri et al. (2012). A trained operator in Eriksonian hypnosis induced a hypnotic state in the participants through a standardized ideomotor general induction, followed by instructions and suggestive symbolic imagery aimed to aid the recall process, including safeguards to avoid a shift from recalling to regressing. When the participants achieved a satisfying hypnotic trance, they were instructed to focus on the memory for 8 min. Further, participants were gently led back to full wakefulness by means of a de-hypnotization process and they were asked to describe the contents of the memory again. All hypnotic procedure was inspired by a psychodynamic, Eriksonian approach to hypnosis. Alongside the whole hypnotic session, encompassing induction and suggestion processes, EEG activity was recorded.

At the end of the second session, the hypnotist operator concluded the protocol according to Holden and MacHovec (1993)'s guidelines for the risk management in hypnotic recall of NDE. This safety procedure included a brief conclusive interview and the administration of the Post-Hypnosis Questionnaire H (Holden and MacHovec, 1993). All the participants in the present study described the hypnotic experience as pleasant or very pleasant (mean pleasantness = 5.9 on a 7-point Likert item) and did not feel any negative, physical, or emotional symptom.

STATISTICAL ANALYSES

Nonparametric tests were used to compare the amount of detail of memories (MCQ) between experimental and control groups and within different recall conditions. Nonparametric statistical methods were preferred to other parametric statistics because they require few if any assumptions about the shapes of the underlying population distributions and are more robust with small sample size (Siegel and Castellan, 1988; Kitchen, 2009). We used Mann-Whitney U test for between-group comparisons and Wilcoxon Signed Ranks Test for within-group ones. For all analyses, 2-tailed p-values of less than 0.05 were considered significant. All analyses were done with SPSS version 18.0.

EEG statistical analyses were conducted on an individual mean value of the spectral power within each frequency band at a subset of pooled electrode sites, resulting in the following regions: frontal (F3/F4), central (C3/C4), parietal (P3/P4), temporal (T7/T8), and occipital (O1/O2). In all multi-factorial analyses (see "EEG spectral power analyses and results"), a Greenhouse-Geisser correction was used where appropriate, i.e., when sphericity assumption was violated (Greenhouse and Geisser, 1959).

RESULTS

CHARACTERISTICS OF MEMORIES IN PRE-HYPNOTIC PHASE

Firstly, we computed the internal consistency of MCQ total score, which resulted in satisfactory scores (Cronbach's alpha of MCQ total score = 0.786).

In order to replicate and extend Thonnard et al. (2013)'s results, we compared MCQ total scores of different memories in the pre-hypnotic phase, considered as a baseline, with the Mann–Whitney U nonparametric between-groups test. Real memories of participants with NDE did not differ from real memories of the control group ($U = 37.5$, $Z = -0.947$, $p = 0.362$), whereas target memories were marginally greater in the experimental group than in the control group (NDEs vs. imagined memories; $U = 26.0$, $Z = -1.817$, $p = 0.069$). In other words, as expected, NDE memories were characterized by a greater amount of detail and richness compared to imagined recalls. In other words, as expected, NDE memories had more characteristics of memories than imagined recalls.

Within-group comparisons with Wilcoxon Signed Ranks Test showed that in the NDE group there were no significant differences between NDEs and real memories in the pre-hypnotic phase (Wilcoxon $Z = -1.023$, $p = 0.330$). In the control group, real memories were significantly greater than imagined memories (Wilcoxon $Z = -2.041$, $p = 0.043$). Taken together, these results suggest that in the pre-hypnotic phase, the recall of NDE memories and real memories had the same amount of detail and that both were more complex than imagined memories (**Figure 1**).

CHARACTERISTICS OF MEMORIES IN THE POST-HYPNOTIC PHASE

The effect of the hypnosis on the characteristics of memories was verified in all experimental conditions (real memories vs. target memories, i.e., NDEs and imagined memories), comparing MCQ total scores collected during the recalls in pre-hypnotic phase with post-hypnotic ones. Hypnosis had a significant effect on memories in all conditions; the amount of detail increased significantly in NDE memories (Wilcoxon $Z = -2.606$, $p = 0.006$), imagined memories (Wilcoxon $Z = -2.403$, $p = 0.016$), and real memories in both groups (Wilcoxon $Z = -2.809$, $p = 0.002$). Moreover, to further understand the effect of hypnosis, we analyzed the difference score (i.e., Δ MCQ) of memory characteristics after hypnosis in all conditions of recall. The difference score was slightly greater in the NDE condition compared to the real condition in the NDE group, but this difference did not reach the statistical significance (median Δ MCQ for NDE memories = 8, median Δ MCQ real memories = 7; Wilcoxon $Z = -0.767$, $p = 0.443$). The difference score was significantly lower in the imagined condition than in the real condition (median Δ MCQ imagined memories = 4; median Δ MCQ real memories = 10; Wilcoxon $Z = -1.990$, $p = 0.047$). Comparison between groups showed no significant differences between NDE and control groups in the difference score for real memories ($U = 29.0$, $Z = -1.596$, $p = 0.111$), and target memories (NDE vs. imagined memories; $U = 31.0$, $Z = -1.441$, $p = 0.150$).

In other words, hypnotic induction proved to be efficacious in all conditions, significantly increasing the complexity and the total amount of detail in all kind of memories. However, the difference score after hypnosis was higher in NDE and real recalls than in imagined ones.

Consistently with these findings, in the post-hypnotic phase we found the same differences among memories that we observed in the pre-hypnotic phase (**Figure 1**). Real memories did not differ between groups ($U = 31.0$, $Z = -1.441$, $p = 0.150$)

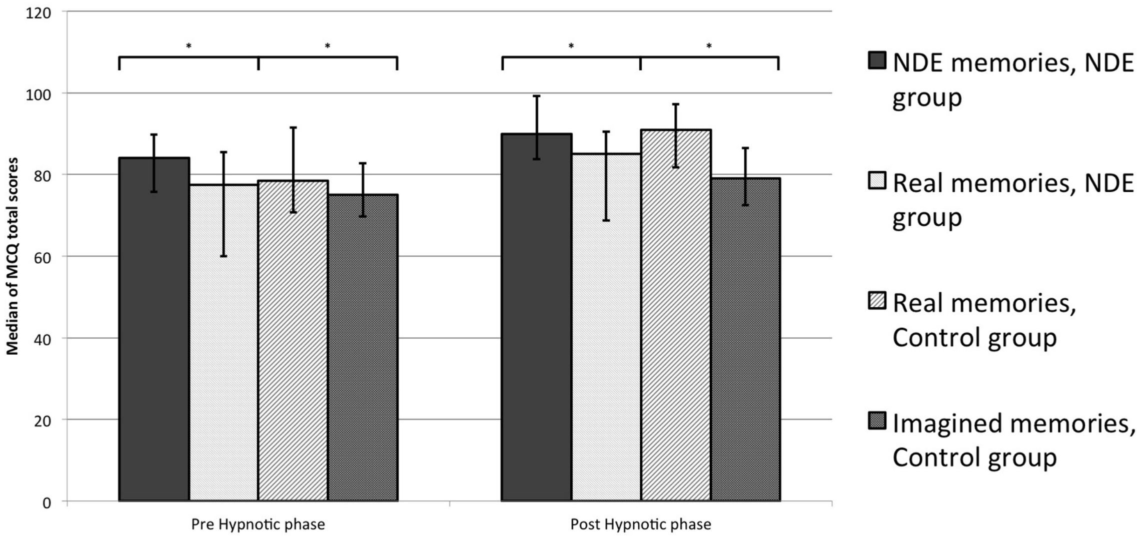

FIGURE 1 | Memory Characteristics Questionnaire (MCQ) total scores for each assessed memory. Median and interquartile ranges are presented (*$p < 0.05$).

whereas there was a significant difference in the target condition. NDE memories significantly resulted in more complexity than imagined memories ($U = 19.5$, $Z = -2.308$, $p = 0.021$). Within-group comparisons showed the same overall picture. NDE memories did not differ from real memories in the NDE group (Wilcoxon $Z = -1.326$, $p = 0.185$); whereas, at the same time in the control group, real memories had greater total scores than imagined ones (Wilcoxon $Z = -2.448$, $p = 0.014$).

FACTORIAL STRUCTURE OF MEMORY CHARACTERISTICS QUESTIONNAIRE

After having replicated and extended the results of Thonnard et al. (2013), we analyzed the composition of MCQ total score and its structure in depth to better understand neuronal underpinnings of specific kind of memories.

The in-depth analysis of the MCQ items led us to question the adequateness of items 10 and 11 that were on a bipolar scale, and of item 12 and 14 that were not specifically targeted to the recall. Having removed these items, an exploratory factor-analysis led us to hypothesize a four-factor internal structure. We tested such a model through a confirmatory factorial analysis (CFA). The results showed that our model had an overall good fit ($\chi^2 = 38.95$, $df = 28$, rmsea $= 0.07$, cfi $= 0.95$, srmr $= 0.06$, nnfi $= 0.92$, bic $= 2794.93$), and fitted our data better than the original with 1 factor composed of 15 items ($\chi^2 = 161.20$, $df = 86$, rmsea $= 0.11$, cfi $= 0.77$, srmr $= 0.10$, nnfi $= 0.71$, bic $= 4230.35$).

The identified four factors or subscales of the new models were: S1] perceptive and cognitive "resolution" (items 2, 8, and 9); S2] "reliving" (items 3, 13); S3] "veracity" (items 4, 5, and 15); and S4] "spatiotemporal organization" (items 5, 6, and 7). The "resolution" subscale included those items linked to the clarity and richness of the memory; the "reliving" subscale was associated with feelings of re-experiencing the event and the original emotions; the "veracity" subscale was associated with the perception of the memory as veridical and the "spatiotemporal organization" subscale comprised those items associated with the perception of the memory as a well-organized sequence of events.

The scores were averaged to the number of items in each subscale and they were used in the EEG analyses. Items and subscales of modified MCQ are presented in **Table 1**.

EEG POWER SPECTRA ANALYSES AND RESULTS

The mean of the spectral power within each frequency band was submitted to repeated measure ANOVAs considering region (5 levels: frontal, central, parietal, temporal, and occipital) and condition (NDE/imagined memories vs. real memories) as within-subjects factors, and group (experimental vs. control participants) as between-subjects factor. The individual mean values of the spectral power within each frequency band for each group and in each memory condition were also correlated (i.e., Pearson's r) with the difference score in MCQ after hypnosis (i.e., Δ MCQ for NDE memories and Δ MCQ for real memories for the experimental group; and Δ MCQ for imagined memories and Δ MCQ for real memories for the control group). Furthermore, to uncover finer relationships between the spectral power within each frequency band and the difference score after hypnosis, the Δ MCQ for each of the four subscales ("resolution," "reliving," "veracity," and "spatiotemporal organization") for each group of participants and for each condition, was also correlated with the spectral power within each band.

Delta band power (2–3 Hz)

The main effect of region was significant, $F_{(2.396,\ 12)} = 23.46$, $p < 0.001$, $\eta_p^2 = 0.610$. Bonferroni-corrected multiple comparison post-tests showed that power in the delta band was lower at temporal region than at all other regions (all ps < 0.001), and that it was higher at parietal region than occipital region ($p = 0.014$). The interaction condition (i.e., NDE/imagined

Table 1 | Modified version of Memory Characteristics Questionnaire (Thonnard et al., 2013).

Item no.	Modified version of Memory Characteristics Questionnaire	Characteristic (Thonnard et al., 2013)	Subscale
1	My memory for this event involves visual details: 1 = none, 7 = a lot	Visual details	NA
2	My memory for this event involves other sensory details (sounds, smells, and/or tastes): 1 = none, 7 = a lot	Other sensory details	S1] perceptive and cognitive resolution
3	While remembering the event, I feel as though I am mentally reliving it: 1 = not at all, 7 = completely	Feeling of re-experiencing	S2] reliving
4	I remember the location where the event took place: 1 = not at all clear, 7 = very clearly	Location	S3] veracity
5	I remember the time of the day when the event took place: 1 = not at all clear, 7 = very clearly	Time	S3] veracity S4] spatiotemporal organization
6	While remembering the event, it comes to me as a coherent story and not as an isolated scene: 1 = not at all, 7 = completely	Coherence	S4] spatiotemporal organization
7	I remember what I did during this event: 1 = not at all, 7 = very clearly	One's own actions	S4] spatiotemporal organization
8	I remember what I said during this event: 1 = not at all, 7 = very clearly	One's own words	S1] perceptive and cognitive resolution
9	I remember what I thought during this event: 1 = not at all, 7 = very clearly	One's own thoughts	S1] perceptive and cognitive resolution
10	Previous studies have shown that people can report that they can visualize different memories from different points of view. Using the bellow mentioned categories, from which point of view do you see yourself? (A) In your memory, you imagine the scene as an observer could see it. As an observer, you can see yourself and other aspects of the situation. (B) In your memory, you imagined the scene from your own point of view (through you own eyes). You are an actor. (C) Any of the above mentioned perspectives described the way you remember the situation. At which point are you observer or actor in the situation: 1 = totally observer; 7 = totally actor	Visual perspective	NA
11	When the event happened, my emotions were: 0 = very negative, 7 = very positive	Valence	NA
12	This event is important to me (it involves an important theme or episode in my life): 1 = not at all important, 7 = very important	Personal importance	NA
13	While remembering the event, I feel the emotions I felt when the event occurred: 1 = not at all, 7 = completely	Feeling emotions	S2] reliving
14	Since it occurred, I have thought or talked about this event: 1 = not at all, 7 = very often	Reactivation frequency	NA
15	I believe the event in my memory really occurred in the way I remember it and that I have not imagined or fabricated anything that did not occur: 1 = 100% imaginary, 7 = 100% real	Real/imagine	S3] veracity

memories vs. real memories) × group (i.e., experimental vs. control participants) was also significant, $F_{(1,\,15)} = 5.73$, $p = 0.030$, $\eta_p^2 = 0.276$. Separate ANOVAs for each group revealed that power in the delta band tended to be different between the imagined memories (mean power $1.733\,\mu\mathrm{V}^2$) and the real memories (mean power $1.265\,\mu\mathrm{V}^2$) conditions in the control group, $F_{(1,\,8)} = 3.89$, $p = 0.084$, $\eta_p^2 = 0.327$. For the experimental group, power in the delta band was positively correlated with the total individual scores of additional NDE memories details recalled following hypnosis (i.e., Δ MCQ for NDE memories) at frontal region, $r = 0.778$, $p = 0.023$, and at temporal region $r = 0.716$, $p = 0.046$. This association was particularly evident with regard to the "resolution" (at frontal region: $r = 0.785$, $p = 0.010$; at temporal region, $r = 0.712$, $p = 0.024$), the "reliving" (frontal region: $r = 0.712$, $p = 0.018$), and "spatiotemporal organization" (at all regions; frontal region: $r = 0.732$, $p = 0.020$; central region: $r = 0.652$, $p = 0.040$; parietal region: $r = 0.639$, $p = 0.044$; temporal region: $r = 0.842$, $p = 0.004$; occipital region: $r = 0.634$, $p = 0.046$) aspects of the NDE memories.

In the control group, a negative correlation was observed between the power in the delta band and the total difference score in imagined memories following hypnosis (i.e., total Δ MCQ for imagined memories) at frontal region, $r = -0.677$, $p = 0.045$, and an analogous trend was observed at central and temporal regions; although, only marginally significant, $r = -0.624$, $p = 0.072$, and $r = -0.626$, $p = 0.071$, respectively.

Theta band power (3.5–6 Hz)

The only significant effect was that of region, $F_{(1.992,\ 12)} = 15.35$, $p < 0.001$, $\eta_p^2 = 0.506$. Bonferroni-corrected multiple comparison post-tests showed that power in the theta band was lower at temporal regions than at all other regions (all $ps < 0.05$). Mean theta band power did not correlate with the total difference score in MCQ score following hypnosis (i.e., Δ MCQ). However, when considering separately MCQ subscales, in the experimental group was observed a positive correlation between the power in the theta band and the "spatiotemporal organization" aspect of the NDE memories (frontal region: $r = 0.712$, $p = 0.024$; temporal region: $r = 0.614$, $p = 0.053$; an analogous trend, although only marginally significant, was also observed at central, parietal, and occipital regions ($r = 0.539$, $p = 0.084$; $r = 0.547$, $p = 0.080$; $r = 0.513$, $p = 0.097$, respectively). An opposite relationship (i.e., negative correlations) was observed in the control group between the power in the theta band and the "resolution" (frontal region: $r = -0.609$, $p = 0.041$; central region: $r = -0.594$, $p = 0.046$; temporal region, $r = -0.640$, $p = 0.032$) and "reliving" (central region: $r = -0.648$, $p = 0.029$; an analogous trend, although only marginally significant, was also observed at parietal, temporal, and occipital region: $r = -0.568$, $p = 0.055$; $r = -0.541$, $p = 0.066$; $r = -0.551$, $p = 0.062$, respectively) of imagined memories.

Low alpha band power (7.5–9.45 Hz)

Statistical analyses of mean power in the low alpha band did not show any significant effect (min $p = 0.196$). Mean low alpha band power did not correlate with individual scores of the difference score in MCQ following hypnosis (i.e., Δ MCQ).

Mid alpha band power (9.5–10.45 Hz)

Statistical analyses on mean power in the mid alpha band did not show any significant effect (min $p = 0.491$). Mean mid alpha band power did not correlate with individual scores of difference score in MCQ following hypnosis (i.e., Δ MCQ).

High alpha band power (10.5–12 Hz)

The main effect of region was significant, $F_{(1.290,\ 12)} = 15.67$, $p < 0.001$, $\eta_p^2 = 0.511$. Bonferroni-corrected multiple comparison post-tests showed that power in the high alpha band was higher at occipital and parietal regions compared to the other regions and lower at temporal and frontal regions compared to the other regions (max $p = 0.016$). The main effect of group was also significant, $F_{(1,\ 15)} = 4.962$, $p = 0.04$, $\eta_p^2 = 0.249$, indicating greater power in the high alpha band in the experimental group (mean power $4.51\,\mu V^2$) than in the control group (mean power $1.82\,\mu V^2$). The interaction region × group tended to be significant, $F_{(1.290,\ 12)} = 3.72$, $p = 0.059$, $\eta_p^2 = 0.199$, indicating that the distribution of the high alpha across the scalp tended to be different in the two groups of participants. Separate ANOVAs for each group revealed that power in the high alpha band tended to be lower at parietal region (mean power $2.54\,\mu V^2$) than at occipital regions (mean power $3.58\,\mu V^2$) in the control group, $p = 0.075$.

For the experimental group, power in the high alpha band was negatively correlated with the total individual scores of the difference score of real memories following hypnosis (i.e., Δ MCQ for real memories) at frontal regions, $r = -0.713$, $p = 0.047$. No individual subscales of the Δ MCQ was particularly linked with alpha power. For the control group, power in the high alpha band was negatively correlated with the "reliving" aspect of the real memories (temporal region: $r = -0.603$, $p = 0.043$; and marginally at frontal region: $r = -0.534$, $p = 0.069$).

Beta band power (14–25 Hz)

The main effect of the group was significant $F_{(1,\ 15)} = 6.073$, $p = 0.026$, $\eta_p^2 = 0.288$, indicating greater power in the beta band in the experimental group (mean power $0.82\,\mu V^2$) than in the control group (mean power $0.37\,\mu V^2$). Mean beta band power did not correlate with the individual scores of the difference score in MCQ following hypnosis (i.e., Δ MCQ).

Gamma band power (32–44 Hz)

The main effect of region was significant, $F_{(1.701,\ 12)} = 3.67$, $p = 0.026$, $\eta_p^2 = 0.196$. Bonferroni-corrected multiple comparison post-tests showed that power in the gamma band was significantly higher at frontal region than at parietal region ($p = 0.035$). For the control group, power in the gamma band was positively correlated with the individual scores of the difference score in MCQ for real memories following hypnosis (i.e., Δ MCQ for real memories) at central regions, $r = 0.679$, $p = 0.022$. A finer-grained analysis considering Δ MCQ subscales revealed a richer pattern of results: first, the correlation observed for the control group was particularly evident for the "resolution" (frontal region: $r = 0.755$, $p = 0.009$; at parietal region, $r = 0.817$, $p = 0.004$; at temporal region, $r = 0.679$, $p = 0.022$; at occipital region, $r = 0.713$, $p = 0.016$), the "veracity" (at central region: $r = 0.661$, $p = 0.026$), and the "spatiotemporal organization" (at central region: $r = 0.606$, $p = 0.042$) aspects of the real memories. Furthermore, for the experimental group this finer analysis revealed a positive correlation between power in the gamma band and the "reliving" (temporal region: $r = 0.728$, $p = 0.020$) aspect of the real memories.

Figure 2 shows the scatterplots of the most relevant correlations between memory-related EEG frequency bands (high alpha, theta, and gamma) and individual Δ MCQ scores (or subscales scores) for the real memories and the NDE memories conditions in the experimental group and for the real memories condition in the control group. **Figure 3** shows the scatterplots of a subset of observed correlations between delta band and individual Δ MCQ scores for the NDE memories condition in the experimental group and for the imagined memory condition in the control group.

Table 2 schematically illustrates the pattern of correlations between each EEG frequency band considered in the present study (delta, theta, low alpha, mid alpha, high alpha, beta, and gamma) and Δ MCQ scores and subscales scores for each group of participants (experimental and control groups) and for each type of memory (Real, NDE, and Imagined).

DISCUSSION

In this study, an integrative effort was employed, from a psychodynamic and electrophysiological perspective, to catch an in-depth insight into NDE recall. It is notable that this experience is typically defined by most NDErs as "realer than real" (Blackmore, 1993; Potts, 2002). To investigate this phenomenon, we compared NDE memories with the memories of real autobiographical events and memories of imagined autobiographical events, in a group of NDErs and in a matched control group. NDE memories were verbally recalled both in pre- and post-hypnotic wakeful state. During hypnosis, the free silent recall was EEG recorded.

From a psychological point of view, our findings were in accordance with Thonnard et al. (2013), which inspired our theoretical premises, and with our first hypothesis. Our expectation was to characterize NDE memories as similar to real memories and as different from imagined memories in terms of mnesic cues that can discern one from the other.

In the baseline condition before hypnotic session, NDE memories revealed more detail than imagined memories, as investigated with MCQ questionnaire (Thonnard et al., 2013). Moreover, according to our hypothesis, in the NDE group there were no significant differences between NDE and real memories; consistently with these findings, in the control group, MCQ total scores of real memories were significantly greater than that of imagined memories. Overall, we found that in the pre-hypnosis phase, the NDE memories and the real memories had the same amount of mnesic characteristics and both were more complex and richer than imagined memories. From a phenomenological perspective, it could be inferred that NDE memories showed high similarities with real memories, and profound dissimilarities from imagined memories. NDErs who participated in our study always considered their NDE memories far superior to their real memories from all points of view, despite the efforts of the experimenter to invite them in finding a comparable event that happened in real life. All participants who lived NDEs described them as the most powerful, intense, vivid, important, and founding experience of their life.

Quotation of a NDE participant to our study: "In 45 years I dreamed a lot of things, but I never had a 'dream' like this. (…) When you dream, you know that it is a dream. When I remember my dreams, in the next 5 minutes I'm not sure anymore about their content. This experience (note: NDE) instead, you'll remember it clearly, for years."

Consistently with the literature (Orne et al., 1996; Scoboria et al., 2002) and with predictions originated by the clinical practice, all kind of memories revealed amelioration thanks to hypnotic sessions. In all the experimental conditions (target memories, i.e., NDE memories and imagined memories, and real memories), in facts, hypnosis had a significant facilitating effect. In other terms, the hypnotic procedure significantly increased the complexity and the total amount of detail of all kind of memories, as measured with MCQ. Consequently, MCQ score obtained in the post-hypnotic phase, maintained the same trend and the same level of significance of the pre-hypnotic phase, revealing that NDE memories features are totally similar, in terms of sensory, clarity, self-referential information emotional, and confidence of real memories, and significantly different from more poorly-detailed imagined events memories.

Findings by Thonnard et al. (2013) also suggested that NDE memories are actually perceived although, not-lived in the external world. The authors concluded their manuscript inviting neural investigation to deepen the roots of this phenomenon perceived as so veracious: albeit, it happened in an unconscious state. In this vein, at the neural level, our second hypothesis was to observe a relationship between recall of real memories and the power of those band oscillations associated with memory functioning recorded during silent free recall under hypnosis, i.e., theta, high alpha, and gamma. The most critical issue was whether a relation with these well-known neural indices of memory would have been observed for NDE memories in the experimental group as well. Given the reported *uniqueness* of NDE memories (Thonnard et al., 2013), we extended our analyses to the other EEG bands, and the Δ MCQ for each of the four subscales derived from the MCQ (i.e., "resolution," "reliving," "veracity," and "spatiotemporal organization").

In line with our hypotheses, a better recall of real memories (both total additional memory details recalled following hypnosis, i.e., Δ MCQ for each type of memory, for each group, and Δ MCQ for each of the four subscales) was correlated with a pattern of high alpha power decrease/gamma power increase, in both experimental and control groups of participants. These findings correspond well with previous researches showing a link between these frequency bands and long-term memory performance (e.g., Sederberg et al., 2003; Klimesch et al., 2008). It has been proposed that gamma activity may represent a marker of true memories (Sederberg et al., 2003). This hypothesis views gamma activity as an index of the reactivation of the neural circuits originally recruited during encoding, which usually includes the occipital regions originally engaged in the encoding of visual objects and scenes (Slotnick and Schacter, 2004). This relationship between gamma band and real memories also involved the occipital region. Such a relationship was not observed for NDE memories (possibly suggesting that they were the result of an internally generated experience, e.g., hallucination-like form). In contrast, the increase of theta band power at temporal region positively correlated with the recall of the details of NDE memories

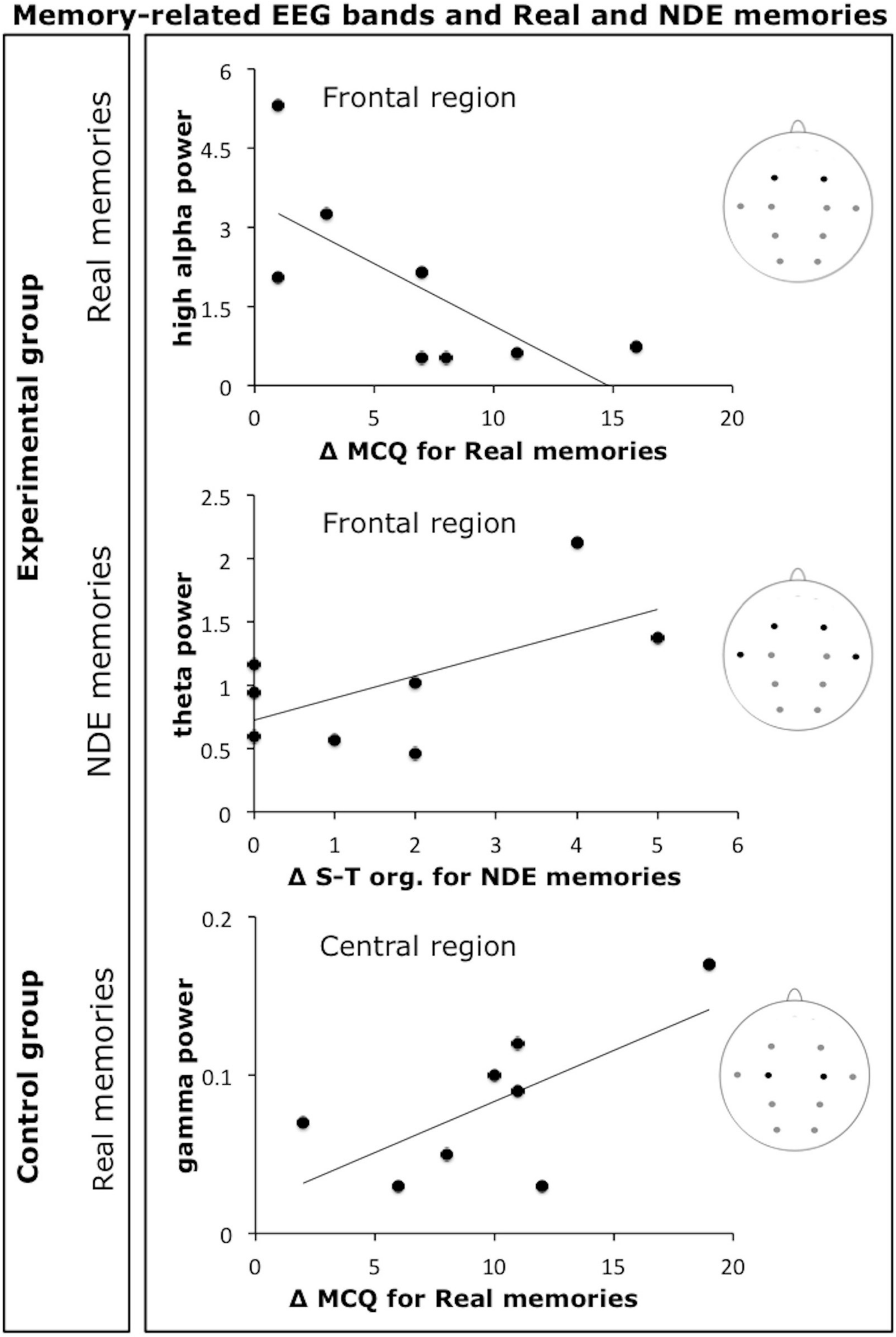

FIGURE 2 | Scatterplots of a subset of observed correlations between memory-related EEG frequency bands (high alpha, theta, and gamma) and individual Δ MCQ scores or Δ MCQ subscales scores. Scatterplots show the most relevant correlations for the real memories and the NDE memories conditions in the experimental group and for the real memories condition in the control group (Δ S-T org. = Δ MCQ scores for the spatiotemporal organization subscale).

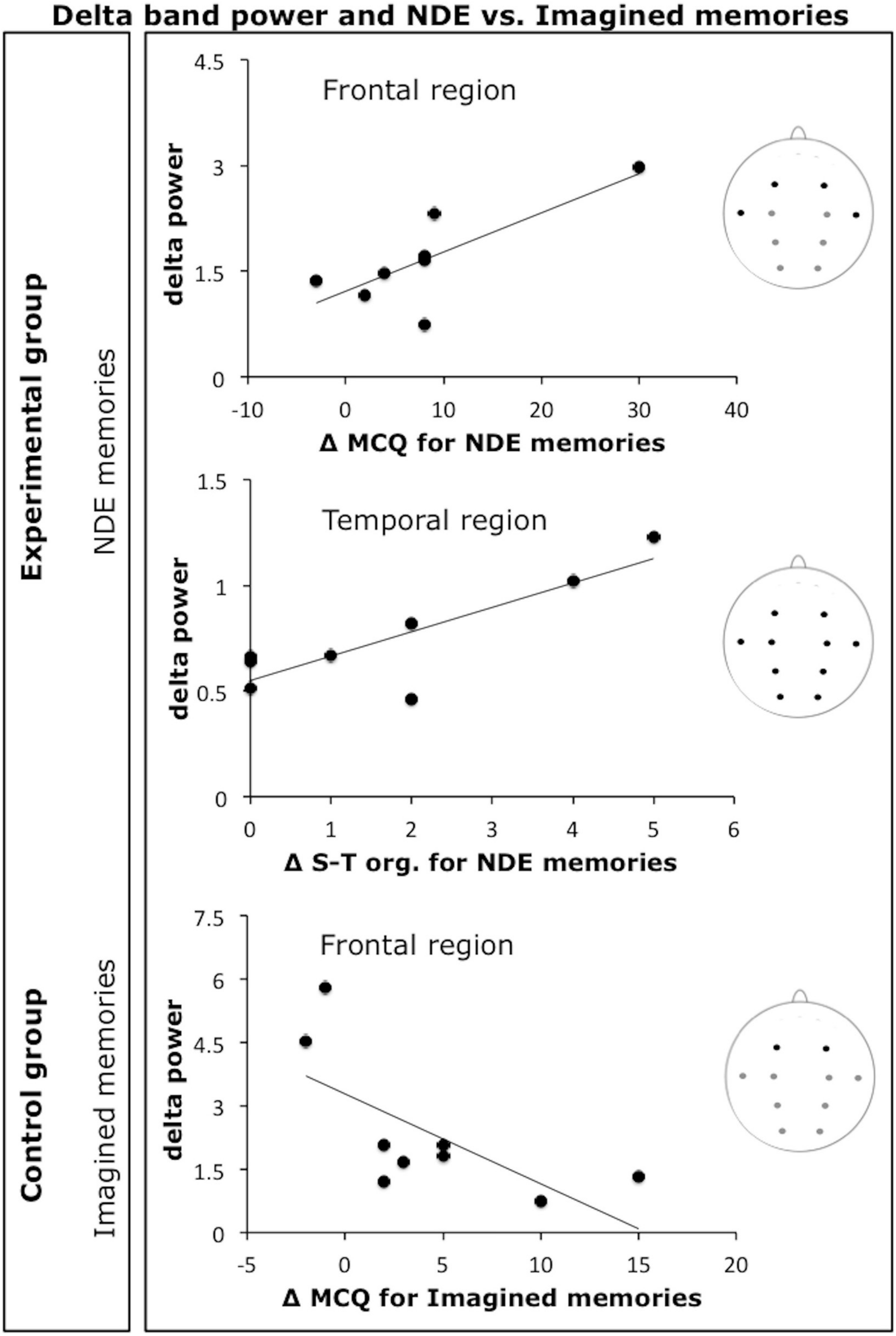

FIGURE 3 | Scatterplots of a subset of observed correlations between delta band and individual Δ MCQ scores or Δ MCQ subscales scores. The first two panels show the correlations with the NDE memories condition in the experimental group and the third panel with the imagined Memories condition in the control group (Δ S-T org. = Δ MCQ scores for the spatiotemporal organization subscale).

Table 2 | Pattern of correlations between each EEG band and Δ MCQ scores.

EEG band	**Experimental group**		**Control group**	
	Real memories	**NDE memories**	**Real memories**	**Imagined memories**
Delta	n.s.	*Positive correlations* with Δ MCQ (at frontal and temporal regions); with Δ MCQ for resolution (at frontal region) and with Δ MCQ for spatiotemporal organization (at all regions). *rs* ranging from 0.634 to 0.842	n.s.	*Negative correlations* with Δ MCQ (at frontal, central, and temporal regions). *rs* ranging from −0.626 to −0.677
Theta	n.s.	*Positive correlations* with Δ MCQ for spatiotemporal organization (at all regions). *rs* ranging from 0.513 to 0.712	n.s.	*Negative correlations* with Δ MCQ for resolution (at frontal, central, and temporal regions) and for with Δ MCQ for reliving (at central, parietal temporal and occipital regions). *rs* ranging from −0.541 to −0.648
Low alpha	n.s.	n.s.	n.s.	n.s.
Mid alpha	n.s.	n.s.	n.s.	n.s.
High alpha	*Negative correlations* with Δ MCQ (at frontal region). $r = -0.713$	n.s.	*Negative correlations* with Δ MCQ for reliving (at frontal and temporal regions). $r = -0.603$ and $r = -0.534$, respectively	n.s.
Beta	n.s.	n.s.	n.s.	n.s.
Gamma	*Positive correlations* with Δ MCQ for reliving (at temporal region). $r = 0.728$	n.s.	*Positive correlations* with Δ MCQ (at central region) and with Δ MCQ for resolution (at frontal and parietal regions). *rs* ranging from 0.606 to 0.817	n.s.

n.s., no significant.

associated with the perception of the memory as a well-organized sequence of events (i.e., "spatiotemporal organization" subscale). Although evidence is not conclusive at present, it is suggested that cortical theta oscillations are connected to intracranial recorded hippocampal theta oscillations. Because the critical role of hippocampus in memory functioning is well established (Squire, 2009), it was hypothesized that cortical and hippocampal theta oscillations dynamically interact, supporting memory operations (Bastiaansen and Hagoort, 2003).

The most recent theoretical scenario supports the notion that hippocampal theta oscillations are mainly associated with the temporal organization of episodic memories (Buzsáki and Moser, 2013), indirectly proposing that the retrieval of highly organized memories in terms of spatiotemporal sequences may also be linked to an increase in cortical theta power. It is noteworthy that the observed correlation between the power in the theta band and the recall of the details of NDE memories associated with the "spatiotemporal organization" subscale, seems to nicely converge with this hypothesis. Importantly, in the control group, the power in the theta band was negatively correlated with additional details of imagined memories reported following hypnosis, particularly in relation to those memory details associated with the perception of clarity and richness (i.e., "resolution" subscale) and the feeling of re-experiencing the event and the original emotions (i.e., "reliving" subscale).

In conclusion, the above-described pattern of findings indicated that "successful" recall of real memories was related with power in the high alpha/gamma bands. Furthermore, NDE memories were also linked with power in the theta band, a well-known marker of episodic memory. Moreover, the EEG pattern of correlations for NDE memory recall critically differed from that observed for imagined memories. As mentioned before, in order to extensively explore the issue of a neural marker of NDE memories, we decided to extend analyses to the other EEG bands. Of particular relevance are the findings relative to delta band oscillations. Power in this band tended to be different between the real memories and the imagined events memories conditions in the control group, but a comparable power was observed for the real memories and the NDE memories conditions in the experimental group. In two recent reviews on delta activity, Knyazev (2012) and Harmony (2013) indicated a variety of conditions and mental functions associated with delta activity, such as those related to evolutionarily old basic processes, motivation, reward, as well as mental concentration. On the basis of extant evidence, one conceivable interpretation of these findings is that the recall of both real and NDE memories were more rewarding than the recall of imagined memories.

Furthermore, power in the delta band was positively (and selectively) correlated with additional details of NDE memories reported following hypnosis, particularly in relation to those memory details associated with the perception of the memory as clear and detailed (i.e., "resolution" subscale), the feeling of re-experiencing the event and the original emotions (i.e., "reliving" subscale), and the perception of the memory as a well-organized sequence of events (i.e., "spatiotemporal organization" subscale). One explanation of this relationship may refer to the hypothesis that delta oscillations are also indicative of inhibition of sensory afferences, a mechanism that will favor internally directed cognition (i.e., "internal mentation"). This internal mentation includes a recollection of the past (Harmony, 2013). In these terms, an increase in delta power may have supported the recollection of NDE memories. Although reasonable, this interpretation does not account for a potentially relevant aspect of this finding, i.e., the selectivity of the correlation between the power in the delta band and additional details of NDE memories.

A different and maybe more appealing perspective may relate to the notion of "state-dependent memory," also called "state-dependent learning," based on which the retrieval of a memory is facilitated by the match between the original state of consciousness experienced at the encoding and the current state of consciousness at retrieval (Overton, 1966). To note, the two perspectives (namely, internal mentation and state-dependent memory) are not mutually exclusive; however they may integrate providing a more comprehensive interpretation of this relation between delta activity and NDE memories. Although evidence is scarce in this regard and sometimes anecdotal, one may speculate that NDE memories were better retrieved when delta power was greater because during the original NDE, delta dominated the EEG pattern, or, at least, it was critically associated with the experience itself. Slow-wave activity has been related to certain trance states and other related portals to transpersonal experience (Hartman and Zimberoff, 2002), including the shamanic state of consciousness, out-of-body experiences, NDEs, and lucid dreaming. Furthermore, Strubelt and Maas (2008) asserted that if, during the NDE, neural circuits (including those of the neocortex) usually engaged in memory encoding are functioning, the experience may be encoded and retrieved later.

As a further argumentation in favor of state-dependent-memory hypothesis, the hypnotic state has seldom been used to evoke previously occurring NDEs; some individuals who experienced this phenomenon were able to remember it only in hypnosis (Schroeter-Kunhardt, 1993). Facco (2012) underlined that some common processes could link the hypnotic state with the NDE experience: both of them have been included in the so-called "altered state of consciousness." Facco (2012) stated that, although NDE and hypnosis are unequivocally two distinct phenomena, some common processes probably link them. For example, experiences similar to those of NDE can be easily generated during hypnosis, such as (a) imagining seeing oneself from the outside, (b) change in time perception, (c) recalling old and non-easily accessible memories, and (d) performing a life review. Holden and MacHovec (1993) quoted a case of a man submitted to hypnosis, who previously had a NDE during an anaphylactic shock. When he recalled it during a hypnosis session, he replicated the whole experience, including negative physical changes, in terms of sudden fall of arterial blood pressure with a great increase of heart rate (up to 190 beats/min), and he re-entered the normal, physiological state after de-hypnotization. Therefore, although it can only be regarded as speculation, our electrophysiological findings fit very well with the hypothesis of the state-dependent memory, such that an EEG pattern similar to that originally present during the NDEs may facilitate a recall of NDE memories.

To summarize the whole pattern of EEG findings, it appears to unveil a peculiar pattern of neural activity associated with the recall of NDE memories linked to slow-wave activity, including both delta and theta oscillations. Theta power represents a well-known marker of memory processing, particularly in relation to episodic memories and their spatiotemporal organization (Buzsáki and Moser, 2013); delta power has also been associated with internal mentation including the recollection of the past (Harmony, 2013). On the other hand, the recall of these NDE memories did not show any relationship with gamma power, which has been designated as a marker of true memories (Sederberg et al., 2003), where "true" indicates that the memory recall reactivates the sensory circuits originally recruited during encoding of objects, scenes, events experienced in the physical world. Whitton et al. (1978) demonstrated that both unmedicated schizophrenics with Schneiderian criteria during hallucinations and healthy control participants during a "creativity" test exhibited an EEG frequency pattern of predominantly delta and theta power. This whole pattern may fit with the proposal of Thonnard et al. (2013) that NDE memories are hallucination-like memories of actually perceived hallucinations. In fact, in the present investigation, NDE recall was related to both delta (recollection of the past but also trance states and hallucinations) and theta power (episodic memory) but not with gamma power (true memories; experienced in the physical world). In synthesis, the EEG findings suggest that NDE memories are episodic memories of events experienced in a peculiar state of consciousness.

To briefly delineate the intriguing theoretical controversy between psychological/biological and survivalist theorists in the matter of NDE memories, it is necessary to begin from the origin of the debate. In general, it is important to take into account that, according to well-established classical findings, memories of human beings originating from real, everyday life, should have more perceptual information (e.g., color and sound), more contextual information, and more details than memories originated from thought (Johnson et al., 1988). Blackmore (1993) proposed a biological/psychological hypothesis that the emerging memories of NDE could be totally or partially imagined, as a result of peculiar neuronal pattern of activation and a reconstructive cognitive process, immediately after the resuscitation, influenced by personal knowledge and expectations. Psychological studies from forensic fields have shown that simple imagining having had a specific experience can create false memories (Loftus, 2001). In other words, it has been proposed that reports of NDEs could be memories of totally or partially imagined events. Survivalist theorists have argued that false memories are hardly conjugated with rich content information that characterized NDE. Moreover, it would not be conceivable that a neural circuit of resource-poor, damaged brain could support false memory (Parnia et al., 2001). Agrillo (2011) argued that, if the brain is too unstable to support such processes, the question would focus on where the NDE memories would be stored. As Braithwaite (2008) outlined, in order to have any experience to be remembered, the memory should in the first place encode and represent the experience.

Finally, our findings seem inconsistent with the idea that such vivid NDE reports can be originated by totally or partially imagined false memory. In contrast, a suggestive interpretation of our EEG results appears to contradict the classic idea (van Lommel et al., 2001) that during a life-threatening event, such as a cardiac arrest, there is no activity of the cortex and the brainstem (implying a transient loss of all functions of the brain). A recent study by Borjigin et al. (2013) was able to reveal brain activity in rats 30 s after a cardiac arrest by using a finer technique, i.e., intracranial EEG recording. This activity was characterized by a transient surge of synchronous gamma oscillations phase-coupled to both slow-wave and alpha oscillations, and the authors suggested that the whole pattern indexed a heightened conscious processing near-death. However, Greyson et al. (2013), in a subsequent commentary, raised some criticisms about the interpretation by Borjigin et al. (2013) of their above mentioned data. Among these criticisms, the fact that the EEG registered in the rats was a tiny fraction of the total neuroelectric power present before the cardiac arrest could be misleading to consider this EEG activity a neural underpinning of conscious processing. According to Greyson et al. (2013), it is impossible to establish what, if anything, the rats were experiencing during the post-arrest period of the surge. In addition, Borjigin et al. (2013) found that the EEG burst did not occur in anesthetized rats, whereas NDEs commonly occur in people who are anesthetized.

Either way, if NDE memory is related to a real event, it should imply that enough neural activation would be available to encode and represent the experience and subsequently to report it. As mentioned above, our results are in line with the hypothesis that the core components of a NDE have a neural counterpart. If we assume that some physiological mechanisms can account for NDEs, then the individual really perceives what was reported later, albeit not necessarily corresponding to occurring events in the external, physical world. In a very speculative perspective, NDE phenomenon could begin some hours, days, even weeks before the effective exitus, in terms of End of Life Dreams and visions (ELDVs). The hypothesis of common neural mechanism between ELDVs and NDEs, where ELDVs phenomenon is a sort of precursor of NDEs, may not be so implausible. Even if scientific literature describes ELDVs and NDEs as two distinct phenomena, a number of common characteristics [i.e., vivid and memorable visions, encounter with deceased loved ones, feeling of joy and serenity, transcendence, spiritual transformation after the experience, Nosek et al. (2014)] make conceivable that they could be two entities of the same continuum.

Agrillo (2011) labels the psychological/biological and survivalist interpretations as "in brain" or "out of brain" theories, respectively, highlighting that survivalist hypothesis do not necessarily exclude the role of biological or psychological components underlying NDE. According to the author, the crucial point is not whether "something" can survive after biological death, because nobody can say anything for sure in this regard, but whether the NDE phenomenon is explicable at least in terms of brain functioning. In this line, our data supporting the idea of a neural counterpart of the phenomenon, are not necessarily in contrast with a more spiritualistic theory. In fact, our findings suggest a neural support that allowed NDE mnesic storage in a brain that was partially functional (e.g., in coma patients, or in cardiac arrest patients), regardless of a flatline EEG, which measures only surface cortical activity, as suggested by some authors (Bardy, 2002; Braithwaite, 2008; Borjigin et al., 2013) or fully functional (e.g., in isolation condition or meditative state: Owens et al., 1990; van Lommel, 2010, 2011) at the moment when NDE happened. In other words, even if the investigation of neural underpinnings in experiencing or recalling NDE could be roughly ascribed to a psychological/biological position, uncovering the neural counterpart of NDE does not exclude *per se* survivalist hypothesis. It is likely that many of the arguments reported to support the former or the latter antipodal positions would be, in fact, not necessarily mutually exclusive, as in the case of our findings.

The main limitation of our research is the relatively small sample size. However, people who experienced NDE classically represent a hard-to-reach population, because of their reluctance in talking about their experience to avoid negative reactions in the others (Schroeter-Kunhardt, 1993; van Lommel, 2011). Further studies including wider samples are warranted.

In conclusion, our integrative-effort study showed that NDE memories are different from imagined autobiographical memories and very similar to memories of real events, in terms of detail richness, self-referential and emotional information. EEG signal recorded during hypnotic sessions, successfully employed to facilitate memory retrieval, revealed a pattern of neural activation during the NDE recall that seemed to have supported the retrieval of additional details. Such neural signature was characterized by slow-wave activity, including both theta (i.e., a marker of memory processing, particularly related to episodic memories with spatiotemporal organization) and delta (which has also been associated with internal mentation and meditative state) oscillations.

Several possible explicative hypotheses, expounded in this section, could arise from our observations, such as the role of dependent-state-memory in NDE recall during hypnosis. Moreover, our impression is that our results could lead to a little, further step in the direction of an understanding of NDE memories; although, many questions remain unanswered and further research is needed to shed light to this intriguing phenomenon of consciousness.

AUTHOR CONTRIBUTIONS

Design and conceptualization of the study: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Paola Sessa. Acquisition of data: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Federica Meconi, Matteo Marangoni, Paolo Barilaro, Alice Broggio, Marco Sambin, Paola Sessa. Statistical analysis: Vincenzo Calvo, Johann R. Kleinbub, Paola Sessa. Interpretation of the data: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Paola Sessa. Drafting the manuscript: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Paola Sessa. Revising the manuscript for intellectual content: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Federica Meconi, Matteo Marangoni, Paolo Barilaro, Alice Broggio, Marco Sambin, Paola Sessa. Final approval of the version to be published: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Federica Meconi, Matteo Marangoni, Paolo Barilaro, Alice Broggio, Marco Sambin, Paola Sessa. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Arianna Palmieri, Vincenzo Calvo, Johann R. Kleinbub, Federica Meconi, Matteo Marangoni, Paolo Barilaro, Alice Broggio, Marco Sambin, Paola Sessa.

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Near-death experiences in non-life-threatening events and coma of different etiologies

Vanessa Charland-Verville*[1]*, Jean-Pierre Jourdan*[2]*, Marie Thonnard*[1]*, Didier Ledoux*[1]*, Anne-Francoise Donneau*[3]*, Etienne Quertemont*[4] *and Steven Laureys*[1]*

[1] *Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium*
[2] *International Association For Near Death Studies, Oraison, France*
[3] *Department of Public Health, University of Liège, Liège, Belgium*
[4] *Department of Psychology, Cognitive and Behavioral Neurosciences Center, University of Liège, Liège, Belgium*

Edited by:
Enrico Facco, University of Padua, Italy

Reviewed by:
Rüdiger Ilg, Technische Universität München, Germany
Christopher Charles French, Goldsmiths, University of London, UK

****Correspondence:***
Steven Laureys, Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Allée du 6 août no 8, Sart Tilman B30, 4000 Liège, Belgium
e-mail: steven.laureys@ulg.ac.be

Background: Near death experiences (NDEs) are increasingly being reported as a clearly identifiable physiological and psychological reality of clinical significance. However, the definition and causes of the phenomenon as well as the identification of NDE experiencers is still a matter of debate. To date, the most widely used standardized tool to identify and characterize NDEs in research is the Greyson NDE scale. Using this scale, retrospective and prospective studies have been trying to estimate their incidence in various populations but few studies have attempted to associate the experiences' intensity and content to etiology.

Methods: This retrospective investigation assessed the intensity and the most frequently recounted features of self-reported NDEs after a non-life-threatening event (i.e., "NDE-like" experience) or after a pathological coma (i.e., "real NDE") and according to the etiology of the acute brain insult. We also compared our retrospectively acquired data in anoxic coma with historical data from the published literature on prospective post-anoxic studies using the Greyson NDE scale.

Results: From our 190 reports who met the criteria for NDE (i.e., Greyson NDE scale total score >7/32), intensity (i.e., Greyson NDE scale total score) and content (i.e., Greyson NDE scale features) did not differ between "NDE-like" ($n = 50$) and "real NDE" ($n = 140$) groups, nor within the "real NDE" group depending on the cause of coma (anoxic/traumatic/other). The most frequently reported feature was peacefulness (89–93%). Only 2 patients (1%) recounted a negative experience. The overall NDE core features' frequencies were higher in our retrospective anoxic cohort when compared to historical published prospective data.

Conclusions: It appears that "real NDEs" after coma of different etiologies are similar to "NDE-like" experiences occurring after non-life threatening events. Subjects reporting NDEs retrospectively tend to have experienced a different content compared to the prospective experiencers.

Keywords: Near-death experiences, Greyson NDE scale, coma, cardiac arrest, traumatic brain injury, memory, non-life threatening events

INTRODUCTION

The expression "Near-Death Experience" (NDE) was first formulated in the nineteenth century when a Swiss geologist collected testimonies from his fellow climbers and himself after making a fall in the Alps (Heim, 1891). Some decades later, Moody (1975) popularized the expression through his best seller "Life after life" in which he defined NDEs as "any conscious perceptual experience occurring in individuals pronounced clinically dead or who came very close to physical death" and drew a list of the most frequently recounted features by individuals who had survived near-fatal incidents. These NDE features included: overwhelming feelings of peacefulness and well-being; painlessness; the impression of being located outside one's physical body; the impression of drifting through a dark environment that looks like a tunnel; the sight of a brilliant light and the feeling of being surrounded by it; the impression of discovering another world described as idyllic; the feeling of a close presence; the encounter and communication with spirits or deceased relatives or experiencing a "life review" (Moody, 1975). More recently, NDEs have been defined as a "profound psychological event including transcendental and mystical elements, typically occurring to individuals close to death or in situations of intense physical or emotional danger" (Greyson, 2000).

Empirical studies of NDEs have mostly been conducted in patients with life threatening situations such as cardiac arrest

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Abbreviations: Near-Death Experiences, NDEs; Near-Death Experiencers, NDErs; Weighted Core Experience Index, WCEI.

(Parnia et al., 2001; van Lommel et al., 2001; Schwaninger et al., 2002; Greyson, 2003a; French, 2005; Klemenc-Ketis et al., 2010) or (albeit more rarely) in patients with severe traumatic brain injury (Hou et al., 2013). To the best of our knowledge, no study has formally compared the influence of the cause of coma to the intensity or content of the NDE. Unlike these "real NDEs" associated with "real" closeness to death or coma, possible NDEs or "NDE-like" experiences have also been reported in situations where there was no genuine threat to the individuals' life. Only a few studies have assessed "NDE-like" phenomena in non-life threatening situations (Gabbard et al., 1981; Owens et al., 1990; Gabbard and Twemlow, 1991; Kelly, 2001; Facco and Agrillo, 2012). Such accounts have also been reported in epileptic patients (Hoepner et al., 2013), syncope (Lempert et al., 1994), intense grief and anxiety (Kelly, 2001), Cotard's syndrome (McKay and Cipolotti, 2007; Charland-Verville et al., 2013) and during meditative state (Beauregard et al., 2009). It remains unclear whether NDEs occurring in life-threatening or non-life threatening situations differ in intensity or core features. In addition to the ill-described relation between the NDE and the precipitating factor, the reliability of NDEs accounts also remains controversial (Martens, 1994; French, 2001). For instance, it seems that fewer cases of NDEs are recounted by individuals interviewed prospectively than when the interviews are conducted retrospectively (Mobbs and Watt, 2011). On the other hand, it has been shown that reports of NDEs were not modified over time even 20 years after the original account (Greyson, 2007).

Using the Greyson NDE scale (Greyson, 1983), the present retrospective study aimed at (1) exploring the NDE intensity and content in "NDE-like" accounts following non-life-threatening events vs. "real NDE" following coma; (2) comparing the "real NDE" characteristics according to the etiology of the brain damage (anoxic, traumatic or other) and (3) comparing our retrospectively obtained data in anoxic coma to historical previously published prospectively collected post-anoxic NDEs.

MATERIALS AND METHODS

Participants were recruited via the website, publications and appearances in local media of the International Association for Near-Death Studies (IANDS France and IANDS Flanders) and the Coma Science Group (University of Liège, Belgium). Written, email or telephone completion of an anonymous questionnaire was voluntary and taken as consent for participation in the survey. The study was approved by the ethics committee of the Faculty of Medicine of the University of Liège. The questionnaire included items about demographic (age at NDE, gender) and clinical data (time since NDE, presence of life threatening event, presence of acute coma (i.e., a period of unconsciousness >1 h; Posner et al., 2007)), etiology of coma (anoxic/traumatic/other) and a standardized characterization of the NDE using the Greyson NDE scale (Greyson, 1983). The Greyson NDE scale is a validated (Lange et al., 2004) 16-item multiple-choice tool used to quantify the intensity of the NDE (i.e., total score ranging from 0 to 32) and to assess core content components of 16 NDE features. For each item, the scores are arranged on an ordinal scale ranging from 0 to 2 (i.e., 0 = "not present," 1 = "mildly or ambiguously present," and 2 = "definitively present"; Greyson, 1983; Lange et al., 2004). For statistical analyses, a feature was considered present when participants scored an item as 1 or 2 (Greyson, 1983, 2003a). Participants whose experience did not meet the accepted criteria of NDE (i.e., Greyson total score <7; Greyson, 1983) were excluded from the present analysis.

First, we verified that "NDE-like" and "real NDE" groups and the 3 coma etiologies of the "real NDE" group (i.e., anoxic/traumatic/other) were matched for gender, age at NDE, and interval since NDE. A Pearson's chi square test with contingency tables was performed to compare the gender ratios between the "NDE-like" and "real NDE" groups as well as between the 3 coma etiologies (i.e., anoxic/traumatic/other) of the "real NDE" group. A Student's t-test was performed to compare age at NDE and time since NDE between the "NDE-like" and "real NDE" groups and a One-Way ANOVA was performed to compare the age at NDE and the time since NDE within the coma 3 etiologies of the "real NDE" group. Next, we looked for differences in NDE overall intensity (i.e., total NDE scale's scores) between "NDE-like" and "real NDE" groups' using Student's t-testing. A Pearson's chi square test with contingency tables was performed to assess for possible discrepancies between the reported features frequencies in "NDE-like" and "real NDE" groups. A One-Way ANOVA was performed in order to test for differences in intensity within the "real NDE" group depending on the etiology of coma. A Pearson's chi square test with contingency tables was performed to assess for possible discrepancies between the reported features frequencies according to the coma etiology. Finally, the present retrospective data in anoxic coma were compared with a historical dataset of prospective data taken from the published literature on NDE after anoxic coma (Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003a). For each feature of the Greyson NDE scale, the proportions of positive answers between retrospective and prospective studies were compared by the classical chi-squared test for contingency tables or by the Fisher exact test. Further, the overall comparison between the two study groups was made by the Generalized Estimating Equations Approach (GEE), which accounts for percentage variability within NDE features.

RESULTS

Results were considered to be significant at the 5% critical level ($p < 0.05$) and were expressed as mean ± standard deviation (SD) for quantitative variables and as counts and proportions (%) for categorical variables. Data analysis was carried out using SAS (version 9.3 for Windows) statistical package. Out of the 215 self-reported NDEs, 25 did not meet the criteria for NDE (i.e., NDE scale total score <7/32) (Greyson, 1983) and were excluded from the current study. **Table 1** shows the demographic characteristics of the different groups constituting the retrospective study cohort ($n = 190$; 104 females (55%); age at NDE 32 ± 14 year; time since NDE 24 ± 15 year). The "NDE-like" group ($n = 50$) included NDEs occurring following a non-life-threatening event such as during sleep ($n = 13$), syncope ($n = 11$), meditation ($n = 5$), drugs and alcohol consumption ($n = 3$), or other non-life threatening situations ($n = 18$). The "real NDE" group ($n = 140$) was divided according to the etiology of the coma: "anoxic" (e.g., cardiac arrest, near-drowning, $n = 45$); "traumatic" (e.g., motor vehicle accident, falls, $n = 30$) and "other" (i.e., non-traumatic events such as an exacerbation of on-going illness, complication during surgery, $n = 65$). There were no significant differences in gender, age at time of NDE and interval since NDE between the "NDE-like" and "real NDE" groups and within the "real NDE" groups depending on etiology.

Intensity (i.e., Greyson NDE scale total score) and content (i.e., NDE scale features) of reported NDEs did not differ between "NDE-like" and "real NDE" groups nor within the "real NDE" group depending on the cause of coma (anoxic/traumatic/other) (see **Table 2**). For all study groups, the most frequently reported core NDE feature was the feeling of peacefulness for all study groups (frequency range: 89–93%). Only 18/190 (10%) did not experience positive emotions such as peacefulness, happiness or joy; 2 of whom explicitly recounted a negative experience (both following a life threatening event; 2 females, aged 31 and 41 who were comatose due to a complication after childbirth and surgery, respectively). Finally, the overall NDE core features' frequencies were significantly higher in our retrospective anoxic cohort ($n = 45$; 20 females 44%) when compared to historical published prospective data (Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003a) obtained after anoxic coma ($p < 0.0001$). An altered time perception, the feeling of harmony and unity, the sudden understanding of everything, heightened senses were more frequently reported in the current retrospective dataset on post-anoxic NDE while encounters with deceased or religious spirits were more frequently reported in previous prospective studies on post-anoxic NDE (see **Table 3**).

Table 1 | NDErs demographic characteristics ($N = 190$).

Demographics	"NDE-like" $n = 50$	"Real NDE" $n = 140$	p	"Real NDE" etiologies			p
				Anoxic $n = 45$	Traumatic $n = 30$	Other $n = 65$	
Gender—female	25 (50%)	79 (57%)	0.43	20 (44%)	15 (50%)	44 (68%)	0.20
Age at NDE	31 ± 11	32 ± 15	0.76	35 ± 16	29 ± 11	31 ± 17	0.26
(Mean in years ± *SD*, range)	4–60	3–76		8–64	6–50	3–76	
Time since NDE	23 ± 16	24 ± 15	0.82	20 ± 14	26 ± 11	25 ± 17	0.10
(Mean in years ± *SD*, range)	0.13–66	0.15–75		0.15–50	3–43	1–75	

Table 2 | NDE intensity (Greyson Scale total score) and content (core features) reported in "NDE-like" and "real NDE" groups–by decreasing order of frequency according to the "real NDE" group (significance level $p < 0.05$).

NDE Scale features	"NDE-like" $n = 50$ (%)	"Real NDE" $n = 140$ (%)	p	"Real NDE" etiologies			p
				Anoxia $n = 45$ (%)	Trauma $n = 30$ (%)	Other $n = 65$ (%)	
"Did you have a feeling of peace or pleasantness?"	45 (90)	127 (91)	0.88	40 (89)	28 (93)	59 (91)	0.81
"Did you feel separated from your body?"	37 (74)	111 (79)	0.44	36 (80)	24 (80)	51 (79)	0.98
"Did you see, or feel surrounded by, a brilliant light?"	42 (84)	106 (76)	0.23	32 (71)	20 (67)	54 (83)	0.15
"Did time seem to speed up or slow down?"	41 (82)	105 (75)	0.31	35 (78)	24 (80)	46 (71)	0.55
"Did you seem to enter some other, unearthly world?"	35 (70)	101 (72)	0.77	33 (73)	21 (70)	47 (72)	0.95
"Did you have a feeling of joy?"	37 (74)	98 (70)	0.59	32 (71)	18 (60)	48 (74)	0.38
"Did you feel a sense of harmony or unity with the universe?"	39 (78)	96 (69)	0.21	33 (73)	21 (70)	42 (65)	0.61
"Did you come to a border or point of no return?"	31 (62)	86 (61)	0.94	22 (49)	20 (67)	44 (68)	0.11
"Were your senses more vivid than usual?"	34 (68)	84 (60)	0.32	25 (56)	16 (53)	43 (66)	0.38
"Did you suddenly seem to understand everything?"	25 (50)	76 (54)	0.60	26 (58)	20 (67)	30 (46)	0.15
"Did you seem to encounter a mystical being or presence, or hear an unidentifiable voice?"	29 (58)	71 (51)	0.38	20 (44)	12 (40)	39 (60)	0.12
"Were your thoughts speeded up?"	20 (40)	62 (44)	0.60	23 (51)	15 (50)	24 (37)	0.26
"Did you see deceased or religious spirits?"	17 (34)	54 (39)	0.57	12 (27)	9 (30)	33 (51)	0.063
"Did you seem to be aware of things going on elsewhere, as if by ESP?"	14 (28)	47 (34)	0.50	10 (22)	9 (30)	28 (43)	0.067
"Did scenes from your past come back to you?"	9 (18)	37 (26)	0.23	11 (24)	11 (37)	15 (23)	0.35
"Did scenes from the future come to you?"	9 (18)	26 (19)	0.93	8 (18)	5 (17)	13 (20)	0.92
Total score (mean ± *SD*, range)	17 ± 7, 7–30	16 ± 6, 7–30	0.10	15 ± 6, 7–28	16 ± 6, 7–26	16 ± 6, 7–30	0.29

Table 3 | Retrospective and prospective anoxic studies' demographics and Greyson NDE scale core features (significance level $p < 0.05$).

Study's demographics	Current data retrospective	Total prospective	Greyson (2003a) prospective	Schwaninger et al. (2002) prospective	Parnia et al. (2001) prospective	*p*	Odds ratio	95% interval
Number of subjects	*N* = 45	*N* = 42	*N* = 27	*N* = 11	*N* = 4			
Age at NDE (years)	35 ± 16, 8–64		56 ± 13	53, 23–84	>18			
Gender	20 females (44%)	19 females (45%)	10 females (37%)	7 females (64%)	2 females (50%)		0.97	0.42–2.26
Etiology	Anoxic/hypoxic		Anoxic/hypoxic	Anoxic/hypoxic	Anoxic/hypoxic			
Time since insult (mean, *SD*, range)	20 ± 14 year 0.15–50 year		"4 days on average"	"2–3 days on average"	"<7 days"			
NDE Scale total score (*SD*)	15 ± 6		13 ± 6	N/D	11 ± 2	0.52		
Peacefulness	40 (89)	37 (88)	23 (85)	11 (100)	3 (75)	0.99	1.08	0.29–4.04
Out-of-body experience	36 (80)	31 (74)	19 (70)	10 (90)	2 (50)	0.49	1.42	0.52–3.87
Altered time perception	**35 (78)**	**21 (50)**	**18 (67)**	**1 (9)**	**2 (50)**	**0.007**	**3.50**	**1.38–8.85**
Unearthly environment	33 (73)	25 (60)	17 (63)	6 (54)	2 (50)	0.17	1.87	0.76–4.62
Harmony/unity	**33 (73)**	**21 (50)**	**14 (52)**	**5 (45)**	**2 (50)**	**0.025**	**2.75**	**1.12–6.74**
Happiness/joy	32 (71)	23 (55)	18 (67)	2 (18)	3 (75)	0.11	2.03	0.84–4.93
Bright light	32 (71)	29 (69)	19 (70)	7 (63)	3 (75)	0.83	1.10	0.44–2.76
Understanding	**26 (58)**	**11 (26)**	**8 (30)**	**2 (18)**	**1 (25)**	**0.003**	**3.86**	**1.56–9.55**
Heightened senses	**25 (56)**	**12 (29)**	**4 (15)**	**6 (54)**	**2 (50)**	**0.011**	**3.13**	**1.28–7.62**
Speeded thoughts	23 (51)	13 (31)	12 (44)	1 (9)	0 (0)	0.056	2.33	0.97–5.61
Border/point of no return	22 (49)	20 (48)	11 (41)	5 (45)	4 (100)	0.91	1.05	0.45–2.44
Mystical being/presence	20 (44)	15 (36)	7 (26)	7 (63)	1 (25)	0.41	1.44	0.61–3.41
Encounter with deceased/religious spirits	**12 (27)**	**24 (57)**	**14 (52)**	**8 (72)**	**2 (50)**	**0.004**	**0.27**	**0.11–0.67**
Extrasensory perception	10 (22)	5 (12)	3 (11)	0 (0)	2 (50)	0.74	2.11	0.66–6.80
Life review	11 (24)	9 (21)	8 (30)	1 (9)	0 (0)	0.20	1.19	0.44–3.23
Precognitive visions	8 (18)	3 (7)	2 (7)	1 (9)	0 (0)	0.14	2.81	0.69–11.41

DISCUSSION

We here used the Greyson NDE scale (Greyson, 1983) to retrospectively assess the characteristics of 190 self-reported NDEs precipitated by a non-life threatening event or coma. The Greyson NDE scale is a widely used and validated tool to assess the intensity and content of NDEs (Greyson, 1990, 2003a,b; Parnia et al., 2001; Schwaninger et al., 2002; Nelson et al., 2006; Lai et al., 2007; Klemenc-Ketis et al., 2010; Hoepner et al., 2013; Hou et al., 2013) and, in contrast to the Weighted Core Experience Index (WCEI; Ring, 1980), provides a cut-off score permitting a standardized identification of NDE experiencers (NDErs). As for other retrospective studies on NDEs (Greyson, 1990; Lai et al., 2007), the interval between the age at study enrollment (mean age 56 ± 13 year) and the occurrence of the NDE (mean age 32 ± 15 year) was several decades (mean 24 ± 15 year). Our study sample did not show a significantly higher proportion of female NDErs. In the "real NDE" coma-survival group, the most frequently reported features (i.e., occurring >75%) include the feeling of peacefulness, out-of-body-experiences, seeing a bright light, alerted time perception. Conversely, precognitive visions (e.g., seeing the future) and the experience of life review were among the least frequently reported core features (i.e., occurring <30%). These results corroborate previous reports on NDE studies using the Greyson NDE scale (Greyson, 1990, 2003a; Parnia et al., 2001; Schwaninger et al., 2002; Nelson et al., 2006; Lai et al., 2007) or the WCEI (van Lommel et al., 2001). According to the etiology of coma, a recent prospective study reporting interview transcripts of post-traumatic coma survivors with a NDE revealed that the most frequently reported elements were the sight of an intense light, feelings of astonishment, pleasure and sense of helplessness (Hou et al., 2013). Although the well-being component is one of the most often reported features in classical NDEs, it is important to note that distressing or hellish experiences can also occur. In line with previous estimations (Lindley et al., 1981; Gallup and Proctor, 1982; Sabom, 1982; Ring, 1984), we recorded an incidence of 1.4% (2/140) of our "real NDE" group that reported to have had a negative NDE.

Some authors have tried to explain the phenomenology of NDE by diverse physiological explanations such as anoxic brain damage (Rodin, 1980; Blackmore, 1993; Greyson, 1998; Els et al., 2004; Woerlee, 2005; Ammermann et al., 2007), hypoxia (Lempert et al., 1994), hypercapnia (Klemenc-Ketis et al., 2010), abnormal temporal lobe dysfunctions (Blanke et al., 2002, 2004; Britton and Bootzin, 2004; Blanke and Mohr, 2005; Arzy et al., 2006; Hoepner et al., 2013), administration of sedatives (Cobcroft and Forsdick, 1993; Osterman et al., 2001; Lopez et al., 2006), or sleep abnormalities (Nelson et al., 2006, 2007). However, to the best of our knowledge, previous studies on NDE after coma have not aimed at identifying differences in NDE characteristics depending on the etiology (i.e., traumatic, non-traumatic anoxic or non-traumatic other acute brain insults) of the prolonged loss of consciousness. Despite our relatively large sample size, our analyses failed to show a significant difference on NDE intensity or content between these different causes of coma (matched for age, gender and interval since NDE). In the current study sample, we did not observe a significant difference in NDE intensity or core feature frequency when comparing "real NDE" after coma to "NDE-like" events occurring after non-life-threatening events. Some authors have argued that the strong belief or fear of dying might be the key determinant for triggering a NDE (Gabbard et al., 1981; Stevenson et al., 1989–1990; Gabbard and Twemlow, 1991) independently of the actual organic brain damage.

Features of a NDE occurring during situations that are not life threatening and that are not perceived as such like during sleep or a meditative state cannot be explained by the expectancy of an incoming death. Individuals put in apparently life-threatening situations (e.g., involved in various accidents or undergoing surgery) might think the worst could happen even though the real medical situations result in none or minor brain insults (Gabbard and Twemlow, 1991; Facco and Agrillo, 2012). Likewise, the first historical reports of NDE testimonies obtained from Alpine mountain climbers who had suffered a non-fatal fall also illustrate the role of psychological reactions to a perceived life-threatening event in the generation of NDEs (Heim, 1891). Owens et al. (1990) reported that both "NDE like" and "real NDEs" showed a comparable phenomenology including positive emotions, out-of-body experiences, tunnel-like perceptions and memory flashbacks. In contrast to our findings they reported that NDErs who had been in a life threatening condition (i.e., "real NDE") tended to more frequently report seeing a bright light and experiencing enhanced cognitive functions (e.g., speeded thoughts and sense of understanding). Gabbard and Twemlow (1991), on the other hand, observed that individuals who self-reported a "close brush with death," as compared to those who did not, experienced more out-of-body experiences. It is difficult to compare these findings with the present data because both previous studies did not employ a standardized scale for the characterization of the NDE. Using the Greyson NDE scale, Kelly (2001) reported that individuals who were close to death more often encountered deceased relatives during the NDE. Furthermore, the reports of those encounters were more frequent when the precipitating factor was a traumatic brain injury or a cardiac arrest than when the NDE was precipitated by a complication during childbirth or surgery (Kelly, 2001). The fact that we did not observe such differences in our current sample could be explained by the heterogeneity of the investigated samples' etiologies as well as the ill-defined nature of the non-life-threatening conditions.

It is important to stress that our study has a number of methodological limitations. Retrospective recruitment of self-reported NDEs may not represent a reliable sample of the NDErs population since they might have greater interest in and knowledge of NDEs. In addition to the probable sample-bias related to the recruitment of medically uncontrolled NDEs, the interval between the occurrence of the NDE and the age at study enrollment was several decades—similar to other retrospective surveys (Greyson, 1990; Lai et al., 2007). We therefore compared our retrospective data with prospectively obtained published datasets. In order to reduce the possible confound of heterogeneity in etiology and NDE characterization we have chosen to compare our retrospective anoxic coma group with results from published prospective NDE studies on anoxic coma also using the Greyson NDE scale (Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003a). Our comparison identified a higher overall frequency of NDE core features occurrence in our retrospective sample (**Table 3**). Similarly, a recent review by Mobbs and Watt (2011) also points to a higher incidence of NDEs in retrospective as compared to prospective studies. These findings could be related to the claim of some authors that NDE reports might suffer from memory reconstructions (French, 2001; Martens, 1994). However, Greyson (2007) has reported that the memories of NDE core features did not modify over time. Moreover, our data suggest that encounters with deceased or religious spirits are more frequently reported *prospectively*. It should be stressed that any statistical comparison of different study designs (retro- vs. prospective) is methodologically problematic because of small sample sizes, high variability and sampling error. Consequently, it is difficult to assign appropriate weights reflecting the relative "value" of the information provided in each study. However, our findings on differences between retrospective and prospective post-anoxic NDE reports seem to be confirmed when extended to other etiologies as illustrated in **Figure 1**. A visual comparison of the weighted ratios of core NDE features calculated from four retrospective studies (Greyson, 1990; Nelson et al., 2006; Lai et al., 2007) (total $n = 429$; including the present dataset) and four prospective studies (Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003a; Hoepner et al., 2013) (total $n = 47$), all using the Greyson NDE scale, illustrates that all items (with the exception of encounters with deceased or spirits) seem more frequently reported retrospectively.

It seems that NDEs cannot be explained solely by the closeness to death or by the etiology of the precipitating factor. The question whether the NDEs' extraordinary features can be fully explained by cerebral activity is still a matter of debate and a challenge awaiting the neuroscientific analysis of this phenomenon is to identify the neural correlates of such a physiologically real yet unexplained cognitive experience. Studying NDEs continues to represent a methodological challenge and investigators must rely on testimonies and indirect ways to understand the brain mechanisms associated with such an experience. When we compared our medically uncontrolled retrospectively obtained results to historical data from controlled prospective trials, several core features seemed to be more frequently reported when retrospectively collected (i.e., altered time perception, harmony, understanding and heightened senses). In line with our findings and as previously stressed (Facco and Agrillo, 2012), NDE research might benefit from the introduction of a new terminology to account for "NDE-like" experiences. In addition to the use of closed NDE questionnaires, which only leave restricted choices for describing the experience, future studies should employ statistical examination of freely expressed NDEs narratives using automated user-independent qualitative analyses of their content (Hou et al., 2013), taking into account the clinical data and study design.

AUTHOR CONTRIBUTIONS

Vanessa Charland-Verville and Steven Laureys designed the study, wrote the manuscript and conducted the analyses. Vanessa Charland-Verville, Jean-Pierre Jourdan, Marie Thonnard, Steven Laureys, collected all data and contributed to the final manuscript. Anne-Francoise Donneau, Didier Ledoux and Etienne Quertemont contributed to the analyses and to the revision of the final manuscript. Jean-Pierre Jourdan and Steven

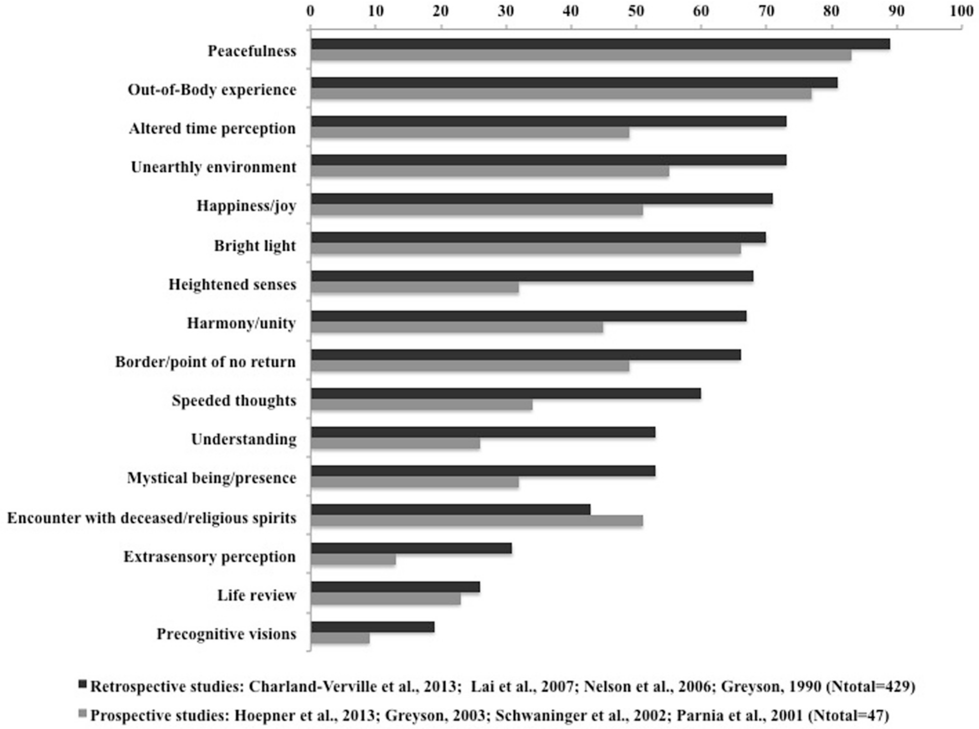

FIGURE 1 | Frequency of NDE features in retrospective and prospective studies (all etiologies) according to the Greyson NDE scale by decreasing order according to the retrospective data.

Laureys provided conceptual input and contributed to the final manuscript. All authors approved the final version of the manuscript.

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Out-of-body experiences associated with seizures

Bruce Greyson[1]*, Nathan B. Fountain[2], Lori L. Derr[1] and Donna K. Broshek[3]

[1] Division of Perceptual Studies, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA
[2] F.E. Dreifuss Comprehensive Epilepsy Program, Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA, USA
[3] Neurocognitive Assessment Laboratory, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA

Edited by:
Etzel Cardeña, University of Lund, Sweden

Reviewed by:
Andrea E. Cavanna, Birmingham and Solihull Mental Health NHS Foundation Trust, UK
Enrico Facco, University of Padua, Italy

***Correspondence:**
Bruce Greyson, Division of Perceptual Studies, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, 210 10th Street NE, Charlottesville, VA 22902-4754, USA
e-mail: cbg4d@virginia.edu

Alterations of consciousness are critical factors in the diagnosis of epileptic seizures. With these alterations in consciousness, some persons report sensations of separating from the physical body, experiences that may in rare cases resemble spontaneous out-of-body experiences. This study was designed to identify and characterize these out-of-body-like subjective experiences associated with seizure activity. Fifty-five percent of the patients in this study recalled some subjective experience in association with their seizures. Among our sample of 100 patients, 7 reported out-of-body experiences associated with their seizures. We found no differentiating traits that were associated with patients' reports of out-of-body experiences, in terms of either demographics; medical history, including age of onset and duration of seizure disorder, and seizure frequency; seizure characteristics, including localization, lateralization, etiology, and type of seizure, and epilepsy syndrome; or ability to recall any subjective experiences associated with their seizures. Reporting out-of-body experiences in association with seizures did not affect epilepsy-related quality of life. It should be noted that even in those patients who report out-of-body experiences, such sensations are extremely rare events that do not occur routinely with their seizures. Most patients who reported out-of-body experiences described one or two experiences that occurred an indeterminate number of years ago, which precludes the possibility of associating the experience with the particular characteristics of that one seizure or with medications taken or other conditions at the time.

Keywords: epilepsy, seizures, out-of-body experience, autoscopy, near-death experience

INTRODUCTION

Alteration and impairment of consciousness are critical factors in the definition and diagnosis of epileptic seizures. There has been growing interest in the subjective descriptions of these consciousness alterations in patients with epilepsy as a source of data, in addition to objective observations of patients' behavior and communications and electroencephalographic (EEG) evidence of altered brain activity (Johanson et al., 2003).

A subjective feature sometimes reported in association with seizures is the sense of being outside the physical body. Devinsky et al. (1989) reported that 10 (6.3%) of 158 patients with epilepsy reported ictal or postictal "autoscopy," a category that included both out-of-body experiences (9 cases) and seeing a visual image of one's double while one's center of consciousness remains inside the body (1 case). Recently, Hoepner et al. (2013) reported 5 patients with ictal autoscopy, 4 of whom reported out-of-body experiences, and all of whom had an epileptic focus "at the temporo-parietal junction or its neighboring regions" (p. 742). Purported out-of-body experiences have previously been associated with electrical stimulation of the angular gyrus near the right tempo-parietal junction (Blanke et al., 2002).

This study was designed to identify and characterize reports of out-of-body experience associated with seizure activity. We compared these reports of out-of-body experience with EEG evidence of seizure focus, in order to increase our understanding of the role of neurophysiological factors in such experiences; and with scores on a standardized measure of epilepsy-related quality of life.

MATERIALS AND METHODS

PARTICIPANTS

Patients attending the University of Virginia's F. E. Dreifuss Comprehensive Epilepsy Program were invited by their neurologists to participate in the study. After providing written informed consent, patients who agreed to participate were interviewed by one of us (Bruce Greyson or Lori L. Derr) regarding their recall of experiences associated with seizures.

We interviewed 100 patients with seizures. We excluded patients who had psychogenic seizures only, as well as those with intellectual impairment or psychotic symptoms severe enough to render their responses unreliable. Patients were obtained nonconsecutively, as time constraints made it impossible to interview all patients with epilepsy; additionally, those patients who lacked the intellectual and linguistic capacity to be interviewed were not invited by their neurologist to participate in the study. The mean age of the 100 patients interviewed was 39.7 years ($SD = 12.8$), with a range from 18 to 70. The sample included 51 women and 49 men. The mean education level of the patients was 13.1 years ($SD = 2.6$), with a range from 4 to 19. The 100 patients included 84 Euro-Americans, 14 African Americans, and 2 Latino-Americans.

PROCEDURE

After soliciting an unstructured narrative description of subjective experiences associated with seizures, we administered to all patients interviewed, whether or not they claimed to recall any subjective experience, the Near-Death Experience (NDE) Scale, which includes a question specifically asking if they had ever felt separated from the body. We chose to use the NDE Scale specifically because it addressed out-of-body experiences, embedded in a series of questions about other unusual phenomena. Alternative instruments designed to assess alterations of consciousness, such as the Ictal Consciousness Inventory (Cavanna et al., 2008), do not address out-of-body sensations.

The NDE Scale consists of 16 multiple-choice items that address features commonly reported in NDEs, including cognitive changes, affective changes, purportedly paranormal processes including a sensation of being "out of the body," and experiences of transcendence (Greyson, 1983). The NDE Scale has high internal consistency, split-half reliability, test-retest reliability, and correlation with other measures of NDE (Greyson, 1983). A Rasch rating-scale analysis established that the NDE Scale yields a unidimensional measure with interval-scaling properties that differentiates NDEs qualitatively and quantitatively from other responses to the threat of death (Lange et al., 2004).

Patients were also administered the Quality of Life in Epilepsy Scale (QOLIE-10), a 10-item Likert-type instrument designed to screen quality of life in persons with epilepsy (Cramer et al., 1996). The QOLIE-10 was developed as a brief instrument to assess the domains of seizure worry; emotional worry; energy/fatigue; cognition; physical and mental effects of medication; driving, social, and work limitations; and overall quality of life. Factor analysis yielded three factors labeled Epilepsy Effects (e.g., memory), Mental Health (e.g., depression), and Role Function (e.g., work limitations). The QOLIE-10 has demonstrated test-retest reliability, external criterion validity, and discriminant validity (Cramer et al., 1996).

The medical records of participants were examined for data on age of onset and duration of the seizure disorder, seizure frequency, and epilepsy etiology. EEG recordings were examined for EEG evidence of anatomic localization and lateralization of the seizure focus. The International League Against Epilepsy (ILAE) seizure type (Dreifuss et al., 1981), and the ILAE epilepsy syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) were derived from the medical records.

DATA ANALYSIS

Patients were included in the out-of-body experience group ("experiencers") if they either spontaneously described a sense of leaving the body associated with a seizure, or indicated on the NDE Scale that they had "clearly left my body and existed outside it" in association with a seizure. Those patients who did not report out of-body experiences associated with their seizures were designated as the comparison group.

We compared epilepsy clinic patients who reported out-of-body experiences associated with their seizures and a comparison group of patients who did not report out-of-body experiences on various facets of their seizures and neurological history and evaluation. We included comparisons involving neurophysiological data from the patients' clinic medical records, including their EEG recordings, to ascertain the anatomic focus of the seizure, the type of seizure, and the specific epilepsy syndrome; historical data on age of onset and duration of the seizure disorder, and maximum number of seizures per month.

RESULTS

SUBJECTIVE EXPERIENCES ASSOCIATED WITH SEIZURES

Of the 100 patients interviewed, 55 were able to recall some subjective experience associated with their seizures. Of those 55 patients, 29 (53%) reported that they could recall more than 10 seizure-associated subjective experiences, 23 (42%) reported between 2 and 10 seizure-associated experiences, and 3 (5%) reported that they could recall only 1 seizure-associated subjective experience. Thirty-nine of those patients (71%) reported that those experiences occurred during an aura immediately before their seizures, 30 (55%) reported experiences during their seizures, and 25 (45%) reported experiences during the postictal period immediately following their seizures. Percentages total more than 100% because some patients attributed their subjective experiences to more than one time period, and some could not determine when the experiences had occurred. For these reasons, it was not possible to distinguish precisely between aural, ictal, and postictal experiences. Most of these reports of subjective experience consisted of only brief, fragmentary sensory impressions rather than coherent narratives.

The kinds of subjective experiences patients reported were primarily changes in emotional state, cognitive changes, other consciousness alterations, sensory distortions, paresthesias, and other somatic sensations. Emotions, reported by 44 patients, included feeling scared, anxious, sad, apprehensive, threatened, and feeling pursued; less commonly, patients reported feeling euphoric or "protected." Cognitive changes, reported by 40 patients, included déjà vu, racing thoughts, indecipherable thoughts, confusion, single words repeating in one's thoughts, and flashbacks from childhood. Other consciousness alterations, reported by 32 patients, included feeling tired, sleepy, "spacey," dazed, fatigued, exhausted, intoxicated, feeling as if one is "falling into darkness," and "no sense of order."

Sensory distortions, reported by 55 patients, included seeing flashing lights, wavy lines, insects, geometric colored shapes, and kaleidoscopic vision, monochromatic vision, and seeing as if through a film; hearing music, pulsing noises, "a sound like Rice Krispies," and hearing voices as if from far away or slowed down; smelling sulfur, burning, watermelon, ammonia, and pungent spices; and a bad taste in one's mouth. Paresthesias, reported by 23 patients, included feeling lightheaded, dizzy, tingling, electric jolts in the body, a stunned sensation like a nerve block, facial numbness, feeling "a sugar rush," "butterflies," waves of energy pulsing through the body, and burning sensations. Other somatic sensations, reported by 31 patients, included headache, pounding in one's head, tightness in the head, head swimming, nausea, sweatiness, warmth, coldness, palpitations, feeling pulled or twisted, feeling one's energy drained, weakness, and stomach ache.

FEATURES OF NEAR-DEATH EXPERIENCE

The mean score of all participants on the NDE Scale was 1.72 ($SD = 1.72$), with a range from 0 to 6, with none of the 100 patients meeting the standard criterion of 7 points for NDEs. The number of patients endorsing each item on the NDE Scale is presented in **Table 1**. The most commonly reported features in association with a seizure were a sense of being out of the body and distortion of the sense of time. No patients endorsed a speeding up of their thoughts, a sense of revelation or sudden understanding, feeling of joy, sense of cosmic unity or oneness, increased sensory vividness, apparent extrasensory perception, or vision of deceased or religious spirits.

REPORTS OF OUT-OF-BODY EXPERIENCE

Of the 100 patients interviewed, none spontaneously reported out-of-body experiences as part of their open-ended narrative description of subjective experiences associated with seizures. However, in their subsequent responses on the NDE Scale, 7 patients reported a sensation of having left their bodies at some point during a seizure. When asked why they had not mentioned out-of-body experiences during their open-ended narratives, the patients commented either that they had forgotten about the out-of-body sensations until the interviewer mentioned them, or that they did not think that was what the interviewer had meant by "experiences associated with seizures." Note that this figure of 7% represents a lifetime prevalence of out-of-body experiences associated with seizures, rather than the incidence of out-of-body experiences with seizures:

Table 1 | Frequency of affirmative responses to NDE Scale items associated with seizures ($N = 100$).

NDE Scale item	Affirmative responses
COGNITIVE FEATURES	
Time distortion	7
Life review or panoramic memory	2
Thought acceleration	0
Revelation or sudden understanding	0
AFFECTIVE FEATURES	
Overwhelming peace	1
Experience of brilliant light	1
Feeling of joy	0
Sense of cosmic unity or oneness	0
PURPORTEDLY PARANORMAL FEATURES	
Out-of-body experience	7
Vision of future events	2
Increased sensory vividness	0
Apparent extrasensory perception	0
TRANSCENDENTAL FEATURES	
Experience of another realm or world	3
Experience of a spiritual being or voice	2
Experience of a border or point of no return	1
Vision of deceased or religious spirits	0

(1) A 28-year-old female graduate student with symptomatic localization-related epilepsy due to periventricular nodular heterotopia had both complex partial and simple partial seizures. She also had Dandy-Walker malformation, Marfan syndrome, polycystic ovarian disease, and an extra vertebra. She reported 2-3 simple partial seizures a week, which she described as "the world coming in" without attenuation of consciousness. These events began at age 24 and lasted about 30 s. She reported about 1 complex partial seizure a month, which involved staring and inability to speak (i.e., she could think of words to say but could not produce meaningful speech) and inability to comprehend written language (i.e., printed words appeared as gibberish). The complex partial seizures could last up to 20 min, and were followed by postictal fatigue or confusion for up to 1–2 h. Her EEG showed independent bilateral temporal epileptiform spikes (left greater than right) and left parasagittal spikes. Her MRI showed bilateral periventricular nodular heterotopia and a Dandy-Walker malformation.

She reported leaving her body during every complex partial seizure: while her body became immobile, she felt she was floating above it and could view her body and its surroundings from above. However, she reported a dual consciousness in which, while seeming to hover above her body, she also remained aware of bodily sensations. She reported that if someone brushed against her body, the sensation would "snap" her back into her body and end the seizure. The experience of being out of her body was unpleasant and alarming, as she feared something might happen to her body when she was not in control of it. She believed her perceptions from an out-of-body visual perspective were accurate and that her mind physically separated from her body, but she did not attribute any spiritual significance to that event, regarding it rather as "just something that happens" when her brain misfires. This was the only patient to report definitively that her out-of-body experiences commonly included verifiable perceptions, and the only patient to report that she had left her body frequently during seizures.

(2) A 43-year-old unemployed man with cryptogenic localization-related epilepsy of unknown etiology had 2–3 complex partial seizures a year, starting at age 6. He was also diagnosed with bipolar affective disorder without psychosis, alcohol dependence, and cocaine abuse; and he had a chronic daily throbbing headache, occasionally with blurred vision, photophobia, and gastric distress. He reported that his seizures were often precipitated by stress, and he described their phenomenology as becoming unclear in his thoughts, followed by shaking and loss of consciousness, without tongue biting or loss of bowel or bladder control, followed by up to 2 hours of confusion. His EEG and MRI were normal.

He reported having had two out-of-body experiences associated with seizures. The first occurred about 15 years ago: he felt that he definitely left his body and was flying, and that he encountered many people whom he had known in his childhood in another city. He had a profoundly beautiful experience in which a person he had known previously came to him "in an angel form" to show him a woman he would later marry, but whom he had not yet met at that time. Around 4–5 years ago he had a second out-of-body experience during a seizure: he again felt he left his body and was flying, but this time encountered no one. He had beautiful feelings of peace, love, and "oneness," feeling that everything was interconnected; and he felt that his marriage, which was failing at that time, held a profound meaning of which he was previously unaware. This was the only patient to report a pleasurable out-of-body sensation or to attribute any spiritual significance to it.

(3) A 26-year-old male college student with symptomatic localization-related epilepsy had a maximum of 20 intractable complex partial seizures a month with secondary generalization since age 15, for which he had undergone left frontal lobectomy at age 20. His seizures were described as 1 min of unresponsiveness with eyes deviating to the left, followed by progression to shaking of his right face and right upper extremity. Intensive telemetry video EEG showed independent left and right temporal slowing and frequent left central spikes; during 42 brief seizures consisting of the head moving forward and looking to the left with behavioral arrest, lasting for approximately 15–20 s, he had bihemispheric slowing, more prominent over the left, followed by diffuse attenuation of faster frequencies, and postictal slowing also more prominent over the left. MRI showed left frontal encephalomalacia and gliosis related to his surgery, and additional foci of encephalomalacia and gliosis within the right anterior frontal lobe and lateral aspect of the temporal lobes. PET/CT also showed postsurgical changes with encephalomalacia in the left frontal lobe with corresponding diminished FDG uptake. Single photon emission computed tomography (SPECT) showed increased radiotracer activity in the left temporal lobe. He was also diagnosed with depression, anxiety, and sleep apnea.

He reported a recurrent but vague sense of leaving his body during seizures ("I feel like I'm seeing myself from somewhere else on occasion") but could not elaborate on that description nor could he say how many times it had occurred.

(4) A 30-year-old unemployed woman with symptomatic localization-related epilepsy due to subependymal cortical heterotopias had a maximum of 300 complex partial seizures a month since age 15, with rare secondary generalizations. Her seizures were characterized by behavioral arrest with right facial clonic jerking, aphasia, confusion, and postictal sleepiness. Prolonged video EEG monitoring showed interictal bilateral multifocal epileptiform discharges, most prominent in the left frontocentral region. Observed seizures were associated with frontally dominant generalized spike and wave discharges. An ictal SPECT showed increased uptake in the left temporal region. A brain MRI showed multiple bilateral subependymal heterotopias in the superior lateral aspect of the lateral ventricles. She also had been treated for depression and anxiety, with compulsive skin-picking.

She reported 2–3 out-of-body experiences associated with seizures, which lasted between 10 and 20 s: she stated that she felt herself lift up and looked down at her inert body and could see and hear others; she stated that she felt weightless during this experience and found that frightening. She added: "It seems real, but I know it couldn't be; it's too far-fetched. I didn't see anything surprising. It may be my imagination telling me what I would look like."

(5) A 42-year-old unemployed man with symptomatic localization-related epilepsy secondary to traumatic brain injury at age 25 that required multiple craniotomies ultimately leading to a metal plate being surgically installed had a maximum of 5 complex partial seizures a week and frequent secondary generalized seizures. Prolonged video EEG monitoring showed interictal intermittent left temporal theta slowing, and independent, bilateral, frontotemporal spike discharges, more frequent on the left compared to the right. During the observed complex partial seizures, there were no definitive clinical lateralizing features, but electrographically there was evidence for left hemispheric onset. An interictal SPECT scan showed a small right temporal lobe in keeping with encephalomalacia. An MRI showed right frontal and temporal encephalomalacia with minimal left frontal encephalomalacia, as well as changes of left parietal cranioplasty exerting a mild mass effect on the underlying brain parenchyma. He described an aura of feeling lightheaded, followed by staring and drooling and a change in demeanor, with occasional hand automatisms, sometimes subsequently generalizing to a tonic clonic seizure.

He reported one out-of-body experience associated with a seizure: he stated that he was awake during the seizure and watched himself going through it, falling down to one knee. He reported that he was aware of his brother entering the room and tried to tell his brother to stop him. He claimed to have dual consciousness in that he felt the bodily sensations of going through the seizure but also saw himself going through it. He added: "I don't remember any of the details of it. It's like a dream in my memory now." When asked whether he believed he had left his body, he answered: "Well, obviously I don't think that sort of thing can really happen."

(6) A 30-year-old unemployed woman with idiopathic generalized epilepsy of unknown etiology had 1–2 catamenial absence seizures a month since age 15, characterized by eye fluttering and staring, and unresponsiveness that lasted up to 30 min. She also had myoclonic head jerking precipitated by stress and 1–2 tonic-clonic seizures a year. Intensive video EEG monitoring showed generalized fast spike and wave discharges consistent with the interictal findings seen in idiopathic generalized epilepsy, but no seizures were observed. A head CT and MRI were normal. She was also diagnosed with bipolar disorder, attention deficit hyperactivity disorder, and schizotypal personality disorder.

She reported one out-of-body experience associated with a seizure 15 years ago: she felt herself rise 5–10 feet above her body and saw her body "folded up on itself." She saw her sister run up to her, and then "everything went blank." This patient also reported another out-of-body experience that was not associated with a seizure but rather during an "astral projection workshop," which she felt was quite different from her seizure-related experience.

(7) A 46-year-old female caretaker at a group home for disabled children, with cryptogenic localization-related epilepsy, had

a maximum of one simple partial seizure a month since age 9, and tonic-clonic seizures without tongue biting or urinary incontinence less than once a year. Her typical seizures were characterized by an aura of déjà vu followed by staring, unresponsiveness, and rocking activity, followed by postictal confusion lasting up to an hour with body aches, headache, and fatigue. She also had depression, sleep apnea, hypothyroidism, and type 1 diabetes mellitus, and reported that her seizures seemed to be precipitated by hypoglycemia or emotional stress. She had had two head injuries, at ages 23 and 45, from falls secondary to hypoglycemia. Her EEG showed left temporal sharp waves, but her MRI and head CT were normal.

She reported one episode of feeling as if she were looking into her head, as if she were an observer of her own thoughts. She felt at that time as if she were "floating in the universe," seeing blackness, but with planets and stars. She reported that experience as very frightening because she had no control over the floating.

DEMOGRAPHIC AND SUBJECTIVE EXPERIENTIAL CORRELATES OF OUT-OF-BODY EXPERIENCE

As shown in **Table 2**, the 7 patients who reported out-of-body experiences and the remaining 93 patients who did not were statistically comparable in terms of age, gender, education, and ethnicity.

The frequency of recalled subjective experiences associated with seizures was statistically comparable between those patients who reported out-of-body experiences and those who did not ($\chi^2 = 2.78$, $df = 3$; NS). Among the 7 patients who reported out-of-body experiences associated with their seizures, 2 (29%) attributed their recalled subjective experiences to the aura prior to the seizure, 5 (71%) to the seizure itself, and 1 (14%) to the postictal period. The percent of patients who reported out-of-body experiences and of those who did not were statistically comparable for those experiences attributed to the pre-ictal aura ($\chi^2 = 1.88$, $df = 1$; NS), for the seizure itself ($\chi^2 = 1.13$, $df = 1$; NS), and for the postictal period ($\chi^2 = 2.21$, $df = 1$; NS).

Table 2 | Demographics among patients with and without out-of-body experiences (OBEs).

	OBE ($N = 7$)	No OBE ($N = 93$)	Statistical test
Mean age	34.1 ($SD = 8.5$)	40.2 ($SD = 13.0$)	$t = 1.20$, $df = 98$; NS
Gender			$\chi^2 = 0.11$, $df = 1$; NS
Female	4 (47%)	47 (51%)	
Male	3 (43%)	46 (49%)	
Years of education	13.7 ($SD = 1.9$)	13.0 ($SD = 2.7$)	$t = 0.64$, $df = 98$; NS
Ethnicity			$\chi^2 = 0.15$, $df = 2$; NS
Euro-American	6 (86%)	78 (84%)	
African-American	1 (14%)	13 (14%)	
Latino-American	0 (0%)	2 (2%)	

As shown in **Table 3**, with the Bonferroni correction for multiple simultaneous statistical tests, those patients who reported out-of-body experiences scored higher than did other patients on the NDE Scale and on the individual items assessing out-of-body experience and a sense of being in an unearthly realm.

SEIZURE HISTORY

The mean age at onset of seizures for the 97 patients for whom such data were available was 18.7 years ($SD = 13.1$), with a range from 0 to 65. The mean duration of the seizure disorder for those 97 patients was 20.9 years ($SD = 13.5$), with a range from 1 to 57 years. The mean maximum seizure frequency of the 91 patients for whom data were available was 42.0 per month ($SD = 72.8$), with a range from <1 to 300.

As shown in **Table 4**, patients who reported out-of-body experiences and those who did not were statistically comparable in terms of age of onset, duration of seizure disorder, and maximum seizure frequency.

SEIZURE CHARACTERISTICS

Epilepsy etiology was unknown for 58 patients. Among the remaining 42 patients, 29 (69%) had seizures related to focal pathology, including focal congenital malformation, mesial temporal sclerosis, chronic localized encephalitis, and benign tumor; and 13 (31%) to generalized or multifocal pathology, including diffuse head injury, generalized congenital malformation, perinatal anoxia, and multiple intracerebral hemorrhages.

Seizure type was classifiable for 97 patients, of whom 71 (73%) had complex partial seizures; 10 (10%) had simple partial seizures, including focal motor, somatosensory, autonomic, déjà vu, and cognitive seizures; and 16 (16%) had generalized seizures, including tonic-clonic, absence, and myoclonic seizures or multiple generalized.

Epilepsy syndrome was classifiable for 56 patients, of whom 44 (81%) had a localization-related syndrome, including mesial temporal lobe (7 patients), frontal lobe (5), parietal lobe (2), as well as non-classified cryptogenic (30); and 12 (22%) had a generalized epilepsy syndrome, including juvenile myoclonic (3 patients), and other idiopathic (7), as well as non-specific symptomatic generalized (1) and cryptogenic generalized epilepsy (1).

Epilepsy etiology, seizure type, and epilepsy syndrome are presented in **Table 5**, listed separately for those patients who did and did not report out-of-body experiences. None of these seizure characteristics differentiated the two groups.

EEG DATA

Sixty-five patients had EEG findings that included localizable epileptiform discharges, among whom 35 (57%) were localized in the temporal lobe, 6 (10%) elsewhere, and 20 (33%) were multifocal. Sixty-one patients had lateralizable epileptiform discharges, of whom 26 (40%) could be localized in the left hemisphere, 11 (17%) in the right hemisphere, 18 (28%) were bilateral, and 10 (15%) generalized. As indicated in **Table 6**, neither discharge

Table 3 | NDE Scale scores of patients with and without out-of-body experiences (OBEs).

	OBE ($N = 7$)	No OBE ($N = 93$)	Statistical test
NDE Scale (range = 0–32)	4.71 ($SD = 1.70$)	1.49 ($SD = 1.50$)	$t = 5.43$, $df = 98$; $p < 0.001$
ITEM (RANGE = 0–2)			
Time distortion	0.71 ($SD = 0.95$)	0.39 ($SD = 0.59$)	$t = 1.35$, $df = 98$; NS
Thought acceleration	0.29 ($SD = 0.49$)	0.13 ($SD = 0.34$)	$t = 1.15$, $df = 98$; NS
Life review	0.43 ($SD = 0.79$)	0.11 ($SD = 0.35$)	$t = 2.12$, $df = 98$; NS
Sudden understanding	0.00 ($SD = 0.00$)	0.03 ($SD = 0.18$)	$t = -0.48$, $df = 98$; NS
Sense of peace	0.00 ($SD = 0.00$)	0.11 ($SD = 0.35$)	$t = -0.82$, $df = 98$; NS
Feeling of joy	0.00 ($SD = 0.00$)	0.03 ($SD = 0.18$)	$t = -0.48$, $df = 98$; NS
Sense of cosmic unity	0.00 ($SD = 0.00$)	0.02 ($SD = 0.15$)	$t = -0.39$, $df = 98$; NS
Bright light	0.29 ($SD = 0.49$)	0.11 ($SD = 0.35$)	$t = 1.28$, $df = 98$; NS
Sensory vividness	0.14 ($SD = 0.38$)	0.19 ($SD = 0.40$)	$t = -0.33$, $df = 98$; NS
Extrasensory perception	0.00 ($SD = 0.00$)	0.03 ($SD = 0.18$)	$t = -0.48$, $df = 98$; NS
Precognitive vision	0.00 ($SD = 0.00$)	0.08 ($SD = 0.34$)	$t = -0.59$, $df = 98$; NS
Out-of-body experience	2.00 ($SD = 0.00$)	0.17 ($SD = 0.38$)	$t = 12.69$, $df = 98$; $p < 0.001$
Unearthly realm	0.57 ($SD = 0.98$)	0.04 ($SD = 0.25$)	$t = 3.93$, $df = 98$; $p < 0.001$
Mystical presence	0.29 ($SD = 0.76$)	0.03 ($SD = 0.23$)	$t = 2.22$, $df = 98$; NS
Visible spirits	0.00 ($SD = 0.00$)	0.01 ($SD = 0.10$)	$t = -0.27$, $df = 98$; NS
Border	0.00 ($SD = 0.00$)	0.02 ($SD = 0.21$)	$t = -0.27$, $df = 98$; NS

Table 4 | Seizure history among patients with and without out-of-body experiences (OBEs).

	OBE ($N = 7$)	No OBE ($N = 93$)	Statistical test
Age of onset	15.7 ($SD = 7.7$)	18.9 ($SD = 13.3$)	$t = 0.58$, $df = 94$; NS
Years of seizure disorder	19.3 ($SD = 14.0$)	21.0 ($SD = 13.5$)	$t = 0.29$, $df = 94$; NS
Maximum seizures/month	51.3 ($SD = 110.2$)	41.2 ($SD = 69.8$)	$t = 0.35$, $df = 89$; NS

Table 5 | Seizure characteristics among patients with and without out-of-body experiences (OBEs).

	OBE ($N = 7$)	No OBE ($N = 93$)	Statistical test
Epilepsy etiology			$\chi^2 = 0.01$, $df = 2$; NS
Focal pathology	2 (29%)	27 (29%)	
Generalized pathology	1 (14%)	12 (13%)	
Unknown	4 (57%)	54 (58%)	
Seizure type			$\chi^2 = 0.38$, $df = 3$; NS
Complex partial	5 (71%)	66 (71%)	
Simple partial	1 (14%)	9 (10%)	
Generalized	1 (14%)	15 (16%)	
Unclassified	0 (0%)	3 (3%)	
Epilepsy syndrome			$\chi^2 = 0.87$, $df = 2$; NS
Localization-related	6 (86%)	67 (72%)	
Generalized	1 (14%)	18 (19%)	
Unknown	0 (0%)	8 (9%)	

localization nor lateralization significantly differentiated those patients who did and did not report out-of-body experiences.

QUALITY OF LIFE

The mean score on the QOLIE-10 for the 99 patients who were able to complete it was 25.0 ($SD = 8.1$), with a range from 12 to 44, which was not statistically different from the mean score of 25.6 ($SD = 8.9$) among a normative sample of patients with epilepsy ($t = 0.70$, $df = 98$; NS) (Bautista et al., 2007). The mean scores on the component factors were 7.1 ($SD = 3.2$) for Epilepsy Effect, 7.7 ($SD = 2.4$) for Mental Health, and 10.3 ($SD = 4.5$) for Role Function. These were statistically comparable to normative scores for patients with epilepsy for Epilepsy Effect ($t = 1.54$, $df = 98$; NS) and for Role Function ($t = 0.78$, $df = 98$; NS), but lower (reflecting better quality of life) than the mean score of 8.4 for Mental Health ($t = 3.02$, $df = 98$, $p = 0.003$) (Bautista et al., 2007).

As shown in **Table 7**, patients who reported out-of-body experiences and those who did not were statistically comparable in terms of overall quality of life, as well as for quality of life related to Epilepsy Effect, Mental Health, and Role Function.

DISCUSSION

OUT-OF-BODY EXPERIENCES ASSOCIATED WITH SEIZURES

Among our sample of 100 patients, 7 reported out-of-body experiences associated with their seizures, although some of their descriptions were not definitive. This percent was comparable to the 6.3% prevalence reported by Devinsky et al. (1989), and slightly lower than the 9% prevalence of out-of-body experiences

Table 6 | EEG variables among patients with and without out-of-body experiences (OBEs).

	OBE (*N* = 6)	No OBE (*N* = 80)	Statistical test
Epileptiform discharge localization			$\chi^2 = 1.35$, *df* = 3; NS
Temporal lobe	2 (33%)	33 (41%)	
Other locus	0 (0%)	6 (8%)	
Multifocal	3 (50%)	17 (21%)	
None	1 (17%)	24 (30%)	
Epileptiform discharge lateralization			$\chi^2 = 5.43$, *df* = 4; NS
Left-sided	4 (67%)	22 (28%)	
Right-sided	0 (0%)	11 (14%)	
Bilateral	1 (17%)	17 (21%)	
Generalized	1 (17%)	9 (11%)	
None	0 (0%)	21 (26%)	

Table 7 | Quality of life among patients with and without out-of-body experiences (OBEs).

	OBE (*N* = 7)	No OBE (*N* = 92)	Statistical test
QOLIE total score	24.2 (*SD* = 9.0)	25.1 (*SD* = 8.1)	*t* = 0.30, *df* = 97; NS
QOLIE FACTORS			
Epilepsy effect	7.7 (*SD* = 3.4)	7.1 (*SD* = 3.2)	*t* = 0.52, *df* = 97; NS
Mental health	7.9 (*SD* = 2.9)	7.7 (*SD* = 2.3)	*t* = 0.20, *df* = 97; NS
Role function	10.0 (*SD* = 4.4)	10.3 (*SD* = 4.5)	*t* = 0.30, *df* = 97; NS

typically reported in surveys of the general population (Cardeña and Alvarado, 2013). Three of the patients in our sample reported only one out-of-body experience, 1 reported 2 such experiences, 1 reported "2 or 3" experiences, 1 reported a vague sense of leaving his body but could not estimate how many times that had happened, and 1 reported that she left her body with every seizure.

The finding that 6 of the 7 patients who reported out-of-body experiences associated with seizures described them as occurring only once or twice many years ago raises the question of whether those experiences were truly seizure-related. In view of the fact that 9% of the general population (presumably free of seizures) report out-of-body experiences once or twice in a lifetime (Cardeña and Alvarado, 2013) and the documented unreliability of patients' memories of their seizures (Heo et al., 2006; Quigg, 2011), partly as a result of anterograde amnesia from hippocampal involvement, it is conceivable that at least some of the out-of-body experiences reported in this study may not have been related to seizures but were erroneously attributed to seizures in retrospect.

Patients who reported out-of-body experiences were statistically indistinguishable from others in terms of age, gender, education, and ethnicity. They reported being able to recall subjective experiences associated with their seizures as often as did the comparison patients, and their recollections were assigned to the aura preceding the seizure, the seizure itself, and the postictal period, at the same rate as for comparison patients. Impairment of consciousness associated with seizures is central to the effect of epilepsy on quality of life, primarily due to their unpredictability (Mann and Cavanna, 2011). However, those patients who reported out-of-body experiences and those who did not were statistically comparable in terms of quality of life.

We anticipated that patients who reported out-of-body experiences would also score higher on the NDE Scale than did comparison patients, as a sense of leaving the body is one item on that scale. However, in addition to that item, patients who reported out-of-body experiences also reported with greater frequency a sense of being in some other realm or dimension. It is unclear whether that sense of being in another realm referred to the out-of-body experience itself or to a different experience, as only 1 of the 7 patients (patient # 2) included in his out-of-body experience a sense of leaving the immediate physical surroundings of the body.

COMPARISON TO SPONTANEOUS OUT-OF-BODY EXPERIENCES AND INDUCED BODY IMAGE DISTORTIONS

Although out-of-body experiences commonly reported to occur spontaneously or in NDEs are typically pleasurable and often interpreted as spiritual experiences (Gabbard and Twemlow, 1984; Cardeña and Alvarado, 2013), only one of the patients in this sample reported his seizure-related out-of-body sensations to be pleasurable or attributed any religious or spiritual significance to the sensation of being out of the body (patient # 2). The remaining 6 felt their out-of-body experiences to be unpleasant or frightening, echoing the findings of Devinsky et al. (1989) that two of their patients found autoscopy to be the most troubling aspects of their disorder. Indeed, autoscopy associated with seizures is commonly accompanied by intense horror or fear, and may be associated with suicide (Brugger et al., 1994). Again, this negative affect contrasts with the blissful nature of the out-of-body phenomenon typically reported as part of spontaneous NDEs (Gabbard and Twemlow, 1984), and with the suicide-inhibiting effect of NDEs (Greyson, 1992).

As noted above, purported out-of-body experiences have previously been associated with electrical stimulation of the right angular gyrus near the temporo-parietal lobe (Blanke et al., 2002), and Hoepner et al. (2013) reported that out-of-body experiences were associated with seizure foci at the temporo-parietal junction "or neighboring region." Recently, this link between the temporo-parietal junction and out-of-body sensations has been explored in persons without any known neurological dysfunction. Braithwaite et al. (2011) found that college students who reported spontaneous out-of-body experiences scored higher on a questionnaire designed to assess temporal lobe instability and disruptions in processing of body image than did students without out-of-body experiences. While that study was intriguing, the authors cautioned that questionnaires do not provide direct evidence of underlying neural function, and that if attenuated temporo-parietal discharges did occur in persons without epilepsy, the underlying neurophysiology would be unknown.

Despite these suggestive data, however, the out-of-body experiences reported by the 7 patients in this study were not associated primarily with right temporo-parietal foci. One patient had predominant left temporal discharges, 1 had left central, 1 had bilateral temporal, 1 had bilateral frontal, 1 had bilateral multifocal with left frontal predominance, and 2 had no epileptiform discharges on EEG. This is consistent with the finding of Devinsky et al. (1989) that autoscopic phenomena may be associated with a variety of seizure types, as well as with the general observation that focal seizures can affect distant and widespread regions of the brain (Bagshaw and Cavanna, 2011). Most of the research suggesting temporo-parietal correlates of out-of-body experiences has used imaging techniques that identify relatively focal activity. The development of methods for characterizing the activity of functional networks rather than discrete foci may lead to better understanding of these phenomena, particularly those associated with seizures, which can modify functional connectivity and affect resting state networks (Bagshaw and Cavanna, 2013).

Patients in the current study who did and did not report out-of-body experiences were comparable in their seizure histories, including epilepsy syndrome, epilepsy etiology, and seizure type. Complex partial seizures accounted for about 71% of the seizures in both groups. EEG findings, including lateralization and localization of abnormalities, did not differentiate those who reported out-of-body experiences from those who did not. The curious finding that the only case of déjà vu/jamais vu seizure occurred in a patient who reported an out-of-body experience may bear further investigation.

Studies of out-of-body phenomena associated with seizures have been confounded by conflicting definitions of the experience (Braithwaite et al., 2011). Hoepner et al. (2013) delineated three types of ictal autoscopic phenomena that differ in their degree of disembodiment and visual perspective: in true autoscopy, the self does not feel disembodied but remains in the physical body and visualizes a "double" in the extracorporeal space; in out-of-body experiences, the self feels fully disembodied and visualizes the physical body from an extracorporeal viewpoint; and in heautoscopy, the self feels ambiguously disembodied and the visual perspective changes between the intra- and extracorporeal. It remains an open question whether these various forms of body image distortion are related or distinct phenomena (Braithwaite et al., 2011).

Patients with epilepsy who have perceptual distortions, illusions, or hallucinations associated with their seizures generally have insight into the unreality of such perceptions, since they experience them across a spectrum of unusual experiences on many occasions associated with seizures (Bien et al., 2000; Elliott et al., 2009). In contrast, patients with thought disorders like schizophrenia generally do not have insight into the unreality of their hallucinations. If this distinction holds for out-of-body experiences, then we would expect that patients would recognize such experiences associated with seizures as hallucinatory and not real. In fact, only 1 of our 7 patients who reported out-of-body experiences (patient #1) believed that her out-of-body experiences were real. The other patients either recognized their out-of-body sensations as hallucinatory or expressed doubts, reporting, for example, "It seems real, but I know it couldn't be," "It may be my imagination," "It's like a dream," or, "Obviously, I don't think that sort of thing can really happen."

It is unclear whether a definitive belief that one had truly left the body is a distinct phenomenon or simply the extreme end of a continuum that includes more nebulous reports of out-of-body sensations that the experiencers do not believe was real. Brief survey questions cannot resolve this issue; rather, it requires detailed discussion with the experiencer, as half the people who respond affirmatively on questionnaires assessing belief in anomalous experiences do not in fact understand what they are professing but are expressing "quasi-beliefs"—propositions believed to be true without knowledge of their meaning—rather than informed beliefs, even when they are basing their knowledge on personal experiences (Jinks, 2012).

The experimental literature on *induced* out-of-body experiences has been furthermore confounded by eccentric uses of the term. Some researchers studying sensations induced by exogenous electrical stimulation included as an "out-of-body experience" any distortion of body image, regardless of whether it involved a subjective sense of leaving the physical body. Blanke et al. (2002) described as an "out-of-body experience" induced by electrical stimulation sensations of sinking into the bed, seeing one's legs become shorter or moving quickly toward one's face, and feeling that one's upper body was moving toward the legs. One study that reported "out-of-body experiences" elicited by stimulating the posterior right superior temporal gyrus acknowledged that the patient continued to perceive the environment from his real-person perspective, and not from the disembodied perspective as in spontaneous out-of-body experiences (DeRidder et al., 2007). Another reported an illusion they classified as "belonging to the class of OBEs" elicited by transcranial magnetic stimulation over the cerebellum in which the patient felt her body falling sideways out of her chair, but did not describe any visual impressions (Schutter et al., 2006). Cardeña and Marcusson-Clavertz (2012) have recently highlighted the inappropriate use of terms used to denote anomalous experiences by scholars unfamiliar with the clear and specific connotations of those terms as they are used in psychology and related disciplines. They concluded that anomalous experiences must be studied within the context of a thorough understanding of the phenomena and the correct use of terms (Cardeña and Marcusson-Clavertz, 2012).

It is unclear how comparable seizure-related autoscopy and heautoscopy or electrically induced body image distortions are to spontaneous out-of-body experiences. As noted above, the unpleasant affect associated with seizure-related out-of-body sensations is unlike the blissful sensations usually accompanying spontaneous out-of-body and NDEs. Furthermore, the sense of disembodiment induced by electrical stimulation is limited to a fixed location; experiencers perceive the environment from the visual perspective of the physical body; and experiencers perceive the event as illusory. In contrast, spontaneous out-of-body experiences often involve accurate perception of the environment (including the physical body) from an extracorporeal visual perspective; the disembodied center of consciousness may seem to move about independently of the physical body; and experiencers usually perceive the event as profoundly real (Greyson et al., 2008). Patients who report body image distortions during brain stimulation do so when their eyes are open, but not when their eyes are closed, unlike spontaneous out-of-body experiences, which typically occur with the eyes closed (Giesler-Petersen, 2008). Body image distortions elicited by brain stimulation are transitory, disappearing when the patient attempts to inspect the illusory body part, whereas spontaneous out-of-body experiences are not transitory but are maintained during examination of the body image (Neppe, 2002). Finally, somatic illusions induced by brain stimulation typically involve viewing only part of the body, usually include distortions like shortening or lengthening of limbs and movement, and are experienced as confusing; whereas spontaneous out-of-body experiences involve seeing the entire body from an extracorporeal perspective, do not include distortions, and are experienced as exceptionally lucid (Holden et al., 2006).

Whereas there is no way to establish that autoscopy and heautoscopy are anything more than illusions, it is possible to test whether subjective out-of-body experiences are more than illusions by seeking verification of the veridicality of perceptions from the extracorporeal perspective. Although people who report out-of-body experiences that occur spontaneously or in NDEs often claim to have accurate perceptions from a disembodied visual perspective (Greyson et al., 2008), only one patient in our sample (not the patient who described the sensations as pleasurable) believed unambiguously that her out-of-body perceptions were accurate perceptions of reality that could be corroborated by others. Four others described viewing events from an out-of-body perspective that they thought might or might not have been accurate, and 2 of the 7 expressed outright disbelief in the reality of their out-of-body sensations.

The term "altered state of consciousness," which is commonly used to encompass a wide range of pathological and non-pathological conditions, including epileptic seizures and spontaneous out-of-body experiences, carries for many the implication of abnormality or dysfunction. The alternative term "non-ordinary mental expression" (NOME) has been suggested to designate anomalous experiences and related neuropsychological processes without implying pathology. Although reductionistic pathophysiological models may not encompass the entire range of such phenomena, brain areas and neurotransmitters involved in these experiences may provide a common terrain for both pathological and non-pathological NOMEs, creating a substrate for the association of phenomena such as out-of-body experiences with neuropathologic events such as epileptic seizures.

METHODOLOGICAL ISSUES

The data from this study must be interpreted with some caution. First, the small number of patients who reported out-of-body experiences reduced the likelihood of finding significant statistical differences from the patients who did not. It is possible that with a much larger sample, some of the non-significant trends noted in this study might prove to differentiate patients who report out-of-body experiences and those who do not, such as the somewhat higher incidence of left-sided and multifocal discharges among those who reported out-of-body experiences.

Another factor to be considered in evaluating the implications of this study was the role of comorbid psychiatric disorder in the association of out-of-body experiences with seizures. Sensky (1983a) noted that interest in anomalous subjective states in epilepsy was advanced by Slater and Beard (1963) and Dewhurst and Beard (1970), who specifically studied patients with comorbid psychosis and epilepsy. Of the 7 patients in our study who reported out-of-body experiences, 3 had been diagnosed with depression, 2 others with bipolar disorder, 2 with anxiety, 2 with sleep apnea, and 1 each with attention deficit hyperactivity disorder, schizotypal personality disorder, compulsive skin-picking, alcohol abuse, and cocaine abuse. Only 2 of these 7 patients who reported out-of-body experiences were not in concurrent psychiatric treatment. It is unclear whether psychiatric comorbidity may have influenced reports of out-of-body experiences in this study; that question may be a fruitful direction for future research.

As noted above, we chose to identify out-of-body experiences by administering the NDE Scale because that instrument explicit addresses the phenomenon. There are, however, other scales that may yield additional helpful information about alterations of consciousness associated with seizures. One of the most detailed measures for quantifying various aspects of consciousness, the Phenomenology of Consciousness Inventory (Pekala, 1991), has been used to examine dimensions of consciousness and its distortions during seizures (Johanson et al., 2008). However, that instrument is quite long and some of its items are complicated and difficult to understand, and some items have different meaning for patients with epilepsy than for other persons (Johanson et al., 2008, 2011); it is intended for use within 20 min of an experience (Pekala, 1991); and it does not specifically explore out-of-body experiences. The shorter and less demanding Ictal Consciousness Inventory (Cavanna et al., 2008) was specifically designed to measure level and content of consciousness during seizures, but it also does not address out-of-body experiences. It may be instructive, however, to include the Ictal Consciousness Inventory in future research on such phenomena associated with seizures. Reports of anomalous phenomena like out-of-body experiences during seizures may also be explored through unstructured interviews, such as EpiC, the Epilepsy-specific Content analysis method, although that technique is much more time-consuming and may be less practical in a clinic setting (Johanson et al., 2011).

Finally, in studying the association of out-of-body experiences with seizures, and particularly with complex partial seizures, it should be borne in mind that patients with complex partial seizures tend to have more frequent attacks, take more drugs, and suffer more adverse psychosocial stresses than patients with generalized seizures, all of which may interact to play a role in psychological symptoms (Reynolds, 1983). Additionally, it may be misleading to regard all patients with complex partial seizures as a homogenous group, as laterality and age of onset of the disorder may importantly influence psychological manifestations (Sensky, 1983b).

CONCLUSION

This study elicited reports of out-of-body sensations associated with seizures in 7% of patients with epilepsy, but found no differentiating traits that were associated with patients' reports of out-of-body experiences with their seizures, either in terms of demographics, medical history including seizure risk factors and precipitants, seizure characteristics including localization and type of seizure, ability to recall subjective experiences associated with their seizures, or quality of life.

Considerable progress has been made in recent decades elucidating the neurobiologic correlates of altered states of consciousness, or NOMEs (Bagshaw and Cavanna, 2011, 2013), and specifically the role of epilepsy in elucidating the neural correlates of consciousness (Mann and Cavanna, 2011). In particular, there has been a wealth of suggestive evidence bearing on the neurological foundations of body image distortions (Blanke et al., 2002; Schutter et al., 2006; DeRidder et al., 2007). However, it may be premature to conclude from these suggestive correlations that out-of-body experiences are an epiphenomenon of particular neurophysiological conditions (Neppe, 2002; Holden et al., 2006). As noted above, the body image distortions elicited by electrical or magnetic stimulation of the brain differ phenomenologically from spontaneous out-of-body experiences in several important ways. The data from this study suggest that out-of-body experiences associated with seizures are not linked to any one region of the brain. Moreover, the findings that out-of-body experiences were reported slightly less often by patients with epilepsy than in surveys in the general population, and that patients with epilepsy who do describe out-of-body experiences report them occurring in only a small minority of their seizures, raise cautions about inferring a causal link between the seizure activity and out-of-body experiences.

AUTHOR CONTRIBUTIONS

Bruce Greyson contributed substantially to the conception and design of this research; to the acquisition, analysis, and interpretation of data for the work; to drafting the work and revising it critically for intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Nathan B. Fountain contributed substantially to the conception and design of this research; to the interpretation of data for the work; to revising the work critically for intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Lori L. Derr contributed substantially to the conception and design of this research; to the acquisition of data for the work; to revising the work critically for intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Donna K. Broshek contributed substantially to the conception and design of this research; to the interpretation of data for the work; to revising the work critically for intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Near death experiences: a multidisciplinary hypothesis

István Bókkon[1], Birendra N. Mallick[2] and Jack A. Tuszynski[3]*

[1] Neuroscience Department, Vision Research Institute, Lowell, MA, USA
[2] School of Life Sciences, Jawaharlal Nehru University, New Delhi, India
[3] Department of Physics, University of Alberta, Edmonton, AB, Canada

Edited by:
Christian Agrillo, University of Padova, Italy

Reviewed by:
Michael A. Persinger, Laurentian University, Canada
Arianna Palmieri, University of Padova, Italy

****Correspondence:***
István Bókkon, Neuroscience Department, Vision Research Institute, 25 Rita Street, Lowell, MA 01854 USA
e-mail: bokkoni@yahoo.com

Recently, we proposed a novel biophysical concept regarding on the appearance of brilliant lights during near death experiences (NDEs) (Bókkon and Salari, 2012). Specifically, perceiving brilliant light in NDEs has been proposed to arise due to the reperfusion that produces unregulated overproduction of free radicals and energetically excited molecules that can generate a transient enhancement of bioluminescent biophotons in different areas of the brain, including retinotopic visual areas. If this excess of bioluminescent photon emission exceeds a threshold in retinotopic visual areas, this can appear as (phosphene) lights because the brain interprets these intrinsic retinotopic bioluminescent photons as if they originated from the external physical world. Here, we review relevant literature that reported experimental studies (Imaizumi et al., 1984; Suzuki et al., 1985) that essentially support our previously published conception, i.e., that seeing lights in NDEs may be due to the transient enhancement of bioluminescent biophotons. Next, we briefly describe our biophysical visual representation model that may explain brilliant lights experienced during NDEs (by phosphenes as biophotons) and REM sleep associated dream-like intrinsic visual imageries through biophotons in NDEs. Finally, we link our biophysical visual representation notion to self-consciousness that may involve extremely low-energy quantum entanglements. This article is intended to introduce novel concepts for discussion and does not pretend to give the ultimate explanation for the currently unanswerable questions about matter, life and soul; their creation and their interrelationship.

Keywords: brilliant lights during near death experiences, phosphenes, biophotons, biophysical picture representation, unconscious cognitive processes, rapid eye movement sleep (REMS), out-of-body experience (OBE), quantum entanglements

INTRODUCTION

An experience of seeing brilliant light is one of the last phenomena in a series of events reported to frequently occur during NDEs. Recently, we suggested that the experience of seeing shining lights in NDEs may be due to the reperfusion that causes overproduction of free radicals that can generate a transient enhancement of bioluminescent biophotons in different areas of the brain, chief among them being visual areas. When bioluminescent photon emission exceeds a threshold, this can lead to the emergence of lights (phosphenes) and the brain interprets these intrinsic bioluminescent photons in visual areas as if they were derived from the external visual world. First, we present important experimental studies reported by several groups (Imaizumi et al., 1984; Suzuki et al., 1985) that support our previously published conception proposing that seeing lights in NDEs may be due to the transient enhancement of bioluminescent biophotons. We briefly present our novel biophysical visual representation concept and theorize that through NDEs, intrinsic visual perceptions and imageries may be due to the rapid eye movement sleep (REMS) associated dream-like biophysical picture representation created from long-term visual memory. Finally, we link our biophysical visual representation notion to self-consciousness that may involve extremely low-energy quantum entanglements by means of biophotons. The aim of this paper is to propose novel ideas rather providing a final explanation of the currently unanswered questions about matter, creation, soul, and life.

NEAR DEATH EXPERIENCES

During NDEs, the subjects' heartbeat and breathing are temporarily suspended, and they exhibit flattened brain waves in the electroencephalogram (EEG) and absence of auditory evoked potentials from the brainstem. NDEs include a wide range of subjective experiences associated with the impending death. NDEs consist of some frequent components such as out-of-body experience (OBE) (separation of consciousness from the physical body), passage through a dark tunnel, encounters with bright lights, meeting deceased relatives, meeting guardian spirits and mystical beings, sensing a border, etc. The subjects' decision of its "SELF" to return into the material body may be voluntary or involuntary (Greyson, 2000; van Lommel et al., 2001; French, 2005; Parnia et al., 2007). NDEs reported by children are similar to those described by adults although their levels of learning and worldly experiences may differ. The characteristics of subjects experiencing NDEs are similar worldwide irrespective of language, culture and age. In general, after NDEs subjects report being happier, less materialistic, more altruistic, and not afraid of death compared with those who did not have this experience, although there have also been reports of fearful experiences similar to nightmares (Agrillo, 2011).

Numerous mechanisms have been hypothesized to elucidate NDEs. The main scientific ideas proposed as interpretations of NDEs phenomena are: temporal lobe malfunctions; imbalances of various neurotransmitters (such as glutamate, noradrenaline, dopamine, endogenous opioids, serotonin); electrolyte disturbances during times of physical crises; REM-sleep intrusions; lack of oxygen in the brain or too much carbon dioxide; similarities between NDEs and effects of hallucinogens; activation of the limbic system; to name a few (Carr, 1981; Persinger and Makarec, 1987; Blackmore and Troscianko, 1988; Appelby, 1989; Jansen, 1989; Lempert, 1994; Blackmore, 1996; Beauregard and Paquette, 2006; Bonilla, 2011; Facco and Agrillo, 2012a).

Let us take a closer look at some examples. Electrical stimulation of the temporo-parietal lobe could induce similar dissociation to that during NDEs and OBEs. Blanke et al. (2002) reported the experience of a 43-year-old woman who had a rare form of epilepsy. These authors used focal electrical stimulation of the brain's right angular gyrus to distort the patient body image and induced OBEs, as well as vestibular and somatosensory responses. During this procedure, the patient thought that she was either larger or smaller or outside her body. Anoxia (Whinnery, 1997) or hypercarbia (abnormally high level of carbon dioxide in the circulating blood) (Meduna, 1950) can produce phenomena such as seeing brilliant lights, reliving past memories and having OBE. The visual cortex dysinhibition that is associated with anoxia (not the anoxia *per se*) has been suggested as an interpretation of tunnel-like perception during NDEs (Blackmore, 1996). Clinical observations support that REMS intrusion can contribute to NDEs (Nelson et al., 2006). Recently, Kevin Nelson (2011) proposed that the common factor in these experiences may be reduced oxygen supply to the brain. If the oxygen supply of the temporo-parietal lobe is cut off, this could start an OBE.

In addition to the neurobiological theories, psychosocial concepts also tried to explain NDEs. These include: expectation hypothesis (when life-threatening situations can initiate NDEs as a projection of expectancy of the afterlife.); depersonalization (during NDEs, depersonalization is a form of detachment including heightened arousal, disorganized emotion, sensation, reality, and experience of time that occurs as a psychological defense against the fear of death); memory of birth (when a baby is born, he/she leaves the womb to travel down a tunnel toward a light and waits for a great deal of love. In contrast, when death is approaching the stored memory contains the events that happened since the individual's life began.); fantasies and imagination (Noyes and Kletti, 1977; French, 2001, 2005; Greyson et al., 2009; van Lommel, 2010). A recent (open access) paper by Facco and Agrillo (2012a) is an excellent summary and evaluation of the various hypotheses proposed to elucidate NDEs.

However, none of the above mentioned concepts itself could elucidate all the reported common characteristics of NDEs. While some features of NDEs may be attributed to neural mechanisms or to psychological phenomena, nevertheless, currently we do not have reasonable explanations of all the reported features of NDEs.

PHOSPHENES AND BRILLIANT LIGHTS DURING NDEs BY BIOLUMINESCENT BIOPHOTONS

Biophotons (also referred to as ultraweak (bio)chemiluminescent photons, ultraweak visible spontaneous electromagnetic radiation, etc.) are spontaneous ultraweak photons that are continuously emitted by all living cells and in particular by neurons without external excitation (Tilbury and Cluickenden, 1988; Devaraj et al., 1991; Scott et al., 1991; Cohen and Popp, 1997; Zhang et al., 1997; Takeda et al., 1998; Nakano, 2005; Chang, 2008; Kobayashi et al., 2009; Rahnama et al., 2011). Biophotons originate from natural bioluminescent radical reactions and the deactivation of energetically excited molecules. Neurons also constantly produce biophotons through bioluminescent radical reactions during normal metabolism (Isojima et al., 1995; Kataoka et al., 2001). In addition, the intensity of biophoton production in the rat brain *in vivo* has been correlated with cerebral energy metabolism, EEG activity, cerebral blood flow, and oxidative processes (Kobayashi et al., 1999a,b), which suggests that there is neural activity-dependent biophoton emission taking place in the brain (Isojima et al., 1995).

Phosphenes represent a perceived sensation of flashes of light in the absence of external visual stimulation. The most common phosphenes are pressure phosphenes, caused by rubbing the closed eyes. Earlier, we have proposed (Bókkon, 2008) that the phosphene phenomenon is due to the intrinsic perception of induced (mechanical, electrical, magnetic, etc.) or spontaneous increased bioluminescent biophoton emission of cells in various parts of the retinotopic visual system. Induced or spontaneous unregulated overproduction of free radicals and energetically excited molecules can create a brief increase of the generation of bioluminescent biophotons in the visual system. When this excess biophoton emission can exceed a threshold, they appear as phosphene lights in the subject's mind.

Our hypothesis that phosphene lights are due to biophotons is supported by several sets of experiments. Catalá (2006) has shown that radicals from lipid peroxidation of the photoreceptors can create (bio)chemiluminescent photons (bioluminescence is a type of chemiluminescence, which naturally occurs in living organisms) in the visual spectrum. Subsequently, our prediction regarding one specific kind of phosphenes (i.e., retinal phosphenes during space travel) was supported by Narici et al. (2009). According to this latter work, ionizing radiation (cosmic particle rays) induced free radicals which produce chemiluminescent photons through processes including by lipid peroxidation. Chemiluminescent photons are then absorbed by the photoreceptors and initiate a photo-transduction cascade, which results in the perception of phosphenes. Narici et al. (2012) also revealed that the lipid peroxidation of the photoreceptors can produce (bio)chemiluminescent photons that generate anomalous visual effects, such as those associated with retinal phosphenes. Recently, the first experimental *in vitro* evidence was presented (Wang et al., 2011) for the existence of spontaneous and visible light induced biophoton emission from freshly isolated whole eye, lens, vitreous humor, and retina samples from rats. It also supports the hypothesis that phosphene lights are produced by biophotons. Since phosphenes can be produced by direct stimulation of the visual cortex without a retinal photo-transduction cascade, this suggests that retinal and visual cortical phosphenes are generated by similar mechanisms, and both may be due to the transiently and locally increased ultraweak biophotons.

Several experiments demonstrated that during post-ischemic reperfusion, there is considerable overproduction of oxygen free radicals generated in the brain and the retina (Agard et al., 1991; Ophir et al., 1993; Basu et al., 2011). In the recovery phase, the overproduction of free radicals and excited species in the visual areas, among others, can produce significant bioluminescent biophotons by means of lipid peroxidation.

Based on the above-mentioned experiments and notions generated by their interpretation, we proposed an original biophysical hypothesis regarding the appearance of brilliant lights during NDEs (Bókkon and Salari, 2012). In particular, we suggested that perceiving shining lights during NDEs may be due to bioluminescent biophotons simultaneously produced in the recovery period in several areas of the visual system and the brain interprets these biophotons as if they originated from the external visual world. It means that brilliant light experiences in NDEs can be simply interpreted as simultaneously produced phosphenes (biophotons) in numerous visual areas during the recovery phase.

To test the validity of our idea we suggested (Bókkon and Salari, 2012) that *in vitro* or *in vivo* increases of ultraweak bioluminescent photon emission should be measured from hemispheres in *in vivo* animal experiments before, during and after the recovery period during experimental cardiac arrest. However, through an extensive literature search, we have found relevant experimental studies (Imaizumi et al., 1984; Suzuki et al., 1985) that support our previously formulated hypothesis regarding the appearance of brilliant lights during NDEs.

ULTRAWEAK (BIO)CHEMILUMINESCENCE IN HYPOXIC BRAIN: CORRELATION BETWEEN ENERGY METABOLISM AND FREE RADICAL REACTION

In 1984 Imaizumi et al. determined the ultraweak (bio)chemiluminescence value at pre-hypoxia, during hypoxia and at post-hypoxia states in rat brains. Brain hypoxia was produced by arterial hypoxemia (PaO2 17–22 mmHg), normocapnia (PaCO2 28–38 mmHg) and normotension (MABP 100–140 mmHg). Rat brain samples were collected at pre-hypoxia, at 3 and 5 min during hypoxia and at 5 and 30 min during post-hypoxia states.

Ultraweak chemiluminescence values were 11 ± 15 counts/10 s-g in pre-hypoxia state, risen to 231 ± 35 counts/10 s-g at 3 min, slightly decreased to 154 ± 62 counts/10 s-g at 5 min of hypoxia, and rose to 217 ± 79 counts/10 s-g at 5 min of posthypoxia. Finally, at 30 min of post-hypoxia, values returned to low levels 10 ± 13 counts/10 s-g which are similar to the prehypoxic values. Chemiluminescence spectral peaks of intensity were found at 480, 520–530, 570, 620–640 and 680–700 nm. This suggests that ultraweak luminescence originated from singlet oxygen species. Regarding the energy metabolism, during the hypoxic state, ATP (Adenosine 5′-triphosphate) and glucose exhibited a slight decrease, while ADP (Adenosine 5′-diphosphate) showed an increase that suggests disorders in the tricarboxylic acid cycle (TCA), glycolysis, and mitochondrial oxidative phosphorylation. In the post-hypoxic state all metabolites were recovered at 30 min, which suggests that brain hypoxia was reversible. Suzuki et al. (1985) suggested that the major source of free radicals originated from lipid peroxidation, since the ischemic brain is associated with membranous lipid peroxidation.

In the second series of experiments (Suzuki et al., 1985), (under circumstances similar to those in the first experiments, Imaizumi et al., 1984) researchers evaluated the effect of pre-treatment with protective drugs such as vitamin E, betamethasone and mannitol on free radical reactions in hypoxic rat brain tissue by ultraweak chemiluminescence measurements. Pre-treatment with vitamin E and betamethasone diminished all chemiluminescence intensity peaks, but little decrease occurred after mannitol was administered. These results indicate an *in vivo* free radical scavenging effect of these drugs.

IMPLICATIONS OF THE RESULTS OF IMAIZUMI ET AL. AND SUZUKI ET AL.

- Experiments by Imaizumi et al. (1984) and Suzuki et al. (1985) support our notion (Bókkon and Salari, 2012) that perceiving lights during NDEs may be due to bioluminescent biophotons that originate from unregulated overproduction of free radical bioluminescent biochemical reactions and the brain interprets these biophotons as if they originated from virtually the external visual world.
- Perturbation of mitochondrial oxidative phosphorylation also supports our hypothesis, because mitochondria are major sources of free radicals and biophotons (Thar and Kühl, 2004).
- Ultraweak (bio)chemiluminescence spectral intensity peaks were observed at 480, 520–530, 570, 620–640 and 680–700 nm. However, there were significant individual differences in measured intensity of ultraweak (bio)chemiluminescence during and after hypoxia states. This can explain the fact that some subjects experienced light perception but other subjects did not experience this during NDEs. In particular, the individual brain structures and the individual oxidative metabolic processes may explain which person can remember the lights and which cannot remember them during NDEs.
- We also proposed that lights in NDEs may be experienced in the recovery period in several areas of the visual system. In contrast, experiments by Imaizumi et al. (1984) and Suzuki et al. (1985) revealed that increased ultraweak (bio)chemiluminescence can emerge after the induction of hypoxia states and this increased biophoton production can persist throughout all hypoxia and post-hypoxia (reperfusion) states, i.e., up to 30 min after reperfusion when values returned to low levels 10 ± 13 counts/10 s-g that were similar to the pre-hypoxic values. Although it is likely that seeing lights in NDEs may occur in the reperfusion state, experimental outcomes by Imaizumi et al. (1984) and Suzuki et al. (1985) also suggest that the light sensing may occur at any state in NDEs.

INTRINSIC VISUAL SENSATION AND IMAGERY BY ULTRAWEAK (BIO)CHEMILUMINESCENCE IN NDEs

Since enhanced ultraweak (bio)chemiluminescence can appear after the induction of hypoxia states and this increased biophoton emission can persist throughout all hypoxia and post-hypoxia (reperfusion) states, this raises a further possibility regarding

NDEs. Namely, NDEs consist of some recurrent components among which meeting deceased relatives, meeting guardian spirits and mystical beings or sensing a border are common occurrences. These intrinsic visual experiences during NDEs can be linked to our recently suggested biophysical visual representation concept (Bókkon, 2009; Bókkon and D'Angiulli, 2009).

According to our novel biophysical representation idea (Bókkon, 2009; Bókkon and D'Angiulli, 2009) objects in the visual field can be directly represented in the retinotopically organized neural networks of striate cortex (also known as primary visual cortex or V1) by congruent patterns of biophotons generated from regulated bioluminescent radical/redox processes, and iterative computation (Bókkon et al., 2011a). Our concept of intrinsic biophysical visual virtual reality by bioluminescent photons in early retinotopic areas may simply be a first possible biophysical basis of Kosslyn's depictive pictorial theory (Kosslyn, 1994; Lewis et al., 2011; Cichy et al., 2012). It claims that visual perception and imagery share common neural substrates, and that both visual perception and imagery induce activation in retinotopically organized striate and extrastriate regions.

Specifically, photons reflected from objects are absorbed by photoreceptors and converted into retinal electrical signals. Next, retinotopic electrical signals are conveyed to the V1, where spike-related electrical visual signals are induced along classical axonal-dendritic pathways. These spike-related electrical visual signals travel along classical axonal-dendritic pathways and concurrently produce spike-related (neural activity-dependent) biophotons within the same population of retinotopic V1 *neurons* through mitochondrial redox processes. These synchronized and activity-dependent biophotons can spatially and temporally create intrinsic pictures in the early visual area. Thus, retinal visual information can be re-represented through regulated biophotons in retinotopically organized, mitochondrial cytochrome oxidase-rich visual areas during visual imagery, visual perception as well as during REMS associated dreams or visual hallucination.

Small groups of retinotopic V1 neurons with biophotons might act as "nonlinear visual pixels" with respect to the topological distribution of photonic signals in the retina. As a result, we can obtain a biophysical picture of the objects created through biophotons in the retinotopic V1 (see **Figure 1**). Our theory implies that there could be a literal image, albeit abstract, in the visual brain's neurons of which the subjects are conscious, and biophotons act as the physical substrate of its subjective experience.

The visual content of biophysical representations generated from regulated biophotons is progressively degraded during the transmission along pathways from V1, V2 (extrastriate visual cortical area), and additional visual areas to higher-level associative regions. Furthermore, higher-level cognitive processes might become progressively more abstract or schematic. The biophysical hypothesis suggests that binding between analogic-perceptual and propositional-abstract formats might appear as a natural consequence of the dynamic "crosstalk" between the visual system and the rest of the brain.

Long-term visual memories are not stored as biophysical pictures but as redox regulated epigenetic codes[1]. During visual imagery, top-down processes trigger and regulate the epigenetic encoded long-term visual information. Next, according to retrieved neural epigenetic information, mitochondrial networks in synchronized neurons generate patterns of biophotons through redox reactions, which can produce intrinsic biophysical pictures in retinotopic and mitochondrial rich visual neurons during visual imagery, REMS associated dreams or visual hallucination (Bókkon, 2009; Bókkon and D'Angiulli, 2009; Bókkon et al., 2010a). First biophoton experiments may support our biophysical pictures representation. Namely, Dotta and Persinger (2011) and Dotta et al. (2012) observed cognitive coupling with biophoton emission in the brain during subjective visual imagery. In addition, the biophoton emissions were strongly correlated with EEG activity and the emergence of action potentials in axons. In addition, Sun et al. (2010) revealed that biophotons can conduct along the neural fibers which supports our biophysical picture hypothesis. It appears that biophotonic and bioelectronic activities are not independent biological processes in the nervous system, and their synergistic action may play a significant role in neural signal processes.

One might argue that neurons in early retinotopic visual areas could be activated by biophotons released as a consequence of spiking activity. We should stress that neural electrical signals (spiking activity) run along retinotopic visual neurons, but external neural biophotons cannot activate other neurons because visible biophotons can be easily absorbed within neural cells. Thus, the emergence of intrinsic biophysical pictures is due to the synchronized biophoton production created within retinotopic neurons during synchronized neural electrical discharges. In addition, our calculations (Bókkon et al., 2010b) indicate that the biophoton intensity within retinotopic neurons might be sufficient for creating a biophysical pictorial representation of a single-object during visual perception.

One might also argue that there does not exist an analog for the photon-dependent 11 cis-trans retinal conversion that occurs in retinal photoreceptors occurring in populations of cortical neurons, which could then account for perceptual representation of such events. However, the emergence of intrinsic biophysical

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[1] There is increasing experimental evidence that epigenetic modifications *(i.e., the regulation of chromatin structure through methylation of DNA or post-translational modification of histone proteins, including methylation, acetylation, and phosphorylation)* within neurons are fundamental mechanisms for the formation and storage of behavioral memory (Nelson and Monteggia, 2011; Lipsky, 2013; Zovkic et al., 2013; Rudenko and Tsai, 2013). Most recent studies imply that epigenetic modulation of the genome is a necessary for the neuronal plasticity and long-term memory (Feng et al., 2007). Chromatin arrangement can represent a memory and allow for temporal integration of spaced signals or metaplasticity of synapses (Levenson and Sweatt, 2005). According to the epigenetic concept, cognitive and memory functions are performed not only by neural networks but also by intrinsic processes of neurons (Arshavsky, 2006). The synaptic plasticity (neural networks) concept does not contradict the epigenetic idea, because networks can operate as constantly variable information channels among neurons, but long-term memory can have epigenetic nature in individual neurons.

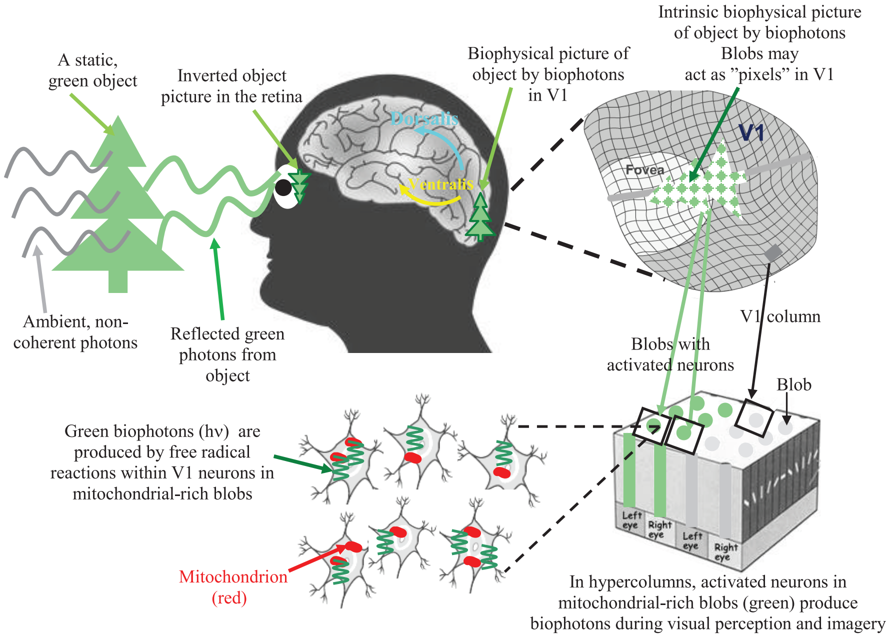

FIGURE 1 | A simple illustration of the biophysical picture representation idea (also called intrinsic biophysical virtual visual reality) during visual perception and imagery (Bókkon, 2009; Bókkon and D'Angiulli, 2009). External photon signals reflected from an object are converted into retinotopic electrical signals inside the retina. Next, retinotopic electrical signals are conveyed to the V1 and transformed into controlled biophotons by mitochondrial redox processes within the V1 neurons. Specifically, spike-related, retinotopic electrical signals create synchronized biophotons along classical axonal-dendritic pathways through a redox reaction within retinotopic V1 neurons. Small groups of visual neurons can function as "visual pixels" that are appropriate to the topological distribution of the retina's photonic signals. Thus, we can get an intrinsic computational biophysical picture of the object created by biophotons in the retinotopic V1. The long-term visual information is not stored as pictures but as epigenetic codes. We are able to identify objects since the same epigenetic processes are activated every time we see an object. Therefore, the representation stored in long-term visual memory will match the representation that is created while the object is seen again. Top-down mechanisms control the epigenetically encoded, long-term visual information during visual processing. Then, according to this retrieved epigenetic information, synchronized retinotopic neurons generate dynamic patterns of biophotons through redox reactions. Finally, biophotons within the millions of synchronized neurons (Bókkon et al., 2011a,b) can create biophysical pictures in the early retinotopic visual area. During visual perception and imagery, visual information is linked and combined with different sensory modalities and higher-order associational areas during multisensory interactions. It should be emphasized that neural electrical signals are transmitted between neurons, but biophotons are generated within retinotopic visual neurons. In addition, intrinsic biophysical pictures (images) are not like rigid objects but we can alter images *ad-lib*, which make it possible that the visual system can also produce irrationally assembled pictures and scenes during REM dreams and visual hallucinations.

pictures is not due to the conversion of biophotons but to the synchronized production of biophotons within retinotopic visual V1 neurons. In other words, there is an intrinsic biophysical picture re-representation of perceived visual scene (reflected photons from an external object) by means of synchronized production of biophotons in retinotopic V1.

Regarding our biophysical visual representation idea, it should be stressed that the phrase "ultraweak biophoton emission" is confusing, as it suggests that ultraweak biophotons are not important in cellular mechanisms but are by-products of free radical reactions. In contrasts, it is plausible that externally measured ultraweak biophoton emission from cells and neurons is principally produced from natural oxidation processes on the surfaces of cellular membranes as demonstrated by Blake et al. (2011). However, the real biophoton intensity can be fundamentally higher inside cells and neurons (Bókkon et al., 2010b) compared with the biophoton intensity in their surrounding environment which makes it possible for the emergence of intrinsic biophysical pictures in V1 visual areas.

REMS ASSOCIATED DREAM-LIKE BIOPHYSICAL INTRINSIC VISUAL IMAGERIES DURING NDEs

Some clinical studies suggest that REMS intrusion may contribute to NDEs and that near-death experiences are likely to mix up (lucid or conscious) dreams and reality (Nelson et al., 2006). Recently, we argued (Bókkon and Mallick, 2012) that activation of the retinotopic visual areas is central to REMS associated dreams and that REMS associated dreaming and visual imagery may have co-evolved in homeothermic animals during evolution. In addition, visual imagery during REMS utilizes a common visual neural pathway similar to that used in wakefulness and during dreams expressed during REMS (Braun et al., 1998; Cantero et al., 1999; Gottesmann and Gottesman, 2007; Miyauchi et al., 2009; Horikawa et al., 2013). This pathway subserves visual processes accompanied by auditory experiences and intrinsic feelings. We also suggested earlier that a protoconscious state manifested during REMS, which may be compared with that introduced by Hobson (2009) many years ago, may be a basic visual process. According to Thonnard et al. (2013), "NDE memories have more characteristics than any kind of memory of real or imagined events and of other memories of a period of coma or impaired consciousness following an acquired severe brain dysfunction." These authors suggested that the physiological origins of NDEs possible are hallucinations or dream-like events that have rich characteristics like memories of real events.

Concerning our biophysical picture representation idea, during NDEs, intrinsic visual perceptions and imageries may be due to the REMS associated dream-like biophysical biophotonic representations originated from long-term visual memory. During NDEs, these REMS associated dream-like biophysical biophotonic representations may occur in the reperfusion state but are also possible at any state of NDEs.

One might argue that the experience of light can also occur under circumstances that have nothing to do with heart-stopping, anoxia, etc. (Cardeña, 2005; Facco and Agrillo, 2012b). The term entoptic phenomena (subjective visual phenomena) refer to visual (light) experiences derived from within the eye or brain that are not due to the external perception of visible photons in normal vision (Tyler, 1978; Lewis-Williams and Dowson, 1988). Phosphenes, form constants (form constants are complex and reproducible phosphenes) and more complex visual hallucinations are entoptic phenomena that are not only associated with emotional factors, drugs, alcohol, stress, fever or psychotic conditions (Cervetto et al., 2007) and can be early symptom of a variety of diseases of the retina and the visual pathways, but healthy individuals can perceive them as well (Lewis-Williams and Dowson, 1988; Bókkon, 2008). Phosphene lights can be elicited by various stimuli (mechanical, electrical, magnetic, etc.) of cells in the visual systems as well as random firing of cells in the visual areas (Reznikov, 1981; Lindenblatt and Silny, 2002; Merabet et al., 2003). The briefly described concept of phosphenes (Bókkon, 2008) together with the intrinsic biophysical visual pictures by bioluminescent photons during visual perception and imagery, as well as in visual REMS associated dreams and visual hallucination, is able to explain the subjective sensation of light that can also occur under circumstances that have nothing to do with heart-stopping, anoxia, etc. (Bókkon, 2009; Bókkon and D'Angiulli, 2009; Bókkon et al., 2010b). Namely, our intrinsic biophysical visual picture representation concept is not restricted to visual phenomena during NDEs, but can present a common and convergent interpretation for entoptic visual phenomena during normal, pathological, NDE-like and in NDEs circumstances.

In addition, it is possible that entoptic visual phenomena such as phosphenes, form constants and complex visual hallucinations are due to transient or continuous deafferentation and disintegration of certain visual structures that produce an increase in excitability of deafferented neurons (Burke, 2002). This deafferentation can be linked to an increase in spontaneous activity and synchronization of nerve discharges. Thus, visual hallucinations may be considered as local paroxysms in visual structures that can produce dream-like pictures by bioluminescent biophotons in the retinotopic visual areas. These unregulated dream-like pictures by bioluminescent photons can then break into the waking consciousness (Bókkon, 2005; Gottesmann and Gottesman, 2007).

EVANESCENT BRAIN PROCESSES IN NDEs?

Chawla et al. (2009) reported observations involving patients who were neurologically intact before the decision to withdraw life-support devices due to general systemic critical illness. EEG monitoring devices were placed on the patients' forehead. When life-support devices were switched off and blood pressure of these patients was stopped, the monitored EEG activity began to decline. However, declining EEG activity was followed by a short-lived (from 1 to 5 min) but high intensity transient spike in EEG activity. In a transient EEG surge, a high frequency (high frequency gamma oscillations) waveform emerged that is generally related to consciousness. Chawla et al. (2009) proposed that the resuscitated patients could recall their experiences related to the EEG surge that appear similar to what a large number of people described in NDEs. This study can be criticized for its methodology since the subjects were dying and were not resuscitated. Consequently, there is no information available whether the subjects had experienced anything at all.

According to Hameroff and Chopra (2010a), the observed gamma oscillations reported in the studies of Chawla et al. (2009) can be linked to consciousness states that involve particularly low-energy quantum entanglements that persisted over time while other brain functions have run out of energy supply. Consciousness could persist outside the physical body but remains localized on the level of Planck-scale geometry (Hameroff and Chopra, 2010b). "A quantum basis for consciousness also raises the scientific possibility of an afterlife, of an actual soul leaving the body and persisting as entangled fluctuations in quantum spacetime geometry" (Hameroff and Chopra, 2010b). When the patient's physical body is resuscitated, the quantum information can reenter it, and the subjects may be able to recall their experience involving NDEs.

Previously, we emphasized (Bókkon and Vimal, 2010) that retained, subliminal visual representation processes cannot be detected by even the most modern neural recording procedures, but require active stimulation to emerge. This active stimulation can be performed by artificial (external) stimulations, such as TMS (transcranial magnetic stimulation), or by natural (internal) stimulations, like active visualization processes. The idea that evanescent processes cannot be revealed by means of the most modern neural recording procedures may be also applicable to the case of EGG in NDEs. Namely, in regard to the flat EEG in NDEs, EEG determines electric neural activity that occurs very poorly below the upper layers of the cortex. Signal-to-noise ratio is also very low. Spontaneous activity is usually considered to be noise if one is interested in stimulus processing and the level of error increases with the depth below the surface of the cortex (Šobajic, 2002). Since EEG only measures the surface of the brain function, there could be deeper processes taking place that we are unaware of at the present time. Hence, the flat EEG in NDEs does not mean that evanescent brain processes cannot be realized, we simply cannot rule out this possibility (Agrillo, 2011).

Very recently, Borjigin et al. (2013) recorded EEG signals over the frontal, parietal, and occipital cortices bilaterally in rats during wakefulness, anesthesia, and cardiac arrest. Within the 30 s after the rats' hearts stopped beating it was revealed that cardiac arrest produced a transient and global surge of synchronized gamma oscillations of brain activity that exceeded the waking state. In addition, researchers found the high levels of global alpha–gamma coupling that suggest the visual cortex can be highly activated in cardiac arrest. Previous studies indicated that alpha–gamma coupling is especially important for visual perception (Spaak et al., 2012). Dr Jimo Borjigin said (Morelle, 2013), "... it was feasible that the same thing would happen in the human brain, and that an elevated level of brain activity and consciousness could give rise to near-death visions." "The fact they see light perhaps indicates the visual cortex in the brain is highly activated—and we have evidence to suggest this might be the case, because we have seen increased gamma in area of the brain that is right on top of the visual cortex." The results of these experiments are consistent with our biophysical picture representation idea during NDEs (Bókkon, 2009; Bókkon and D'Angiulli, 2009; Bókkon et al., 2010a).

To summarize it briefly, it is probable that during NDEs, the increased biophoton production (Imaizumi et al., 1984; Suzuki et al., 1985) can occur at any state in NDEs. In addition, declining EEG activity was followed by a short-lived (from 1 to 5 min) but high-intensity transient spikes in EEG activity (Chawla et al., 2009) when life-support devices were switched off and blood pressure of patients was stopped. In addition, according to the experiments of Kobayashi et al. (Kobayashi et al., 1999a,b), *in vivo* imaging of spontaneous biophoton emission from a rat's brain correlated with cerebral energy metabolism, EEG activity, cerebral blood flow, and oxidative stress. Moreover, Isojima et al. (1995) reported neural activity-dependent biophoton emission from hippocampal slices of rat brain. Thus, the biophoton emission of neurons is in direct correlation with biochemical processes of neurons, i.e., there is a neural activity-dependent biophoton emission in the brain. The high-intensity transiently synchronized gamma oscillations in EEG activity (Chawla et al., 2009; Borjigin et al., 2013) may also reflect an increased biophoton production in NDEs.

Our biophysical visual representation idea may explain not only brilliant lights experienced during NDEs (by phosphenes as biophotons) and REMS associated dream-like intrinsic visual perceptions and imageries through biophotons in NDEs, but also can be linked to the idea by Hameroff and Chopra (2010b) since consciousness involves extremely low-energy quantum entanglements that can return to the material body if the person is resuscitated.

OUT-OF-BODY EXPERIENCE AND OUT-OF-BODY-LIKE EXPERIENCE

OBE is a common experience that occurs, most notably with NDE. During an OBE, people are in an awake-like state and feel that their self or awareness is placed outside of their physical body and rather elevated. The various proposed scientific explanations (see a good summary paper by Neppe, 2011) try to relate the OBE phenomenon to different dysfunctions and pathologies of the brain that are caused by stroke, autoscopy, epilepsy, drug abuse, traumatic experiences such as car accidents, etc., or by artificial electrical stimulation of the brain's angular gyrus stimulating illusory own-body perceptions (Blanke et al., 2002). For instance, Ehrsson (2007) induced an illusion of being outside the physical body in healthy voluntaries by means of manipulation of visual and tactile perceptions. However, in many cases during OBE experience, people involved in them could recall and report specific details of events that have taken place when they had been unconscious (van Lommel et al., 2001; van Lommel, 2006). Although neurophysiological processes must take part in various organs of a person involved in an NDE, in the cases when people could account about specific details of events that have taken place when they had been unconscious, this challenges currently accepted conventional medical science.

The OBE component of NDEs actually offers an opportunity to determine the relationship between consciousness and brain function as well as if there is self-consciousness outside of the physical body during NDEs, although in this latter case it is very difficult to obtain concrete and reliable results. In 2008 the AWARE (Agrillo, 2011; see also the AWARE link in References) study was launched by the Human Consciousness Project in which 25 hospitals took part in Europe and North America via international collaboration of scientists, physicians, and nurses studying subjects who could survive cardiac arrest and report about a NDE. A clever idea was implemented in AWARE as special shelving was placed in resuscitation areas and images were put on shelves that could only be seen from above. If a patient could see (report) the picture, it would indicate whether or not the patient's experiences were illusions or false memory, or if there was indeed self-consciousness present outside of his/her body during OBE. At the moment, AWARE scientists unfortunately are not able to release any information until the conclusion of the study but indications have been given that the results, obtained during the first five years, can be released throughout 2013 through appropriate scientific publications.

Nevertheless, we should make a phenomenological distinction between OBE and out-of-body-like experience (Neppe, 2011). The latter can be explained by diverse forms of dysfunction and pathologies of the brain or can be produced in healthy persons in the laboratories, but the former cannot be explained yet but may be related, for example, to quantum mechanisms. So, we may definite the OBE if a person could report about specific details of events that have taken place when they had been unconscious, and person's narrative can be genuinely checked afterwards similar to goal of the mentioned Human Consciousness Project.

SOME REFLECTIONS: EXTENDING THE IDEA OF HAMEROFF AND CHOPRA RELATED TO NDEs

Recently, we have suggested that characteristics of homeothermic states make the development of explicit memory possible in evolution (Bókkon, 2005). Our idea appears to be related to Hobson's protoconscious notion (2009), i.e., protoconscious state may emerge from implicit memory in homeotherms during the evolution of REMS. We also suggested that the REMS protoconscious state may be basically a visual process and REMS associated visual dreams and visual imagery may have co-evolved in homeothermic animals in evolution (Bókkon and Mallick, 2012).

It is possible that the appearance of self-consciousness in humans is due to the emergence of a very well structured neocortex and the development of language. According to Hassin (2013), "unconscious processes can perform the same fundamental, high-level functions that conscious processes can perform."

van Gaal et al. (2008) stated that "unconscious stimuli can influence whether a task will be performed or interrupted, and thus exert a form of cognitive control." In addition, although the neural correlates of consciousness have traditionally assigned a key role to the prefrontal cortex generating consciousness and high-level conscious control, present neuroscientific experiments reveal that prefrontal cortex can be activated unconsciously (van Gaal et al., 2008) and challenge the fundamental function of the prefrontal cortex in consciousness (van Gaal and Lamme, 2012). It seems that definite brain regions (cognitive modules) can support specific cognitive roles but that consciousness is independent of this (van Gaal and Lamme, 2012). These findings challenge traditional views concerning the proposed relationship between awareness and cognitive control and stretch the alleged limits and depth of unconscious information processing." Moreover, according to recent studies, when the subject's decision reached awareness it had been influenced by unconscious brain processes for up to 10 s (Soon et al., 2008; Bode et al., 2011; Soon et al., 2013). However, future studies should reveal if unconscious and conscious decisions and representations may share common neural processes and substrates.

We proposed that the human unconscious can operate through intrinsic dynamic biophysical pictures and we link these picture-representations to each other during language learning processes (Bókkon, 2009; Bókkon and D'Angiulli, 2009; Bókkon et al., 2011a). Thus, the human self-consciousness in the waking state may be an abstract language dependent manifestation of the unconscious. Our thinking processes and indeed every decision made at a given moment can be a coherent and convergent dynamic (discrete events) manifestation of our unconscious cognitive (essential picture-representation) processes due to the billions of non-conscious processes.

Popper et al. (1993) stated: "I wish to propose here as a hypothesis that the complicated electro-magnetic wave fields which, as we know, are part of the physiology of our brains, represent the unconscious parts of our minds, and that the conscious mind—our conscious mental intensities, our conscious experiences—are capable of interacting with these unconscious physical force fields, especially when problems need to be solved that need what we call "attention." This admittedly vague working hypothesis appears to me as a small yet significant progress within a so far hopelessly difficult part of physiology." It seems that Popper's notion (electro-magnetic wave fields represent the unconscious parts of our minds and that the conscious minds are capable of interacting with these unconscious physical force fields) is very similar to our biophysical representation concept by ultraweak electromagnetic biophotons.

The idea by Hameroff and Chopra (2010b) that the self-consciousness could continue outside the body but remains at a level of Planck-scale geometry (Planck length is about 10^{-33} cm), may be realized by potential quantum-like properties of biophotons (and by virtual photon particles, see in Bókkon, 2003). We hypothesize that human self-consciousness is an individual-specific abstract manifestation of language and experience-dependent expression of conscious plus unconscious exposure and experiences of an individual. Here we talk about self-unconsciousness that performs cognitive processes through intrinsic dynamic biophysical pictures. Extending the idea of Hameroff and Chopra (2010b) ("A quantum basis for consciousness also raises the scientific possibility of an afterlife, of an actual soul leaving the body and persisting as entangled fluctuations in quantum space-time geometry."), we propose that self-consciousness originates within the core of the living body having all the metabolic properties intact. The latter having wave properties possesses the potential to propagate and thus, may manifest around the physical limits of the body.

Furthermore, we hypothesize that in the cases of NDE and OBE, because of the decreasing cellular metabolic activities, the internal as well as external inputs to the brain (cortex) are significantly reduced and therefore, the self-consciousness perceives and manifests other experiences. This gives the impression that the cognitive processes of the individual continue outside the body and if the body can be resuscitated, the quantum-like self-unconsciousness re-enters the physical body and the subjects may be able to recall and report their experience in terms of NDEs, which are modulated by their idiosyncrasies. If resuscitation happens to be unsuccessful and the subject dies, then self-unconscious [or implicit self (soul) awareness] as an entity may return into the subspace void where it blends and combines with the self-sustaining creation. This, however, cannot be reported back to the mortal living beings for obvious reasons.

The most ancient philosophical and conceptual works, the *Upanishads* claim that the mind experiences self through extra-fine thread like connections, the "*nadi*," which has been defined as finer than a thousandth part of a hair and it carries different "*hues*" of varying intensity (Mallick and Mukhopadhyay, 2011). The dimension of the latter is in the range of nanometers, which is practically the unit of wavelength of visible light photons (300–700 nm). It is interesting that this ancient concept may be explained by assuming that the mind and self-communicate through bioluminescent biophotons, which may support our proposed biophysical concept (Bókkon, 2009; Bókkon et al., 2010a, 2011a,b) that intrinsic biophysical pictures (also referred to as biophysical visual virtual reality) can emerge during visual imagery associated to dreams during REMS.

The above mentioned notions are consistent with Hameroff's ideas (2012) expressed in the following statements: "Support for consciousness as sequences of discrete events is also found in Buddhism, trained meditators describing distinct "flickerings" in their experience of pure undifferentiated awareness (Tart, 1995, pers. communication). Buddhist texts portray consciousness as "momentary collections of mental phenomena," and as "distinct, unconnected and impermanent moments which perish as soon as they arise." Buddhist writings even quantify the frequency of conscious moments. For example, the *Sarvaastivaadins* (von Rospatt, 1995) described 6,480,000 "moments" in 24 h (an average of one "moment" per 13.3 ms, 75 Hz), and some Chinese Buddhism as one "thought" per 20 ms (50 Hz), both in gamma synchrony range" and description of comparable concepts may be found in still earlier *Vedic, Upanishadic* and other *Hindu* philosophic scriptures.

SHORT SUMMARY

Here we presented some novel ideas to stimulate new concepts that may facilitate the understanding of the phenomena of NDEs. First, we reviewed and evaluated relevant literature that reported experiments (Imaizumi et al., 1984, Stroke; Suzuki et al., 1985, Stroke) that support our previously published conception, i.e., that seeing lights in NDEs may be due to the transient enhancement of bioluminescent biophotons. Then, we described our biophysical visual representation notion and theorized that through NDEs, visual imageries may be due to the REMS associated dream-like biophysical picture representation created from long-term visual memory. This is certainly a complex process, however, understanding the neurophysiological and neurochemical substrates of REMS regulation is likely to provide insights and eventually a better understanding of this phenomenon. However, Agrillo (2011) raised an crucial question regarding NDEs, "It is worth noting that most of the recurring features are visual experiences (seeing a light, seeing a tunnel, deceased people, or heavenly or hellish landscapes). This raises an interesting question: why would an out-of-body mind still perceive the reality mainly driven by visual processes?" Our briefly described biophysical visual representation concept may present a possible answer to the question why most of the recurring features are visual experiences during NDEs.

Hameroff and Chopra (2010b) speculated that self-consciousness involves extremely low-energy quantum entanglements that could return to the material body if the person is resuscitated. We linked our biophysical visual representation notion to self-consciousness that may involve extremely low-energy quantum entanglements by means of biophotons.

It is interesting to note that the *Upanishads* that are the most ancient philosophical and conceptual works containing the mature wisdom of the East can be seen to be consistent with our recently proposed biophysical concept that intrinsic biophysical pictures may appear by regulated biophotons during visual imagery and REMS associated dream visual imagery.

Although many phenomena of NDEs may be explained scientifically, however, phenomenon such as the OBE is not likely to be explained by mere conventional physical and neurological processes. Nevertheless, the final explanations involving the conscious mind, subconscious, matter, life, soul, and the creation are currently unavailable. According to Facco and Agrillo (2012a), "It is now time to remove the ongoing cultural filters and include consciousness, spirituality, and the highest mind expressions in neuroscience in a free, secular, and scientific perspective to overcome old prejudices."

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Low and then high frequency oscillations of distinct right cortical networks are progressively enhanced by medium and long term Satyananda Yoga meditation practice

John Thomas[1]*, Graham Jamieson[2] and Marc Cohen[1]

[1] School of Health Sciences, RMIT University, Bundoora, VIC, Australia
[2] School of Behavioural, Cognitive and Social Sciences, University of New England, Armidale, NSW, Australia

Edited by:
Etzel Cardeña, Lund University, Sweden

Reviewed by:
Thilo Hinterberger, Universitätsklinikum Regensburg, Germany
Vilfredo De Pascalis, La Sapienza University of Rome, Italy

***Correspondence:**
John Thomas, School of Health Sciences, RMIT University, 8/393 Cambridge St., Wembley, WA 6014, Australia
e-mail: johnthomas7@bigpond.com

Meditation proficiency is related to trait-like (learned) effects on brain function, developed over time. Previous studies show increases in EEG power in lower frequency bands (theta, alpha) in experienced meditators in both meditation states and baseline conditions. Higher gamma band power has been found in advanced Buddhist meditators, yet it is not known if this occurs in Yoga meditation practices. This study used eLORETA to compare differences in cortical source activity underlying scalp EEG from intermediate (mean experience 4 years) and advanced (mean experience 30 years) Australian meditators from the Satyananda Yoga tradition during a body-steadiness meditation, mantra meditation, and non-meditation mental calculation condition. Intermediate Yoga meditators showed greater source activity in low frequencies (particularly theta and alpha1) during mental calculation, body-steadiness and mantra meditation. A similar spatial pattern of significant differences was found in all conditions but the number of significant voxels was double during body-steadiness and mantra meditation than in the non-meditation (calculation) condition. These differences were greatest in right (R) superior frontal and R precentral gyri and extended back to include the R parietal and occipital lobes. Advanced Yoga meditators showed greater activity in high frequencies (beta and especially gamma) in all conditions but greatly expanded during meditation practice. Across all conditions (meditation and non-meditation) differences were greatest in the same regions: R insula, R inferior frontal gyrus and R anterior temporal lobe. Distinct R core networks were identified in alpha1 (8–10 Hz) and gamma (25–42 Hz) bands, respectively. The voxels recruited to these networks greatly expanded during meditation practice to include homologous regions of the left hemisphere. Functional interpretation parallels traditionally described stages of development in Yoga proficiency.

Keywords: meditation, Yoga, EEG, eLORETA, neural networks, default mode network

INTRODUCTION

The introduction of Yoga and Buddhist meditation practices into Western countries has extended their application beyond their original spiritual goals (Shapiro, 2003) to include a range of mind-body interventions for health-related problems (Ospina et al., 2007). Research has explored the neurophysiology of meditation during the actual practice (as examples of specific altered states of consciousness) and changes persisting into non-meditation conditions (as examples of neuroplasticity). A central question in this investigation is how the level of meditator proficiency contributes to the development of these effects.

As yet there is no accepted objective measure of meditator proficiency. Most studies report proficiency in years, although a more recent trend uses the more accurately calculated "hours of practice," "based on daily practice and time spent in meditative retreats" (Brefczynski-Lewis et al., 2007). The term "advanced" has usually been reserved for meditators with more than 20 years' experience (Arambula et al., 2001). Numerous studies conducted over the last 40 years with Western meditators, usually with less than 10 years' experience, have reported increased power and coherence in the alpha and theta frequency bands during meditation practice (Cahn and Polich, 2006). Striking increases in gamma band power have also been reported in studies with "advanced" Buddhist monks as meditators (Lehmann et al., 2001; Lutz et al., 2004). A recent study also found significantly increased gamma power at parieto-occipital electrodes in a group of "advanced" Western Vipassana meditators (with mean 20 years' meditation experience—although the nature of that experience is undefined) engaged in a "mindfulness" body-scan meditation when compared to a deliberate mind-wandering instruction condition (Cahn et al., 2010).

Fell and colleagues proposed that meditators from different traditions progress through similar developmental stages, which are marked by changing EEG frequency patterns (Fell et al., 2010). Initial expertise is reflected in changes in slower (specifically theta and alpha) frequency bands, but these effects are not considered to be meditation-specific. The authors propose that an "advanced" stage, only reached by experts, is marked by increased synchronized (fast) gamma band activity, related to "processes of cortical restructuring and learning" which facilitate "specific meditation-related states of consciousness," with unique electrophysiological signatures.

A recent focus in EEG and brain imaging meditation studies has been on the pivotal role of the modulation of the "default mode network" (DMN) in the understanding of meditation training effects (Brewer et al., 2011; Berkovich-Ohana et al., 2012; Malinowski, 2013). This neural network is considered to be active when effortful attention is not required to direct responses to the external environment. Anatomically the DMN consists of two major interacting subsystems defined by the cluster of activations and functional connections around medial prefrontal and medial parietal hubs, respectively (Buckner et al., 2008). A series of both EEG and fMRI studies have converged on the finding of reduced activity in these major hubs of the DMN during Buddhist and/or mindfulness meditation practice (Farb et al., 2007; Hölzel et al., 2007; Berkovich-Ohana et al., 2012). The DMN is known to be activated by spontaneous self-related mentation, directed to either the future or the past (Schooler et al., 2011), characteristic of distraction or mind wandering. Both Yoga and Buddhist meditation traditions[1] note the emergence and progressive resolution of distraction and mind wandering during the early phases of mediation training irrespective of content. Rather than belonging to the essence of states cultivated by respective meditation practices, current DMN findings may only reveal the expectable psychological effects of early steps in the process of learning to meditate.

Recent brain imaging techniques have begun to reveal training effects of a variety of meditations, across a range of practice periods, on the neuroplastic response of the brain in both gray matter and white matter structures (Lazar et al., 2005; Pagnoni and Cekic, 2007; Holzel et al., 2008, 2011; Luders et al., 2009, 2011, 2012a,b; Vestergaard-Poulsen et al., 2009; Grant et al., 2010; Tang et al., 2010; Murakami et al., 2012; Kang et al., 2013; Leung et al., 2013). In EEG studies Berkovich-Ohana et al. (2012) found significantly greater gamma-band activity at rest in mindfulness meditators than controls in a cluster of electrodes in the right parieto-occipital region and the reverse in a cluster of electrodes in the right frontal region, however no significant relationship was reported for these measures with meditation experience within the mindfulness meditation group. Cahn et al. (2010) found gamma power at occipital electrodes increased significantly from rest to "vipassana meditation" in those with greater than 10 years of daily practice but only marginally in those with less than 10 years of daily practice. Although their findings vary widely (as might be expected from their methodological differences) these studies point to the importance of evaluating both the long-term impact of specific meditation practices and the way in which that impact unfolds over time. Understanding these medium and longer term changes may require a focus beyond the role of the DMN.

Within the Yoga tradition sequential stages in the development of meditation proficiency are delineated in the "eight-fold" path of Patanjali's Yoga Sutras (Radhakrishnan, 1999). Following four "external" stages, the practitioner progresses through the "internal" stages of "*pratyahara*" (sense withdrawal), "*dharana*" (concentration), "*dhyana*" (absorption), and finally "*samadhi*" (self-realization). Repeated experience of these states during meditation practice leads to a long-term progressive refinement in the "sense of self" (*asmita*). One's self-identity becomes progressively detached from identification with externally-oriented perceptions, then from identification with the body, then from identification with thoughts, to absorption in the object of meditation in *samadhi*. The process has been likened to peeling the skins from an onion (Maheshwarananda, 2005). However, the electrophysiological changes corresponding to such a developmental sequence will not be evident within current cross-sectional designs comparing only short-term and non-meditators or short-term and long-term meditators. While longitudinal studies are ideal, as a first step it is necessary to track the transition between medium term and long term effects of Yoga meditation training.

The present study made use of the long period of establishment of Satyananda Yoga in Australia for the availability of "advanced" Western practitioners with over 30 years' experience. The study compared "advanced" Australian Satyananda Yoga teachers (SYT) with students studying to become SYT (having an intermediate level of experience). Two meditation practices were used for the study. The first "*kaya sthairyam*" is a preparatory body-steadiness practice designed to take the practitioner into the "*pratyahara*" stage (withdrawal of the mind from the external world). The second practice "*japa*" uses mental repetition of a personal mantra to move from "*pratyahara*" to the "*dharana*" stage (a focussed internal awareness of the mantra). Advanced practitioners may progress further to "*dhyana*" (absorption in the mantra) or even "*samadhi*" in this practice (Saraswati, 1983). Based on this tradition, we hypothesized that student meditators are more likely to experience sense withdrawal; the advanced practitioners are more likely to progress to the later stages when engaged in these practices.

In keeping with results from moderately experienced Western meditators and the demands of sensory inhibition, we hypothesized firstly that the Satyananda students (with an intermediate level of meditation practice) would show more EEG activity in the lower frequency bands (theta, alpha1, and alpha2). It was expected that this activity would be higher in the students than in the SYT group as a consequence of the teachers' development beyond this stage of practice. Secondly, it was expected that the SYT would show greater activity in the higher frequency bands (beta and gamma) compared to the Satyananda Yoga student group in both meditation conditions. Thirdly, extended practice (spanning years) in both student and teacher groups was expected to result in enhanced neural connectivity and thus trait activation in networks habitually activated in each group during meditation outside the context of meditation itself. Fourth and

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[1] In the present study Buddhist and Yoga meditation practices are neither assumed to be equivalent nor different at a neurophysiological and/or psychological level, rather this is something to be established by empirical investigation.

finally, to the extent that Yoga meditation practices engender similar DMN changes to the Buddhist-mindfulness practices recently investigated by meditation researchers, it was expected that the cortical foci of these length of practice differences would lie in the anterior and posterior midline hubs of the DMN at least during active meditation practice[2].

MATERIALS AND METHODS

PARTICIPANTS

Twelve Satyananda Yoga practitioners (teachers and students) were recruited for the study from the Satyananda Yoga Academy in Mangrove Creek, NSW, Australia by the first author. At the time of the study, he was a resident lecturer at the Academy. In his sixties, he is a *karma sannyasin* disciple of Swam Satyananda of Munger, India. Participants were recruited initially by direct contact for a qualitative study of meditation. Following that study, participants for the EEG study were selected from suitable volunteers. All the teachers had received initiation as *sannyasin* disciples of Swami Satyananda and had been regular meditators for over 20 years. The student group was studying an accredited course to qualify as SYT. All participants had received a personal mantra from their guru (Swami Satyananda or his successor, Swami Niranjanananda), which they used in this study. In pre-study interviews, all reported they were free from medical, psychiatric, or drug usage issues that might alter their brain functioning.

The participants were divided into two groups—SYT, three male and three female, age range from 44 to 63 years (mean = 54 years, $SD = 6.5$ years) and Satyananda Yoga students (SYS), three male and three female trainee Yoga teachers, age range 30–51 years (mean = 42 years, $SD = 8.0$ years). The teacher group was significantly older [$t_{(11)} = 2.90$, one-tailed, $p < 0.05$]. The SYT group had a mean of 30 years regular practice (range: 24–37 years) and the SYS group a mean of 4 years (range: 3–5 years). Based on an average of 1 h regular practice a day, this would equate to a mean of 11,000 h for the SYT group and 1500 h for the SYS group.

SETTING

The study was conducted in a small meditation room at the Satyananda Yoga Academy to provide an "ecologically valid" situation conducive to the attainment of deep meditation states. After being fitted with the Compumedics 32 channel EEG "Quik Cap," participants sat in their usual cross-legged meditation position on the floor, supported by cushions, with the room dimly lit by a candle on a meditation table. The small battery-operated Compumedics "Siesta 802" recording unit attached to the "Quik Cap" was the only electronic device in the meditation room. This unit transmitted signals by radio to a laptop computer in an adjacent room.

PROCEDURE

To obtain the most authentic meditation experience possible, the sequence of conditions was selected to resemble the practitioners' usual meditation practices. We considered that a design incorporating a counterbalanced order of conditions would introduce a conflict with traditional practice, as *kaya stairyam* would usually precede but not follow *japa* (Saraswati, 1981). Following the mental calculation condition, the participants performed four meditation practices in the same order (for brevity only the first two of these are reported here).

The experimental conditions were:

- Non-meditation condition—"Calculation"—mentally counting backwards from 200 by 4 s—(5 min).
- Meditation 1—"Body-steadiness"—Satyananda Yoga practice "*kaya stairyam*"—awareness focused on body-steadiness and awareness of flow of the natural breath—(5 min).
- Meditation 2—"Mantra"—Satyananda Yoga practice "*japa*"—mental repetition of personal mantra, using mala (beads). The mantra consisted of a short Sanskrit phrase—(10 min) (Saraswati, 1981).

All conditions were performed, sitting in cross-legged meditation posture, with eyes closed. Self-report ratings of "meditation depth" for each condition were obtained immediately following the EEG recording. These ratings were made on a ten-point visual analog scale, based on the "Meditation Depth Questionnaire" of Ulrich Ott (2001). The zero point was "no meditation state" and ten was "deepest meditation I have experienced."

The study was approved by the RMIT University Human Research Ethics Committee.

EEG DATA COLLECTION

EEG signals were obtained using a Compumedics "Quik Cap" from 25 scalp electrodes, based on the International 10/20 system, referenced to left mastoid. Electrodes were placed at FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, Oz, TP7, TP8, CP3, CP4, FC3. Four additional channels were allocated to eye movement detection, with electrodes positioned on the outer canthi of each eye and above and below the left eye. The sampling rate was 256 Hz. Data was acquired via radio signal to a laptop computer running Compumedics Profusion EEG software.

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[2] The research reported here formed part of the Ph.D. thesis of the first author, supervised by the second and third authors. Following the framework of Cahn and Polich (2006) the thesis sought to determine expected trait (length of practice) effects, state (meditation vs. non-meditation) effects and state by trait interaction effects of Yoga meditation practice in EEG cortical source activity. Specific trait expectations (see above) were principally based upon the work of Farb et al. (2007) (for cortical regions) and Fell et al. (2010) (for frequency bands) and it is the results pertaining to these hypotheses that are reported here. It was expected that state effects would be found in higher high (i.e. gamma) frequency source activity in cortical regions specialized in processing the different contents of specific meditations (e.g., bilateral parietal and somatosensory cortex for body scan and left inferior frontal gyrus for mantra) during those specific meditations as compared to the non-meditation condition. Following the person by situation interactionist approach in personality psychology it was expected that state by trait interaction (as distinct from additive) effects would be highly significant (and informative) although the specific form of those effects was not predicted. Neither the expected state nor state by trait interaction effects were found. We consider these null findings to be highly informative (although beyond the scope of the current report) and they have reorientated our perspective to focus on the understanding of trait changes arising over the long term time course of meditation practice.

EEG DATA PRE-PROCESSING

Following the recording session, the data was exported from the Profusion EEG in EDF format for input into the EEGlab (Delorme and Makeig, 2004) program running in Matlab. Data was preprocessed through the FASTER algorithm (Nolan et al., 2010) which employs independent components analysis (ICA) to identify and remove both physiological (eye movements/blinks, muscle movement, skin potentials) and non-physiological (electromagnetic interference, electrode pop offs and drift, shifting electrodes and residual white noise) sources of artifact from the recorded EEG. FASTER interpolated missing or bad channels, re-referenced to the common average and applied a bandpass filter of 1–45 Hz to remove drift and further high frequency artifacts. FASTER detects and removes ICA components with properties uncharacteristic of cortical signals or conversely with properties characteristic of specific artifact sources. Z-score thresholds for rejecting artifactual components were set at 3.0 (except for eye movement, which was set at a threshold of 1.8). EEGLAB version 9 (Delorme and Makeig, 2004) was employed for criterion-based artifact rejection of epochs with values greater than ±75 mV. The recorded EEG was then subject to visual inspection as a final check of artifact removal.

Ten sample epochs, each of 5 s duration, were extracted for the first 5 min of each condition for each participant from the cleaned datasets, commencing 100 s from the start of the practice and then at 20 s intervals. If a selected epoch showed residual artifacts on visual inspection, the subsequent 5 s epoch was selected. The epochs were analyzed using a user defined frequency allocation into bands of: delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta (12–25 Hz), and gamma (25–42 Hz).

Precautions were taken to ensure the gamma band analysis was not confounded by electromyographic (EMG) muscle activity or eye-saccades artifacts. All conditions were conducted with eyes-closed. Each epoch was visually inspected for artifacts and the cut-off frequency for gamma was set well below the EMG frequency range, which peaks at 70–80 Hz (Lutz et al., 2004).

EEG SOURCE ANALYSIS

Based on the scalp-recorded electric potential distribution, the exact low resolution brain electromagnetic tomography (eLORETA) software (publicly available free academic software at http://www.uzh.ch/keyinst/loreta.htm) was used to compute the cortical three-dimensional distribution of current source density (CSD). The eLORETA method is a discrete, three-dimensional (3D) distributed, linear, weighted minimum norm inverse solution. The particular weights used in eLORETA endow the tomography with the property of exact localization to test point sources, yielding images of current density with exact localization but low spatial resolution (neighboring neuronal sources will be highly correlated). The description of the method together with the proof of its exact zero-error localization property, are described in two papers by Pascual-Marqui (2007, 2009). It is important to note that eLORETA has no localization bias even in the presence of structured noise which constitutes an improvement over the previous tomographies of LORETA (Pascual-Marqui et al., 1994) and the standardized version sLORETA (Pascual-Marqui, 2002). It is important in the context of assessing length of practice related differences in anterior and posterior hubs of the DMN that activity in these deep structures can be correctly localized with these methods (Pizzagalli et al., 2001; Zumsteg et al., 2006).

Current eLORETA computations were made using a realistic head model (Fuchs et al., 2002), using the MNI152 template (Mazziotta et al., 2001), with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). Standard electrode positions on the MNI152 scalp were taken from Jurcak et al. (2007) and from Oostenveld and Praamstra (2001). The intracerebral volume is partitioned in 6239 voxels of $5 \times 5 \times 5\,\text{mm}^3$ spatial resolution. These eLORETA images represent the electric activity at each voxel in Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels and/or Brodmann areas are reported using MNI space, with correction to Talairach space (Brett et al., 2002).

The KEY Institute eLORETA software package was used to perform these statistical analyses. The methodology used is non-parametric. It is based on estimating, via randomized permutation testing, the empirical probability distribution for the value of the maximum statistic across all voxels under the null hypothesis. This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all discrete frequencies). Due to the non-parametric nature of the method, its validity need not rely on any assumption of Gaussianity. The reader is referred to Nichols and Holmes (2002) for a detailed overview of this methodology.

RESULTS

SUBJECTIVE RATINGS

The subjective reports of "meditation depth" are shown in **Figure 1**. A low level of "meditation depth" was reported in the non-meditation (Calculation) condition, with increasing depth reported with progression through the meditation conditions. The highest rating for meditation depth was for Meditation 2 (Mantra), although this may include a duration effect. The reported levels of ratings were similar between the groups, but with slightly higher levels for the student group (SYS) than the teacher group (SYT).

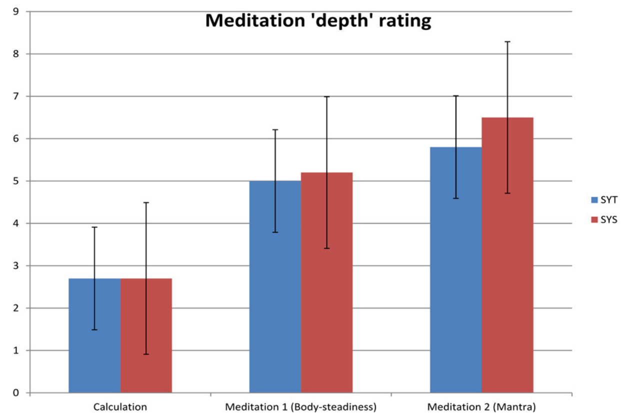

FIGURE 1 | Subjective ratings of meditation "depth."

COMPARISON OF GROUPS ACROSS CONDITIONS

We conducted a single test for CSD differences between SYS and SYT groups including all frequency bands (delta, theta, alpha1, alpha2, beta, and gamma). Voxel by voxel the between group log F ratio (equivalent to a t-test statistic) was calculated for each frequency band considered simultaneously, resulting in 6239×6 comparisons. Following the procedure of Nichols and Holmes (2002) implemented in the KEY Institute eLORETA software package, we applied 5000 random permutations to calculate the distribution of the F-max voxel statistic (the maximum F-value for the full voxel set). The resulting distribution establishes the threshold for significance of the F statistic obtained at individual voxels in a way which controls for the family-wise error rate due to multiple testing. The p-values presented below represent the probability of the obtained F statistic at each voxel under the null hypothesis while simultaneously correcting for multiple testing.

Tables 1–3 show for each frequency band the region, Brodmann area (BA), Tailairach coordinates and the (absolute) maximum voxel F statistic or statistical difference between SYT and SYS groups and total number of significant voxels (two tailed threshold) for Meditation 1 (Body-steadiness), Meditation 2 (Mantra), and the non-meditation condition (Calculation), respectively.

DIFFERENCES BETWEEN GROUPS ON SOURCE ACTIVATION FREQUENCY AND LOCATION IN MEDITATION CONDITIONS

The two meditation conditions showed a similar pattern, the SYS (intermediate group) having voxels with significantly higher CSD in the lower frequencies (theta, alpha1) and the SYT (advanced group) having voxels with significantly higher CSD in the higher frequencies (beta, gamma). The SYS group had significantly higher CSD voxels in the alpha2 band in Meditation 1 (Body-steadiness) but not Meditation 2 (Mantra). No significant voxel differences were found in either meditation condition in the delta band.

For the SYS group compared to the SYT group the greatest number of voxels with significantly higher CSD values were

Table 1 | SYT > SYS comparison for Meditation 1—(Body-steadiness).

Band	Max/min region	Lobe	Max/min BA	Tailairach coordinates	Max/min F-value	No. of voxels $p < 0.05$
Delta	Inf parietal lobule	Parietal	R40	40, −40, 60	−0.729 ns	
Theta	Inf parietal lobule	Parietal	R40	45, −45, 60	−1.32**	490
Alpha1	Precentral gyrus	Frontal	R4	55, −10, 45	−2.01**	1827
Alpha2	Inf parietal lobule	Parietal	R1	45, −30, 65	−1.08*	30
Beta	Sub−gyral	Temporal	R20	40, −10, −25	1.03*	33
Gamma	Fusiform gyrus	Temporal	R20	40, −15, −30	1.65**	1631

*$p < 0.05$, **$p < 0.01$.

Table 2 | SYT > SYS comparison for Meditation 2—(Mantra).

Band	Max/min region	Lobe	Max/min BA	Tailairach coordinates	Max/min F-value	No. of voxels $p < 0.05$
Delta	Ant cingulate	Limbic	L32	−10, 35, −5	0.822 ns	
Theta	Inf parietal lobule	Parietal	R40	50, −50, 55	−1.52**	613
Alpha1	Precentral gyrus	Frontal	R4	50, −10, 50	−1.97**	1676
Alpha2	Sup temp gyrus	Temporal	R22	45, −20, 0	1.10 ns	
Beta	Rectal gyrus	Frontal	L11	−10, 40, −25	1.30*	917
Gamma	Insula	Sub−lobar	R13	30, 20, 15	1.92**	2092

*$p < 0.05$, **$p < 0.01$.

Table 3 | SYT > SYS comparison for control condition (Mental calculation).

Band	Max/min region	Lobe	Max/min BA	Tailairach coordinates	Max/min F-value	No. of voxels $p < 0.05$
Delta	Sup temp gyrus	Temporal	R41	55, −25, 5	−1.72**	390
Theta	Sup temp gyrus	Temporal	R22	65, −20, 0	−1.07 ns	
Alpha1	Precentral gyrus	Frontal	R6	45, −10, 40	−1.96**	856
Alpha2	Inf parietal lobule	Parietal	R40	50, −50, 55	−1.43*	123
Beta	Sub−gyral	Temporal	L20	−45, −10, −25	1.07 ns	
Gamma	Fusiform gyrus	Temporal	R20	40, −15, −30	1.52*	85

*$p < 0.05$, **$p < 0.01$.

Positive value for F indicates SYT shows higher CSD than STS, negative value for F indicates SYS has higher CSD than SYT.

in the alpha1 band, predominantly in the right hemisphere. For both meditation practices, the three Brodmann areas in which the highest alpha1 voxel *F*-values were located were, in rank order of that statistic, right BA4 (precentral gyrus), BA6 (precentral gyrus), and BA3 (primary somatosensory cortex). (See **Figures 2**, **3**).

For the SYT group compared to the SYS group, the greatest number of voxels with significantly higher CSD occurred in the gamma band, predominantly in the right hemisphere. In Meditation 1 (Body-steadiness), the highest voxel statistic values were located in right BA20 (fusiform gyrus), BA21 (middle temporal gyrus), BA13 (insula), BA38 (the anterior pole of the temporal lobe). In Meditation 2 (Mantra), the highest voxel statistic values were located in right BA13 (insula), BA45, and BA47 (inferior prefrontal gyrus). (See **Figures 5**, **6**).

DIFFERENCES BETWEEN GROUPS ON SOURCE ACTIVATION FREQUENCY AND LOCATION IN CALCULATION CONDITION

Significant differences were found for voxels across the delta, alpha1, alpha2, and gamma frequency bands, with the SYS group showing significantly higher CSD voxels than the SYT group in delta, alpha1, and alpha2 bands. In these low frequencies, the locations of significant voxels were entirely in the right hemisphere, the voxels with the highest *F*-values being located in rank order in right BA41, 22, 21 in delta; in right BA6, 4, 3 in alpha1; and in right BA40, 7, 19 in alpha2. (See **Figure 4** for alpha1).

In the high frequency gamma band, the SYT group showed voxels with significantly more CSD than the SYS group. Once again these voxels were found entirely in the right hemisphere, the voxels with the highest *F*-values being located in rank order in right BA20, 13, 21. (See **Figure 7** for gamma).

CORTICAL SOURCES OF DIFFERENCES BETWEEN GROUPS IN HIGH AND LOW FREQUENCY BANDS

Across all conditions the number of significant differences was consistently greatest in the gamma band for the high frequencies and the alpha1 band for the low frequencies (highlighted in **Tables 1–3** above). In order to examine the specific regional pattern of these high and low frequency group differences, the number of significant voxels in each (right and left) Brodmann Area are presented for each experimental condition in the alpha1 band and gamma bands in **Tables 4**, **5**.

DISCUSSION

HYPOTHESES 1 AND 2

The first prediction that during Yoga meditation student (trainee-teacher) meditators would show greater CSD in the low frequency bands was supported in the theta, alpha1 and alpha2

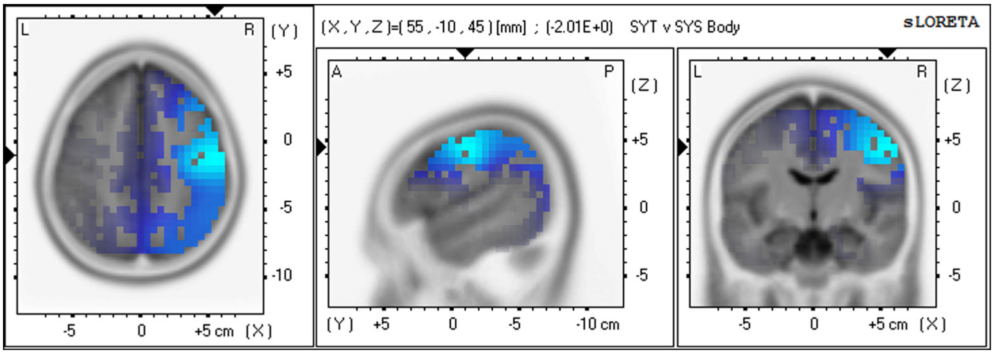

FIGURE 2 | Differences in CSD between groups in alpha1 band—Meditation 1 (Body-steadiness) Increased alpha1 activity (blue) in SYS compared to SYT in right BA4 (precentral gyrus).

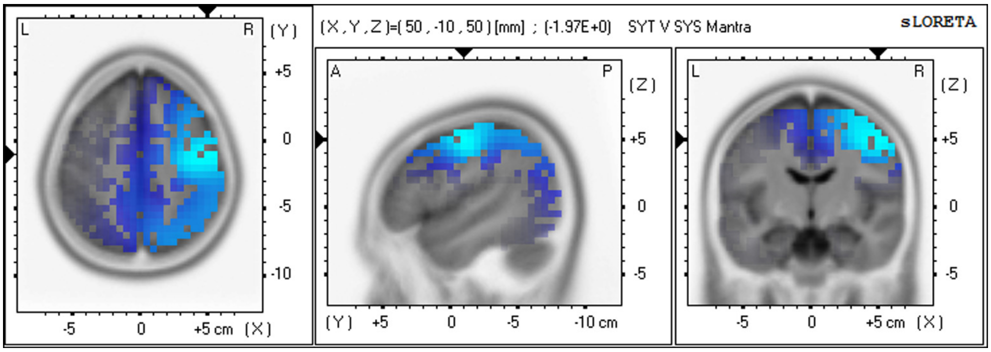

FIGURE 3 | Differences in CSD between groups in alpha1 band—Meditation 2 (Mantra) Increased alpha1 activity (blue) in SYS compared to SYT in right BA4 (precentral gyrus).

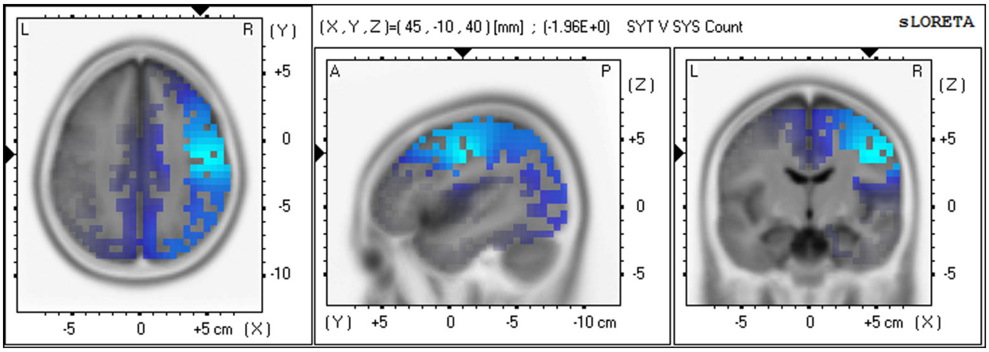

FIGURE 4 | Differences in CSD between groups in alpha1 band—Non-meditation (Calculation) Increased alpha1 activity (blue) in SYS compared to SYT in right BA6 (precentral gyrus).

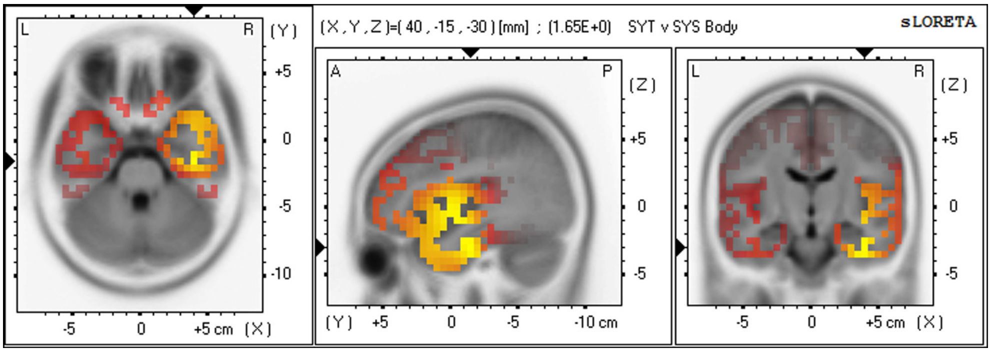

FIGURE 5 | Differences in CSD between groups in gamma band in Meditation 1 (Body-steadiness) Increased gamma activity (yellow) in SYT compared to SYS in right BA20 (fusiform gyrus).

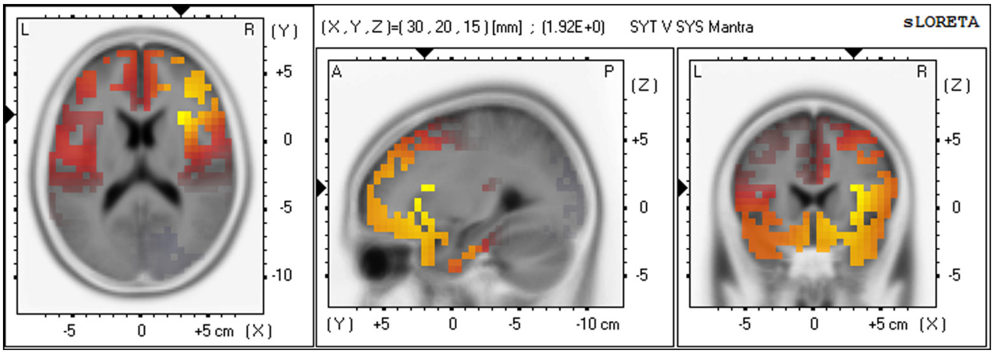

FIGURE 6 | Differences in CSD between groups in gamma band in Meditation 2 (Mantra) Increased gamma activity (yellow) in SYT compared to SYS in right BA13 (insula).

bands for Meditation 1 (Body-steadiness) and theta and alpha 1 for Meditation 2 (Mantra). In both meditations the number of significant voxels at the lower frequencies was overwhelmingly greatest in the alpha1 band (See **Tables 1**, **2**).

The second prediction that advanced practitioners would show greater CSD in the high frequency bands was supported for beta and gamma frequency bands in both meditation conditions. For the higher frequencies the number of significant voxels was overwhelmingly greatest in the gamma band (See **Tables 1**, **2**). This is the first study to show enhanced gamma band activation in advanced Western meditators practicing in the Yoga tradition, compared to less experienced practitioners.

More broadly the *F*-max voxel values for SYT vs. SYS were negative for all low frequencies (delta to alpha2) in all experimental conditions (including mental calculation) and positive for all higher frequency bands (beta and gamma), (See **Tables 1–3**).

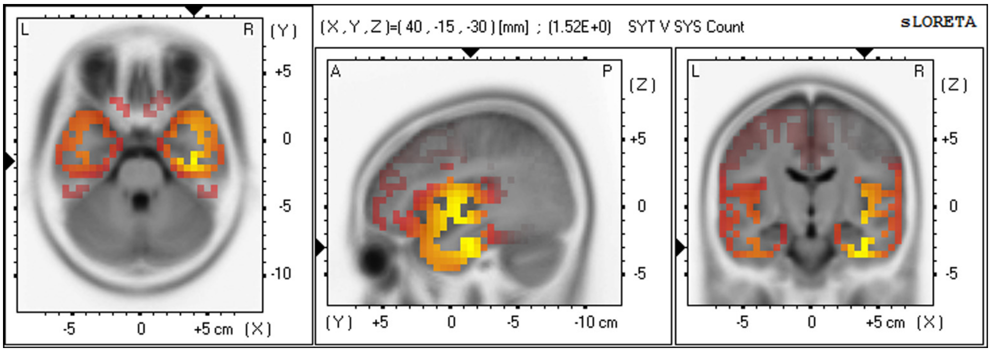

FIGURE 7 | Differences in CSD between groups in gamma band in Non-meditation (Calculation) Increased gamma activity (yellow) in SYT compared to SYS in right BA20 (fusiform gyrus).

It appears then that patterns of increased (low frequency) EEG activity in Yoga meditation students are consistent with the tradition based expectations of pratyahara (somatosensory withdrawal), evidenced by significantly greater low frequency activity corresponding to inhibition of cortical processing, in those regions mediating external sensory and motor processing. By contrast, patterns of increased (high frequency) EEG activity in advanced Yoga teachers most likely correspond to activity in brain regions recruited in the conscious states of concentration and absorption, which emerge in advanced practitioners.

While the relationship of the neural networks engaged by meditation practice and hypnotic induction remains to be determined it is intriguing to note that a recent study of the neurophenomenology of neutral hypnosis (what some would term trance) found that for those with high hypnotic susceptibility self-reported hypnotic depth correlated significantly with EEG activity measures uniquely in beta and gamma band frequency ranges (Cardeña et al., 2013). At the same time the high (but not low or medium) susceptible group reported spontaneous exceptional experiences of positive affect and/or self-transcendence.

HYPOTHESES 3 AND 4

Tables 4, **5** show that for the alpha1 and gamma bands, respectively, only right hemisphere Brodmann Areas show significant differences between SYT and SYS in the non-meditation (counting backwards by four) condition. Looking across the rows of these tables these same regions are also found to have the greatest number of significant voxels in the "Body-steadiness" and "Mantra" meditation conditions (typically with a greatly increased number of significant voxels). We interpret this pattern as support for our third prediction of trait differences in baseline neural activity brought about by long term meditation practice in those regions most engaged by this practice. We further interpret these findings as evidence for a core right-sided (rather than midline) network (or networks if the alpha1 and gamma results are considered separately) that is progressively modulated over the course of Yoga meditation practice. The predominantly right lateralized location of the cortical sources where activation differentiates between the STS and SYT groups can be observed for both alpha1 and gamma in each of the experimental conditions in **Figures 2**, **3**, **5**, **6**. Thus, in the case of Yoga meditation practice (as distinct from recent studies of mindfulness/Buddhist meditation practices) the midline nodes of the DMN, although included in regions of significant voxel differences, do not appear to be a principal locus of practice-related changes in cortical activity (contradicting the fourth prediction above). Our result also differs from the CSD changes in midline DMN structures recently reported in "concentrative" (breath-focused) meditation with "intermediate level" (mean 4 years) practitioners of unspecified tradition compared to controls (Lavallee et al., 2011). It also suggests an important difference (in advanced meditators) with the neutral hypnotic state in so much as hypnotic induction has been found to reduce (fMRI measured) anterior DMN activity in high hypnotically susceptible participants (McGeown et al., 2009).

REGIONAL DIFFERENCES IN EXPERIMENTAL CONDITIONS RELATED TO YOGA MEDITATION PROFICIENCY ALPHA1 BAND

In the alpha1 band, significant voxel differences always showed greater activity in the student than the teacher meditators. In all conditions, the most significant voxel *F*-values were always located in the right somatosensory (BA1, 2, 3, 5), motor (BA4) and premotor cortex (BA6). In the mental calculation condition, a core network of right sided regions can be identified. This was comprised, in addition to those regions identified immediately above, of right occipital (BA17, 18, 19), right parietal (BA7, 39, 40) and right superior frontal gyrus (BA8, 9). These same regions remain the core of the most significant proficiency related differences in both meditation conditions. The key changes are an increase in the number of significant voxels recruited in each region and a spread of significant voxels to the homologous left sided Brodmann Areas, while always retaining a strong imbalance toward right sided voxels (see **Table 4**). Following current models of the functional role of task related topographic differences in alpha band activity, these effects may be interpreted as trained task specific patterns of functional cortical inhibition (Klimesch et al., 2007). Such an interpretation of present alpha1 findings fits remarkably closely with the specific effects of the inhibitory thalamo-cortical mechanism proposed by Austin (2013) to account for states of deep absorption corresponding to Yoga meditation practices. However, in Austin's model these effects would be expected to be greatest in advanced rather than intermediate practitioners.

Table 4 | Number of significant voxels in each Brodmann Area for each condition in alpha1 band.

No. signif voxels	Alpha1 band (8–10 Hz)				SYS > SYT	
BA	Calculation		Body		Mantra	
	L	R	L	R	L	R
1		9		9		9
2		47		49	2	53
3		59	12	72	17	70
4		54	12	63	13	61
5		12	27	50	32	50
6		170	38	265	84	267
7		130	92	208	113	208
8		33		64	1	76
9		55		84		69
17		8		40		13
18		25		158		48
19		64	6	145	2	98
23		3		6		2
24		1		34	14	44
30		1		18		6
31		12	12	90	27	69
32		1		12	2	20
37				14		3
39		28		58		55
40		143		163	3	149
43				3		
44				3		
45		1		6		1
46				4		
Total	0	856	199	1627	310	1371

Brodmann areas with no voxels omitted from table.

Table 5 | Number of significant voxels in each Brodmann Area for each condition in gamma band.

No. signif voxels	Gamma band (25–42 Hz)				SYT > SYS	
BA	Calculation		Body		Mantra	
	L	R	L	R	L	R
4			2	7	4	5
6		1	7	46	9	55
8					4	85
9				22	16	135
10			14	109	133	135
11			101	122	115	122
13		28	51	143	83	79
20		22	56	86	69	50
21		7	40	108	71	45
22		10	34	75	48	27
24			2	3	5	14
25			15	22	16	27
28			10	18	17	18
32			10	24	30	59
34		1	8	16	17	16
35			2	5	3	6
36		1	6	11	9	8
38		9	76	88	76	88
40				6	1	
41				20	10	
42				17		
43			5	12		
44		5	6	28	43	28
45				34	16	34
46				25	13	25
47			97	113	107	113
Total	0	84	542	1162	915	1175

Brodmann areas with no voxels omitted from table.

GAMMA BAND

In the gamma band, significant voxel differences always showed greater activity in the teacher than the student meditators. In the non-meditation (mental calculation) condition all significant voxel differences were found in the right anterior temporal lobe (principally BA20, 21, 22, 38) and right ventral prefrontal cortex (principally BA13 and BA44). All these regions showed a great expansion of significant voxel counts in the body-steadiness and mantra meditations.

In the "Body-steadiness" meditation, 1704 out of a possible 6239 cortical voxels showed significant proficiency differences and in the "Mantra" meditation this rose to 2090 significant voxel differences. A right sided bias continued to be observed for both meditations but was much less extreme than in the alpha1 band. Additional regions showed significant greater CSD in gamma for the long term meditators in both meditations (principally in BA10, 11, 45, 47) (see **Table 5**).

This result adds to the converging lines of enquiry regarding the role of meditation-specific increases in gamma band activity in "advanced" practitioners, adding evidence from Western meditators practicing in an integral Yoga spiritual tradition. The teacher group in this study (mean experience 30 years) displayed striking increases in gamma band activity similar to studies of "advanced" Tibetan Buddhist meditators (Lutz et al., 2004) and Western Buddhist Vipassana meditators with mean experience 20 years (Cahn et al., 2010). Although those studies did not estimate the activity of cortical sources, the high level of gamma activity during meditation in advanced practitioners requires widespread synchronization throughout extensive cortico-cortico and cortico-thalamic neural networks (Lutz et al., 2004).

In Meditation 1, the "Body-steadiness" meditation, the most significant voxel differences were located in the right anterior temporal lobe and the insula. This result aligns with that of an advanced Tibetan Buddhist meditator showing increased gamma activity in right mid temporal gyrus (BA21) in the comparisons of sensory-focused "visualization" meditation vs. the verbal-focussed "mantra" meditation and also in a "self-reconstruction" vs. "self-dissolution" meditation (Lehmann et al., 2001). In Meditation 2, the "Mantra" meditation, the most significant sources were located in the right insula and right inferior frontal gyrus. The right insula has been linked with a more detached and objective awareness of interoceptive sensory events (Farb et al., 2007) involved in the shift from "narrative" to "experiential" self-awareness. Deen et al. (2011) identify three distinct clusters of functional connectivity with network hubs in posterior, mid, and anterior insula, respectively, suggesting that a further parcelation of anatomical and function subregions within the insula will be required to fully understand the role (or roles) it plays in Yoga and Buddhist tradition meditative states. It may be of note that a major white fiber tract, the uncinated fasciculis, mediates bidirectional connections between the high level association cortex of the anterior temporal lobe and the inferior frontal gyrus (Von der Heide et al., 2013), the only such structure which continues to develop beyond the age of 30 (Lebel et al., 2008).

STRENGTHS OF THIS STUDY

A strength of this study is the advanced level of meditation experience in a sample of Western Yoga practitioners following an identical spiritual tradition. All of the "advanced" group were *sannyasin* (initiated) disciples of Swami Satyananda who had spent considerable time in ashrams, both in Australia and India. They were all Yoga teachers. Studies reporting results from large groups of advanced meditation practitioners often combine meditators from different traditions into a single experimental group. Such differences are not considered equivalent by the members of these traditions themselves and any such equivalence must be demonstrated rather than assumed. We have chosen not to make this assumption even at the cost of a lower sample size in order to maintain the validity of our analysis. A further strength was the attention given to preserving the ecological validity of the meditation states attained, the study being conducted in a meditation setting conducive to the participants' usual practice. The intrusion of equipment into this setting was minimized, with the EEG cap and small radio transmitter being the only items in the meditation room.

As with all EEG source analysis methods, eLORETA results are highly susceptible to distortion by artifacts (Pizzagalli, 2007), therefore the quality of data preprocessing is essential to the validity of the results obtained. We adopted a recently developed (Nolan et al., 2010) ICA component rejection procedure for artifact cleaning developed by the Neural Engineering Group at Trinity College Dublin. This is one of a new generation of ICA artifact correction procedures which is guided by a series of objective component parameters rather than the momentary choice of the individual experimenter. We believe the effective utilization of this method for preparing large volumes of clean data was an essential factor contributing to the validity of this research. We strongly recommend the future adoption of this or similar method by related research programs.

LIMITATIONS OF THIS STUDY

Limitations of the study include the small sample size (although that did not prevent significant findings) and the potential confound due to significant age difference between the subject groups. A larger sample size is desirable to enhance the power and generalizability of the current results and would allow the additional possibility of parametric testing (Thatcher et al., 2005). However, the non-parametric statistical mapping method adopted here is well suited to the limitations of the current design and sample size. In fact, one of the worked examples offered by Nichols and Holmes (2002, p. 15) is a PET study with 12 subjects equally divided amongst 2 testing conditions which directly reflects the constraints of the present study. In addition the randomization distribution is known to be overly conservative when the effect is distributed, as occurs in the present results (Troendle, 1995). Therefore, we believe that there is a strong justification for reporting the group effects identified here.

EEG spectral power density changes dramatically with age until early adulthood. From that point changes are slow in healthy aging. Power in lower frequency bands (delta through alpha) decreases throughout this time period (Rossini et al., 2007). The age range of our subjects extends from 30 to 63, so it could be that significantly greater activity in the younger group in these lower bands is due to normal aging rather than years of meditation practice.

A comparison of the effects of normal aging to the presently observed differences between the SYS (younger) and SYT (older) studies of EEG spectral source changes across this part of the lifespan shows that delta decreases in occipital sources (Babiloni et al., 2006), but we only found significant delta differences in one condition (counting) and this was maximal in right BA41 (primary auditory cortex). In normal aging alpha1 and alpha2 decreases in occipital, parietal, temporal and limbic cortices (Babiloni et al., 2006). We found significantly lower alpha1 in occipital and parietal cortex but not in temporal or limbic cortex. Alpha also increases with age in frontal cortex (Basar, 2012) but we found significant alpha *decreases* in superior and middle frontal gyri in the older group and no significant differences in inferior frontal gyri. Once again, the pattern of our findings does not fit with what would be expected if they were due to normal aging.

Despite available data there is no clear evidence for changes due to normal aging through middle age in the high frequency bands. Therefore, we do not consider age differences to be a plausible alternative explanation for those high frequency effects. A confound due to the age difference between the groups fails to account for why the set of BA containing significantly greater low frequency voxel activation in the SYS group forms the complement to the set of BA containing significantly greater high frequency voxel activation in the SYT group. Nor does it explain why a core pattern found in the non-meditation Calculation condition is maintained but greatly expanded in the Body Scan and Mantra meditation conditions. Lutz et al. (2004), in a study with advanced and novice meditators with age means of 49 years and 21 years, found hours of practice, but not age, significantly predicted gamma in their baseline condition.

The additional analysis of age matched subgroups goes some way toward addressing this issue with significant *F*-max voxel findings in both alpha1 and gamma bands located in the same regions as the original group analysis. In this case the further reduced sample size points to the robustness of these effects. Notwithstanding these considerations practice related differences in age will be intrinsic to group membership whenever truly "advanced" (such as the 30 year group in the present study) are compared with medium term practice groups. Now that specific regions of interest have been identified parametric methods which enable statistical control of age effects present a viable option to address this issue in future (larger n) studies.

The density (number) of electrodes in the recording array also places limitations on the resolution of source localization (Pizzagalli, 2007). Dense array recordings are so far limited to laboratory settings, unlike the present study. However, successful validation studies of LORETA, sLORETA and eLORETA use only the original 19 electrodes of the 10–20 system (Pascual-Marqui et al., 2002). Particularly for non-evoked recording conditions, 19 channel recordings are considered adequate and are widely reported for the LORETA family of source analysis methods (Babiloni et al., 2014). By comparison, the current study employed 25 active recording electrodes. A further possible limitation was the fixed sequence of conditions rather than a systematically counterbalanced design. For investigation of deeper meditation states, the benefits of experimental manipulation of conditions and intrusive measuring instruments must be balanced by the need to obtain an authentic meditation experience.

CONCLUSION

This study is the first to report enhanced gamma band activation in advanced Western meditators practicing in the (Satyananda) Yoga tradition, compared to less experienced (intermediate) practitioners. It found significant differences in EEG frequency band sources between "experienced" (mean 4 years) and "advanced" (mean 30 years) meditators in two meditation conditions (Body-steadiness and Mantra) and a mental calculation condition. The findings, strongest in alpha1 and gamma bands, consistently support the frequency band hypothesis proposed by Fell et al. (2010) of enhanced low and high frequency band effects, respectively, for intermediate and advanced levels of meditation experience. It further adds a finding of increased gamma band activity in advanced western Yoga meditators to similar findings in advanced Buddhist meditators. In addition, the Body-steadiness meditation condition in the present study appears to have much in common with Buddhist mindfulness of breathing practice. Both practices direct awareness to the felt quality of bodily sensations. The present findings then call for much closer scrutiny of the distinction, at least in the long term, between the functional networks trained by concentrative and mindfulness meditation methods. Those regions which consistently differentiated between the groups in the low and high frequency bands across all meditation conditions showed similar (but reduced) differences in the non-meditation (counting backwards) condition.

This study extends previous EEG findings by estimating cortical gray matter sources for frequency band specific meditation training effects. The cortical loci of high and low frequency band meditation training effects are both specific and distinct. Approximately one third of available cortical gray matter voxels showed significantly greater gamma band activity in mantra meditation in advanced (SYT) than intermediate (SYS) meditators. Despite this, there is little overlap with those regions which show increased alpha1 in the student meditators. In fact the Brodmann areas in which significant voxel differences are found during meditation in the alpha1 (suggesting functional inhibition) and gamma bands (suggesting integration into consciousness) form almost absolute complement subsets of the full set of cytoarchitecturally defined gray matter regions. We propose that selective inhibition of a right lateralized network comprising visual, somatosensory and body-world self-representations corresponds to the earlier stages of sensory withdrawal and stripping away of the "outer" onion-like layers of self as described in traditional Yoga literature. The subsequent emergence of conscious states specific to advanced practitioners requires both the disengagement from these self-world representational systems and the development of widespread gamma synchronization throughout anterior temporal and ventral prefrontal cortical regions extending from a right sided core network incorporating anterior temporal lobe and insula.

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Nondirective meditation activates default mode network and areas associated with memory retrieval and emotional processing

Jian Xu[1], Alexandra Vik[2], Inge R. Groote[3], Jim Lagopoulos[4], Are Holen[5,6], Øyvind Ellingsen[7,8], Asta K. Håberg[1,5] and Svend Davanger[9]*

[1] Department of Medical Imaging, St. Olavs Hospital, Trondheim, Norway
[2] Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway
[3] Department of Psychology, University of Oslo, Oslo, Norway
[4] Clinical Research Unit, Brain and Mind Research Institute, University of Sydney, Sydney, NSW, Australia
[5] Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[6] Centre for Pain and Complex Disorders, St. Olavs Hospital, Trondheim, Norway
[7] Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[8] Department of Cardiology, St. Olavs Hospital, Trondheim, Norway
[9] Department of Anatomy, Institute of Basic Medical Science, University of Oslo, Oslo, Norway

Edited by:
Enrico Facco, University of Padua, Italy

Reviewed by:
Gaelle Desbordes, Boston University, USA
Maria Engström, Linköping University, Sweden
Annalena Venneri, University of Sheffield, UK

***Correspondence:**
Svend Davanger, Institute of Basic Medical Science, University of Oslo, PO Box 1105 Blindern, 0317 Oslo, Norway
e-mail: svend.davanger@medisin.uio.no

Nondirective meditation techniques are practiced with a relaxed focus of attention that permits spontaneously occurring thoughts, images, sensations, memories, and emotions to emerge and pass freely, without any expectation that mind wandering should abate. These techniques are thought to facilitate mental processing of emotional experiences, thereby contributing to wellness and stress management. The present study assessed brain activity by functional magnetic resonance imaging (fMRI) in 14 experienced practitioners of Acem meditation in two experimental conditions. In the first, nondirective meditation was compared to rest. Significantly increased activity was detected in areas associated with attention, mind wandering, retrieval of episodic memories, and emotional processing. In the second condition, participants carried out concentrative practicing of the same meditation technique, actively trying to avoid mind wandering. The contrast nondirective meditation > concentrative practicing was characterized by higher activity in the right medial temporal lobe (parahippocampal gyrus and amygdala). In conclusion, the present results support the notion that nondirective meditation, which permits mind wandering, involves more extensive activation of brain areas associated with episodic memories and emotional processing, than during concentrative practicing or regular rest.

Keywords: fMRI, meditation, attention, nondirective, brain, default mode network, mind wandering

INTRODUCTION

VOLITIONAL AND SPONTANEOUS ACTIVITIES IN MEDITATION

Many types of meditation used for stress management and health can be described as a cycle of volitional and spontaneous cognitive processes (Cardoso et al., 2004). Attention is intentionally focused on a suitable meditation object, such as mental repetition of a non-semantic meditation sound, sensations associated with breath or specific regions of the body, a physical or mental visual image, or by simply being aware of the shifting flow of inner experiences (Cardoso et al., 2004; Ospina et al., 2007). Focusing on the meditation object is typically interspersed with periods of mind wandering (Cardoso et al., 2004; Ospina et al., 2007; Hasenkamp et al., 2012), which has been defined as being absorbed in spontaneously occurring thoughts, images, sensations, memories, and emotions unrelated to current volitional activity, more or less without really being aware of it (Mason et al., 2007; Christoff et al., 2009). An example of this cognitive cycle is given in a detailed temporal study of meditation with focused attention on the breath (Hasenkamp et al., 2012). Functional magnetic resonance imaging (fMRI) was used to correlate brain activation with cognitive processes that describes the shifting between focusing on the meditation object and spontaneously occurring thought. Mind wandering was associated with activation of the default mode network as well as sensory and motor cortices and posterior insula. Becoming aware that the breath was completely out of the focus of attention was associated with activation of the salience network. Shifting back to the breath and sustaining the focus on it were associated with elements of the executive network (Hasenkamp et al., 2012).

DIFFERENT PERCEPTIONS OF MIND WANDERING

The function of spontaneous mental processes in meditation is controversial. How they are dealt with, depends on the type of practice (**Box 1–3**). In most mindfulness practices and many other techniques associated with Buddhist traditions, mind wandering is considered a distraction and a gateway to rumination, anxiety and depression (Sood and Jones, 2013). An ultimate goal of these methods is therefore to reduce mind wandering

Box 1 | Focused attention

Focused attention practices usually entail paying attention to the physical sensation of the breath wherever it is felt most strongly in the body, without trying to change it in any way. Whenever attention has wandered to something else, the meditator gently but firmly brings it back to the physical sensation of the breath (Brewer et al., 2011). Important aims of the practice are to quickly detect mind wandering and maintain attention more stably on the breath, eventually needing less effort in the task, and over time reducing emotional reactivity (Lutz et al., 2008b). Focused attention practices typically involve a relatively narrow field of focus. As a result, the ability to identify stimuli outside that field of focus may be reduced (Lutz et al., 2008b).

Box 2 | Open monitoring

Open monitoring practices (sometimes called choiceless awareness) are described as paying attention to whatever comes into ones awareness - whether it is a thought, emotion, or body sensation - just following it until something else emerges without trying to hold onto it or change it in any way (Brewer et al., 2011). Even though "effortful selection" or "grasping" of an object as primary focus is gradually replaced by "effortless sustaining of awareness without explicit selection," the core activity of the practice is to sustain attention with the shifting flow of experiences, sometimes detecting emotional tone as a background feature (Lutz et al., 2008b).

Box 3 | Nondirective meditation

In nondirective meditation practices, a relaxed focus of attention is established by effortless, mental repetition of a short sequence of syllables, which may either be a traditional mantra or a non-semantic meditation sound (Benson et al., 1975; Carrington et al., 1980; Ospina et al., 2007; Davanger et al., 2010; Travis and Shear, 2010). Whenever the meditator becomes aware that the focus of attention has shifted to mainly being occupied with spontaneously occurring thoughts, images, sensations, memories, or emotions, attention is gently and non-judgmentally redirected to repetition of the meditation sound. The aim of the practice is to increase the ability to accept and tolerate stressful and emotional experiences as a normal part of meditation as well as everyday life (Davanger et al., 2010). Attention is neither directed toward staying with the meditation object like in focused attention techniques nor directed toward observing the spontaneous flow of experiences like in open monitoring meditation (Lutz et al., 2008b). Consequently, such methods comprise a distinct style of practicing (Cahn and Polich, 2006; Ellingsen and Holen, 2008; Travis and Shear, 2010), that has previously been termed nondirective meditation, as the presence of spontaneously occurring thoughts, images, sensations, memories, and emotions is accepted without actively directing attention toward them or away from them (Ellingsen and Holen, 2008; Lagopoulos et al., 2009; Nesvold et al., 2011). Further details on Acem meditation and its background are provided in previous publications (Ellingsen and Holen, 2008; Davanger et al., 2010).

and its purported negative consequences (Brewer et al., 2011; Sood and Jones, 2013; Taylor et al., 2013). In contrast, some practices consider the spontaneous flow of inner experiences as part of the meditation process. Accepting mind wandering while practicing is a core element in the Relaxation Response, Transcendental Meditation, Clinically Standardized Meditation, and Acem Meditation (Benson et al., 1975; Carrington et al., 1980; Carrington, 1998; Ospina et al., 2007; Davanger et al., 2010; Travis and Shear, 2010). As described below, these techniques may be classified as nondirective, indicating less control of the process while practicing (**Box 3**). It has been proposed that types of meditation that allow spontaneous thoughts, images, sensations, memories, and emotions to emerge and pass freely without actively controlling or pursuing them, over time may reduce stress by increasing awareness and acceptance of emotionally charged experiences (Ellingsen and Holen, 2008; Lutz et al., 2008a; Davidson, 2010). This notion concurs with recent articles suggesting that mind wandering and activation of the default mode network in general may serve introspective and adaptive functions beyond rumination and daydreaming (Ottaviani et al., 2013). Potentially useful functions would include mental simulations, using autobiographical memory retrieval to envision the future and conceiving the perspective of others (Buckner et al., 2008; Andrews-Hanna, 2012). An interesting question is therefore whether type of meditation and mode of practicing might affect the extent of mind wandering and the pattern of default mode activation during meditation.

EXTENT OF MIND WANDERING

It is often assumed that mind wandering is reduced during meditation, and more so in practitioners with many years of experience. The evidence comes from a relatively small number of studies in which the extent of mind wandering was assessed by questionnaire. Self-reported mind wandering during meditation was less abundant in participants with long-term experience in "concentration" (focused attention on breath), "loving-kindness meditation" (exercise oriented toward enhancing unconditional, positive emotional states of kindness and compassion), and "choiceless awareness" (open monitoring of mind wandering) compared to inexperienced controls (Brewer et al., 2011; Hofmann et al., 2011). Self-reported time on task during "mindfulness of breathing" was higher in experienced than in inexperienced participants, indicating less mind wandering with training (Holzel et al., 2007). In contrast, there was no correlation between the number of button presses indicating epochs of mind wandering during focused attention on the breath with years of practice or with high vs. low practice groups (Hasenkamp et al., 2012). In this study, participants recorded an average of one mind wandering per 80 s over a 20-min fMRI session, by pressing a button whenever they realized that their mind had wandered completely away from the breath.

DEFAULT MODE NETWORK ACTIVATION

Many concepts of how meditation affects mind wandering derive from its association with the default mode network. A number of imaging studies have shown that a system of cortical areas increase their activation when the brain is not engaged in an externally defined task, and that the magnitude of increase correlates with the extent of mind wandering (Mason et al., 2007; Buckner et al., 2008). Although some variation occurs, the default network mostly includes medial brain structures, i.e., the ventral medial prefrontal cortex, the posterior cingulate/retrosplenial cortex, the inferior parietal lobe, the lateral temporal cortex, the dorsal medial prefrontal cortex, and the hippocampal formation (Buckner et al., 2008).

A majority of the studies on meditation and mind wandering have measured how fMRI activation and functional connectivity of the default mode network are related to mind wandering. Most of these describe trait differences in brain activation patterns arising from meditation, often showing decreased default mode network activation in experienced meditators compared to novices (Brewer et al., 2011; Sood and Jones, 2013).

Only a few studies have reported state changes, contrasting meditation with various control tasks in the same practitioners, but with varying results. Using rest as a control, Brefczynski-Lewis and coworkers showed activation of a large overlapping network of attention-related cortical regions during "concentration meditation" (focused attention with a simple visual stimulus), including frontal, parietal regions, lateral occipital cortex, and insula (Brefczynski-Lewis et al., 2007). Lazar and coworkers showed activation of dorsolateral prefrontal and parietal cortices, hippocampus/parahippocampus, temporal lobe, pregenual anterior cingulate cortex, striatum, and pre- and post-central gyri during mantra meditation coordinated with breath (Lazar et al., 2000). Generating a list of animals was used as control task. Engström and coworkers compared mantra meditation with silent repetition of a short semantic phrase as control and detected activation in bilateral hippocampus/parahippocampal formations, as well as bilateral middle cingulate cortex and bilateral precentral cortex (Engstrom et al., 2010). Interestingly, Manna and coworkers (Manna et al., 2010) described reduced activation of precuneus (a core default mode network area) compared to rest during meditation with focused attention on the breath, and increased activation during meditation with open monitoring of "any experiential or mental content" (Manna et al., 2010). None of the aforementioned studies assessed the extent of mind wandering.

AIM AND HYPOTHESIS

The aim of the present study was to determine whether nondirective meditation is conducive to default mode network activation. We hypothesized that accepting the spontaneous flow of thoughts, images, sensations, memories, and emotions as part of meditation, without any emphasis on reducing, monitoring, evaluating or directly relating to it, would increase mind wandering and activation of the default mode network, compared to practicing with more emphasis on control and a concentrative focus of attention. We therefore assessed whether practicing the same technique (Acem meditation) with different types of attentional focus would affect the subjective experience and the pattern of brain activation during meditation assessed by fMRI.

METHODS

ETHICS STATEMENT

The National Committee for Medical Research Ethics in Norway approved the study. Informed written consent was obtained from all participants before inclusion.

PARTICIPANTS

Twenty-seven experienced practitioners of Acem meditation (18 men and 9 women) were recruited. All participants were regular practitioners (2 × 30 min daily) and had extensive experience with longer meditation periods, including participation in at least one 3-week long retreat. Twenty-four were right handed, ascertained by the Edinburg Handedness Inventory (Oldfield, 1971). Thirteen participants were excluded from final data analysis due to rigorous quality control; only participants with acceptable recordings from both fMRI sessions were included. Three were excluded because of reported sleep during the recording, two because of significant head motion (≥ 1 mm), one because of error in scanning protocol, and seven because of technical problems that lead to corruption of the fMRI images. Even though the head was securely fixed inside the headcoil according to standard procedure (using triangular shaped foam pads), minor involuntary movements were difficult to avoid during two 20-min recordings in a relaxed reclining condition. Thus, 14 practitioners (8 men and 6 women, 13 right handed), aged 28–61 years (mean 49, SD 9) with 9–38 years of meditation practice (mean 27, SD 9) were included in final data analysis. We included only experienced meditators in our study, since it takes extensive training to reliably distinguish between nondirective and concentrative practicing.

fMRI MEDITATION INSTRUCTIONS

Details on nondirective meditation has been provided above (**Box 3**) and in previous publications (Ellingsen and Holen, 2008; Davanger et al., 2010). Participants were asked to perform Acem meditation in two separate runs of fMRI acquisition. In nondirective meditation the participants were instructed to repeat the meditation sound in a relaxed and effortless manner, in the same way as during home practice. Spontaneous mind wandering was neither prevented nor encouraged. In contrast, during concentrative practicing, the meditation sound was repeated in a more forceful manner, with strict regularity, in order to maintain the focus of attention on the sound, attempting to avoid mind wandering. As expected, mind wandering was not avoided completely, although more of the participants reported decreased mind wandering during concentrative practicing than in nondirective meditation. During data acquisition in the resting blocks (see below) participants were instructed to rest without repeating the meditation sound, allowing mind wandering where spontaneously occurring thoughts, images, sensations, memories, and emotions could emerge and pass freely.

EXPERIMENTAL DESIGN

In order to establish a stable, relaxed resting control state, all participants meditated for 45–60 min before experimental recordings. Each practitioner was scanned in one session with one run of nondirective meditation and one of concentrative practicing (block design), presented in randomized order. In each run the practitioners performed a sequence of four meditation blocks lasting 3, 5, 4, and 3 min respectively, interspersed with five resting blocks lasting 1 min each. Block length was varied in order to avoid "false" fMRI activation induced by expectation. All subjects were scanned with eyes closed. Concentrative practicing and rest were used as contrasts for nondirective meditation. This would minimize the possible effect of underlying traits in the subjects, each subject serving as his or her own control. Immediately following each scanning run, all participants were asked to complete a questionnaire assessing their meditation experiences: extent of mind wandering compared to regular home practice, whether they became drowsy or briefly fell asleep, and to what extent the sound from the MRI scanner was disturbing. They also confirmed whether they had been able to carry out the meditation tasks.

DATA ACQUISITION

Structural and functional scanning was performed using a 3T Philips Intera scanner (Philips Medical, Best, The Netherlands) with an 8-channel SENSitivity Encoding (SENSE) head-coil (InVivo, Gainsville, FL, USA). Using BOLD-sensitive imaging, a total of 400 volumes was acquired for each run with a gradient-echo echo-planar-imaging pulse sequence. Each volume consisted of 44 contiguous axial slices, with the following scan parameters: SENSE-reduction factor = 2.2, $TR = 3000$ ms; flip angle = 90°; $TE = 35$ ms; $FOV = 230$ mm; slice thickness = 2.5 mm; matrix $= 64 \times 64$ giving an in-plane resolution of $3.6\times\ 3.6\,\text{mm}^2$. Also a high-resolution T1-weighted image series was collected using a three-dimensional magnetization-prepared rapid gradient echo sequence (MP-RAGE) consisting of 182 contiguous sagittal slices of 1.2-mm thickness with an in-plane resolution of 1×1 mm. For analysis, all images were reconstructed to $1\,\text{mm}^3$.

DATA ANALYSIS

Imaging data were analyzed using FSL 4.0 (Analysis Group, FMRIB, Oxford, UK; www.fmrib.ox.ac.uk/fsl/). First, non-brain tissue was removed from the T1-weighted anatomical image-series using the Brain Extraction Tool (Smith, 2002). The resulting images were transformed non-linearly to the MNI152 $1 \times 1 \times 1$ mm template (Montreal Neurological Institute, Montreal, QC, Canada), and motion corrected with the median volume of each run as reference using the FNIRT algorithm (Andersson et al., 2007). Then each functional run was co-registered to the corresponding anatomical T1-weighted image-series and transformed into MNI152 space by the transformation matrix obtained from the T1-weighted images. The functional data was smoothed by a 6 mm full-width at half-maximum (FWHM) Gaussian filter, and a temporal high-pass filter with a cut-off time of 350 s.

The two-level random effects statistical analysis of the fMRI data was carried out using Bayesian estimation techniques with FEAT (Smith et al., 2004). Conditions were modeled according to a boxcar stimulus function convolved with a two-gamma hemodynamic response function (Boynton et al., 1996). The first minute of each meditation block was excluded from the analysis by modeling it as non-effect, as meditation activations take time to build up (Davanger et al., 2010). The effect of each condition was estimated according to a general linear model (Friston et al., 1995). A whole-brain analysis was performed using mixed effects FLAME-1 algorithms (Beckmann et al., 2003). Statistical thresholds for contrasts nondirective meditation > rest, and concentrative practicing > rest were set to $p < 0.05$, family wise error rate was corrected using cluster-level interference by setting cluster forming threshold at $z > 3.0$ ($p < 0.0027$). For the contrast nondirective meditation > concentrative practicing it was set to $p < 0.05$ and cluster forming $z > 2.3$ ($p < 0.0214$). To increase sensitivity, the threshold was set less stringently for the latter comparison, because the expected difference between two similar conditions is usually smaller and the variability greater than for respective comparisons with rest. For all three contrasts, correlation analysis with years of experience as independent variable was performed in FEAT using FLAME-1 algorithm. Years of experience was defined as an extra environmental variable for all three contrasts. Brain areas were identified by FSL atlases and other relevant sources for functional data as referenced.

STATISTICAL ANALYSIS OF QUESTIONNAIRE DATA

A post-scan behavior questionnaire comprised three questions (translated from Norwegian): (1) How disturbing was the scanner sound in the background: 0 = not at all, 1 = some, 2 = much. (2) What was the extent of mind wandering compared to regular meditation outside the scanner: 0 = less, 1 = similar, 2 = more. (3) Did you become drowsy or fall asleep: 0 = wakeful, 1 = drowsy, 2 = fell asleep. The questionnaire data were analyzed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Fisher's exact test was performed to assess whether mind wandering, drowsiness and disturbance by scanner depended on the mode of practicing (nondirective vs. concentrative) in 2×2 tables, excluding table lines with zero-cells. As described below, participants who fell asleep during scanning, were excluded from further analyses.

RESULTS

BEHAVIORAL DATA

Data from a brief questionnaire administered immediately after each fMRI recording indicated a trend for less mind wandering with concentrative practicing compared to regular meditation. Even though the meditation blocks were short and the number of participants small, a larger number experienced less mind wandering during concentrative practicing than during nondirective meditation, whereas the numbers of participants who were wakeful/drowsy and disturbed some/much by noise were similar during nondirective and concentrative practicing, respectively (**Table 1**). A majority spontaneously remarked that concentrative practicing was effortful and tiring, although it was not an item in the questionnaire.

fMRI DATA

The fMRI assessments showed that nondirective meditation activated several regions of the cerebral cortex as well as subcortical structures significantly more than during resting. However, compared to nondirective meditation, during concentrative practicing fewer areas were activated more than at rest. Some regions in the right temporal lobe were activated significantly stronger during nondirective meditation than concentrative practicing. The activated areas for each contrast are detailed below. There was no correlation between activation and years of meditation experience.

Table 1 | Meditation experience during scanning assessed by post-scan questionnaire.

	Nondirective meditation	Concentrative practicing	*P*-value
MIND WANDERING			
Less	8	12	
Similar	6	2	0.09
More	0	0	
WAKEFULNESS			
Wakeful	10	9	
Drowsy	4	5	0.29
DISTURBED BY NOISE			
Not at all	1	0	
Some	8	10	
Much	5	4	0.23

For mind wandering, numbers denote participants experiencing less or similar mind wandering in the scanner compared to regular meditations. P-values were assessed by Fisher's exact test, as described in Methods.

NONDIRECTIVE MEDITATION

Increased signal for the contrast *nondirective meditation > rest* was found in several regions, including orbitofrontal, motor, somatosensory, visual, association, and limbic areas (**Figure 1**; **Table 2**). Notably, nondirective meditation increased activity in the *prefrontal* cortex, showing a large cluster with the point of maximal activation in the straight gyrus, covering a large part of the right orbitofrontal cortex as well as medial prefrontal areas. Also the *anterior cingulate cortex*, parts of the parietal lobe (*posterior cingulate cortex, precuneus, anterior/inferior parts of the lateral parietal lobe*) and the temporal lobe (*inferior and medial temporal lobe, hippocampus, amygdala*) were activated more than at rest.

Large clusters were also detected in the occipital lobe covering vision areas in the middle occipital gyrus and striate cortex. In the posterior part of the frontal lobe, activation occurred in *primary* and *supplementary motor* areas of the left hemisphere, extending into Broca's area.

In the left parietal lobe, *sensorimotor* and *secondary sensory* regions including part of the precuneus were activated. There was no change in Wernicke's receptive speech area.

In the right *temporal* lobe, three clusters were found: the fusiform cortex/inferior temporal gyrus/parahippocampal gyrus including the visual processing and facial areas, the hippocampus, and the amygdala.

In the *cingulate* cortex, separate clusters in the right and left anterior regions were activated, as well as in the right posterior regions. Activated clusters were also seen in two non-cortical regions: In the left *basal ganglia* (putamen, globus pallidus, and the nucleus accumbens), and in a right and a left *cerebellar* region.

The opposite contrast, *nondirective meditation < rest*, showed no positive activation.

CONCENTRATIVE PRACTICING

The contrast *concentrative practicing > rest* revealed significant activation in three regions (**Figure 1**; **Table 3**). *Motor area* activation was present in the posterior part of the middle frontal gyrus/premotor cortex, precentral gyrus, the primary motor cortex, and the supplementary motor area/pre-motor cortex. In *visual areas*, we observed activation of the middle and inferior occipital gyrus/lateral occipital cortex, the occipital fusiform gyrus, and the intracalcarine/visual and the occipital pole/visual cortices. Lastly, one cluster was activated in the dorsal aspect of the anterior *cingulate* cortex, bilaterally. No parietal or temporal clusters were seen during concentrative practicing.

The opposite contrast, *concentrative practicing < rest*, showed no positive activation.

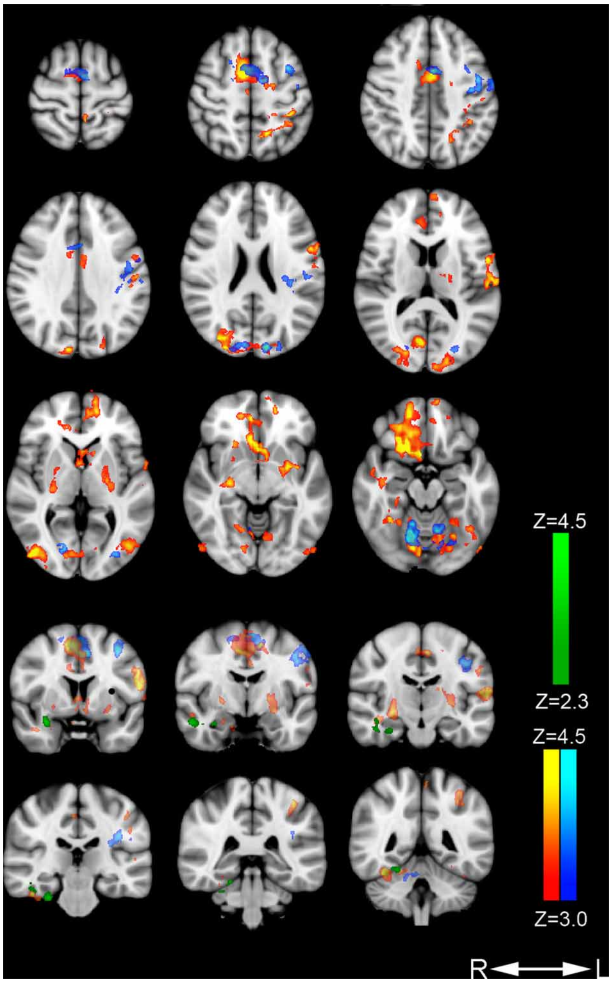

FIGURE 1 | Areas with increased cerebral activation. Color-coded regions show activation above threshold in the following contrasts: *Nondirective meditation > rest* (red-yellow), *concentrative practicing > rest* (dark blue-light blue), and *nondirective meditation > concentrative practicing* (dark green-light green). Activations are superimposed on MNI template (Montreal Neurological Institute).

NONDIRECTIVE MEDITATION vs. CONCENTRATIVE PRACTICING

The contrast *nondirective meditation > concentrative practicing* (**Figure 1**; **Table 4**) revealed higher activation of several areas in the temporal lobe: middle and inferior temporal gyrus, fusiform gyrus, amygdala, and parahippocampal gyrus.

Table 2 | Cerebral regions with increased activity: nondirective meditation > rest.

Nondirective meditation > Rest
z-threshold: 3.0 and Cluster forming P-threshold: 0.05

Anatomical location	Hemisphere	Lobus	*X*	*Y*	*Z*	z-score	Cluster size	*BA*
Straight gyrus (frontal lobe)	R	Frontal	22	36	−21	4.86	25,554	11
Middle occipital gyrus (secondary visual cortex)	R	Occipital	24	−86	27	4.66	18,659	18
Inferior occipital gyrus (secondary visual cortex)	R	Occipital	36	−83	0	4.54	2754	19
Middle occipital gyrus (secondary visual cortex)	R	Occipital	30	−86	20	4.5	18,659	18
Premotor cortex (lateral), (supplementary motor area)	R	Frontal	7	−74	−14	4.35	18,659	17
Precentral gyrus (premotor area, Broca's area)	L	Frontal	−56	5	17	4.32	8340	6, 44
Superior parietal lobule (secondary sensorimotor cortex)	L	Parietal	−14	−56	55	4.24	8340	5, 7
Postcentral gyrus, superior temporal gyrus	L	Parietal	−61	−15	14	4.17	8340	1, 2, 3
Superior parietal lobule (secondary sensorimotor cortex)	L	Parietal	−19	−60	47	4.12	8340	5, 7
Inferior temporal, fusiform, parahippocampal gyrus	R	Temporal	44	−26	−27	4	3196	20
Hippocampus	R	Temporal	27	−17	−6	3.96	3196	N/A
Insula (posterior)	L	Insula	−37	−2	−7	3.91	3173	14
Middle occipital gyrus (secondary visual cortex)	L	Occipital	−20	−74	−12	3.85	18,659	18
Inferior temporal and fusiform gyrus	R	Temporal	38	−27	−32	3.59	3196	20
Anterior cingulate cortex	R	Frontal	8	37	10	3.58	25,554	32
Posterior cingulate cortex	R	Frontal	8	6	31	3.54	25,554	24
Anterior cingulate cortex	L	Frontal	−3	42	−3	3.54	25,554	32
SUBCORTICAL								
Putamen	L	Sub-cortical	−27	−2	−8	4.22	3173	
Nucleus accumbens	L	Sub-cortical	−7	10	−9	4.16	25554	
Pallidum	L	Sub-cortical	−24	−11	2	3.69	3173	
Nucleus caudatus	L	Sub-cortical	−11	15	3	3.6	25554	
Amygdala	R	Sub-cortical	23	−5	−21	3.47	3196	
Thalamus	L	Sub-cortical	−16	−15	15	3.43	3173	
Pallidum	R	Sub-cortical	22	−5	−2	3.39	3196	
Putamen	R	Sub-cortical	25	4	−5	3.15	3196	

The analysis was carried out using whole brain analysis with z-threshold = 3.0 and cluster forming p-threshold: 0.05. Coordinates in MNI coordinates (Montreal Neurological Institute) (R, right; L, left; BA, Brodmann's area).

The opposite contrast, *nondirective meditation < concentrative practicing*, showed no positive activation.

DISCUSSION

The present study sought to investigate state effects of nondirective meditation either compared to rest or to concentrative practicing in participants with long-term experience of Acem meditation. Results are consistent with the notion that nondirective meditation involves more extensive activation of the default mode network, including brain areas associated with episodic memories and emotional processing.

DEFAULT MODE NETWORK ACTIVATION

Compared to rest, nondirective meditation increased activation within all cortical areas defining the default mode network (Buckner et al., 2008), including the ventral medial prefrontal cortex, the posterior cingulate/retrosplenial cortex, the inferior parietal lobe, the lateral temporal cortex, the dorsal medial prefrontal cortex, and the hippocampal formation (**Figure 1**, **Table 2**). The pattern of activations was similar to that associated with mind wandering in a recent study of meditation with focused attention on breath, including posterior cingulate cortex, medial prefrontal cortex, posterior parietal and temporal cortex, and the

Table 3 | Cerebral regions with increased activity: concentrative practicing > rest.

Concentrative practicing > Rest
z-threshold: 3.0 and Cluster forming P-threshold: 0.05

Anatomical location	Hemisphere	Lobus	*X*	*Y*	*Z*	z-score	Cluster size	*BA*
Middle occipital gyrus (secondary visual cortex)	L	Occipital	−13	−89	24	4.17	2086	18
Middle frontal gyrus, premotor cortex	L	Frontal	−36	5	49	4.1	6185	6
Supplementary motor cortex, premotor cortex	L	Frontal	−6	−3	61	4.02	6151	6
Precentral gyrus, primary motor cortex	L	Frontal	−39	−14	41	3.9	6185	4
Middle frontal gyrus, primary motor cortex	L	Frontal	−34	7	55	3.88	6185	6
Middle frontal gyrus, premotor cortex	L	Frontal	−48	−20	37	3.87	6185	3
Calcarine cortex, primary visual cortex	R	Occipital	17	−74	5	3.85	1874	17
Middle frontal gyrus, premotor cortex	L	Frontal	−37	6	58	3.83	6185	6
Calcarine cortex, primary visual cortex	R	Occipital	15	−87	19	3.73	1874	17
Anterior cingulate cortex, dorsal part	R	Frontal	4	11	31	3.63	6185	24
Anterior cingulate cortex, dorsal part	L	Frontal	−1	13	34	3.49	6151	24
Inferior occipital gyrus, secondary visual cortex	L	Occipital	−21	−75	−11	3.46	2049	18
Supplementary motor cortex, premotor cortex	R	Frontal	7	6	53	3.42	6151	6

The analysis was carried out using whole brain analysis with z-threshold = 3.0 and cluster forming p-threshold: 0.05. Coordinates in MNI coordinates (Montreal Neurological Institute) (R, right; L, left; BA, Brodmann's area).

Table 4 | Cerebral regions with increased activity: nondirective meditation > concentrative practicing > rest.

Nondirective meditation > Concentrative practicing
z-threshold: 2.3 and Cluster forming P-threshold: 0.05

Anatomical location	Hemisphere	Lobus	*X*	*Y*	*Z*	z-score	Cluster size	*BA*
Middle temporal gyrus	R	Temporal	52	−6	−22	3.25	3616	21
Parahippocampal gyrus	R	Temporal	28	−24	−32	3.22	3616	
Inferior temporal gyrus, fusiform gyrus	R	Temporal	36	−2	−20	3.13	3616	20
Inferior temporal gyrus, fusiform gyrus	R	Temporal	47	−29	−19	3.12	3616	20
SUBCORTICAL								
Amygdala	R	Subcortical	31	2	−19	3.45	3616	

The analysis was carried out using whole brain analysis with z-threshold = 2.3 and cluster forming p-threshold: 0.05. Coordinates in MNI coordinates (Montreal Neurological Institute) (R, right; L, left; BA, Brodmann's area).

hippocampus (Hasenkamp et al., 2012). In contrast, the control task of concentrative practicing in the present study seemed to have little effect on default mode network activation, including only the anterior cingulate cortex when compared to rest (**Figure 1**, **Table 3**). However, direct comparison of nondirective meditation with concentrative practicing gave only temporal clusters, including parahippocampal areas and amygdala. These observations indicate that the extent of default mode network activation during concentrative practicing probably lies somewhere between nondirective meditation and rest: slightly more than in rest, but evidently not enough to yield significant clusters in most default mode areas. This interpretation is consistent with the trend of less mind wandering reported in concentrative practicing compared to nondirective meditation (**Table 1**).

Our results corroborate previous findings that suggest increased default mode network activation during meditation. Experienced Vipassana meditators (focused attention on breath) showed stronger activation of the anterior cingulate cortex and the dorsal medial prefrontal cortex than control subjects (Holzel et al., 2007). During resting state, practitioners of "brain-wave vibration meditation" (meditative movement) had greater functional connectivity within the default mode network in the medial prefrontal cortex than controls (Jang et al., 2011). Performing Transcendental Meditation (another form of nondirective meditation) gave higher alpha1 EEG activity in midline cortical regions that overlapped with the default mode network (Travis et al., 2010).

Our findings regarding default mode network activation are in contrast with the prevailing view of practices with reference to mindfulness or Buddhist traditions, as recently reviewed (Sood and Jones, 2013). For example, experienced practitioners of "concentration" (focused attention), "loving-kindness" (exercise oriented toward enhancing unconditional, positive emotional states of kindness and compassion), and "choiceless awareness" (open monitoring of mind wandering) showed decreased default mode network activation compared to inexperienced controls (Brewer et al., 2011; Hofmann et al., 2011), and experienced Zen meditators had weaker connectivity between the medial prefrontal cortex and several other default mode network nodes (Taylor et al., 2013). These practices are described as "a training of attention away from self-reference and mind-wandering, and potentially away from default-mode processing" (Brewer et al., 2011). Reduced activation of a core default mode network component (precuneus) has been described in experienced Buddhist monks during focused attention on the breath, whereas the same area had larger activation than rest during open monitoring of "any experiential or mental content" (Manna et al., 2010).

Altogether, present and previous results suggest that the relationship with type of practice and years of experience is more complex than the presumption that "meditation reduces mind wandering and default mode network activation." Our observations indicate a differential effect related to the relaxed focus of attention in nondirective meditation vs. concentrative practicing, actively trying to avoid mind wandering.

PREFRONTAL AND TEMPORAL FUNCTIONS: ATTENTION AND EMOTIONAL PROCESSING

Across several forms of meditation, regulation of attention has consistently been linked to increased activity within the anterior cingulate cortex and the prefrontal cortex (Lazar et al., 2000; Kubota et al., 2001; Cahn and Polich, 2006; Holzel et al., 2008; Chiesa and Serretti, 2010; Davanger et al., 2010; Engstrom and Soderfeldt, 2010; Manna et al., 2010; Hasenkamp et al., 2012). Some studies have indicated that in meditation, the dorsal anterior cingulate cortex is most probably involved in attention and in discriminating between relevant and distracting thoughts, whereas the ventral aspect may serve as a link between emotional processing and autonomic regulation in the hypothalamus (Ongur et al., 1998; Johansen-Berg et al., 2008).

In the present study, the prefrontal cortex was activated in a large orbitofrontal and medial cortex cluster (included in the straight gyrus cluster, frontal lobe) and in an anterior cingulate cluster during nondirective meditation (**Figure 1**, **Table 2**). In contrast, orbitofrontal and medial areas of the prefrontal cortex (excluding anterior cingulate cortex) were not activated during the control task of concentrative practicing (**Figure 1**, **Table 3**). As suggested by observations from other contexts (Etkin et al., 2011), we speculate that part of the activation in these areas might be associated with emotional processing related to mind wandering, which would be an interesting topic for future research. A significant difference between nondirective meditation vs. the control conditions of either rest or concentrative practicing was activation of the anterior hippocampus and amygdala (**Figure 1**, **Tables 2–4**). In addition to spatial orientation, these areas have been associated with memory and emotional processing (Fanselow and Dong, 2010).

Hippocampus activation has been associated with mind wandering by detailed temporal analysis of meditation with focused attention on breath (Hasenkamp et al., 2012); as noted above, it is a core component of the default mode network (Buckner et al., 2008). Concomitant activation of hippocampus and amygdala has been reported in two previous studies of silent nondirective mantra meditation and relaxation response (Lazar et al., 2000; Engstrom et al., 2010). In contrast, amygdala activation was reduced in a study of mindfulness meditation (a breath-focused attention task) (Goldin and Gross, 2010), and in loving-kindness meditation (Brewer et al., 2011). Whereas isolated amygdala activation may indicate psychological strain in post-traumatic stress disorder (Hughes and Shin, 2011), concomitant activation with the dorsolateral prefrontal cortex, anterior cingulate cortex, and the hippocampus may possibly serve to modify stressful emotional memories (Phillips et al., 2003; Shin et al., 2006). On the other hand, activation of amygdala has been correlated with subjective effort (Dyck et al., 2011). Further investigations are needed to determine the function of concomitant activation of hippocampus and amygdala in meditation.

LIMITATIONS

Some of the present experimental conditions differ significantly from actual meditation and may limit generalizability of the results. A major issue was that the participants meditated lying supine in the scanner (as opposed to sitting). As emphasized in a recent source of mindfulness-based cognitive therapy (Segal et al., 2013), reclining with eyes closed predisposes for relaxation, drowsiness, and even brief episodes of sleep, e.g., during body scan (page 156). A consequence of this was a tendency of subtle, involuntary movement during the two 20-min fMRI recordings, despite fixing the head according to standard procedure. Thirteen out of 54 original scans (24%) were excluded, a similar rate as observed in a previous study of mantra meditation (Engstrom et al., 2010). Since data from nondirective meditation and concentrative practicing was analyzed by pair-wise comparison, the whole data set of a participant was removed if one of the recordings was excluded. Thus, exclusion rate seems twice as high as actual problems with recordings. Nevertheless, the number of exclusions was unusually high, and may limit the generalizability of the findings. The low number included in final analyses is a limitation *per se*.

A factor that may have influenced activation patterns during meditation was noise from the scanner, which might explain less mind wandering than "in usual meditation" in more than 50% of the participants (**Table 1**). However, there was a strong trend for less mind wandering during concentrative practicing than during nondirective meditation, indicating their effort to maintain attention with the meditation sound. This suggests that the meditation tasks were largely performed according to instructions. It is also possible that the participants could have been biased toward rating mind wandering more frequently during nondirective meditation, as this was their regular practice. In summary, data from the questionnaire suggest that results from the included participants may be relevant for understanding mechanisms related to mind wandering, although external study conditions varied significantly from actual meditation outside the scanner.

CONCLUSION

The present study demonstrates that nondirective meditation induces more extensive default mode network activation than rest. Even though a core characteristic of the practice is a relaxed focus of attention that accepts mind wandering as part of the process, it is a paradox that the active task of effortless mental repetition of a meditation sound yields larger default mode network activation than the passive task of simply resting. This observation suggests that the nondirective meditation task involves a minimal level of cognitive effort, which is often emphasized as an important characteristic of successful practicing across different types of techniques used for health and wellness, including focused attention, open monitoring, and nondirective meditation. The study also shows that the control task of concentrative practicing of the same technique (Acem meditation), performed with an effort to reduce mind wandering, reduced the extent of default mode network activation compared to nondirective meditation, but not below the level of resting.

Altogether, our findings support the notion that nondirective meditation is conducive for default mode network activation. They also indicate that this activation is related to the relaxed focus of attention, which allows spontaneous thoughts, images, sensations, memories, and emotions to emerge and pass freely, accepting them as part of the meditation process. Since the relaxed focus of attention is a core component of several practices, we speculate that mental activities associated with default mode network activation, may be essential for state and trait effects. Further research is needed to determine whether this activation is associated with retrieval of episodic memories and emotional processing during nondirective meditation.

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The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers

Leor Roseman[1,2]*, Robert Leech[2], Amanda Feilding[3], David J. Nutt[1] and Robin L. Carhart-Harris[1]

[1] Centre for Neuropsychopharmacology, Division of Brain Sciences, Department of Medicine, Imperial College London, London, UK
[2] Computational, Cognitive and Clinical Neuroscience Laboratory, Division of Brain Sciences, Department of Medicine, Imperial College London, London, UK
[3] The Beckley Foundation, Oxford, UK

Edited by:
Enrico Facco, University of Padua, Italy

Reviewed by:
Alexander Schaefer, Max Planck Institute for Human Cognitive and Brain Sciences, Germany
Enzo Tagliazucchi, Goethe University Frankfurt, Germany

***Correspondence:**
Leor Roseman, Department of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK
e-mail: leoroseman@gmail.com

Perturbing a system and observing the consequences is a classic scientific strategy for understanding a phenomenon. Psychedelic drugs perturb consciousness in a marked and novel way and thus are powerful tools for studying its mechanisms. In the present analysis, we measured changes in resting-state functional connectivity (RSFC) between a standard template of different independent components analysis (ICA)-derived resting state networks (RSNs) under the influence of two different psychoactive drugs, the stimulant/psychedelic hybrid, MDMA, and the classic psychedelic, psilocybin. Both were given in placebo-controlled designs and produced marked subjective effects, although reports of more profound changes in consciousness were given after psilocybin. Between-network RSFC was generally increased under psilocybin, implying that networks become less differentiated from each other in the psychedelic state. Decreased RSFC between visual and sensorimotor RSNs was also observed. MDMA had a notably less marked effect on between-network RSFC, implying that the extensive changes observed under psilocybin may be exclusive to classic psychedelic drugs and related to their especially profound effects on consciousness. The novel analytical approach applied here may be applied to other altered states of consciousness to improve our characterization of different conscious states and ultimately advance our understanding of the brain mechanisms underlying them.

Keywords: psilocybin, MDMA, serotonin, 5HT2A, resting state, functional connectivity, brain networks, psychedelic

INTRODUCTION

Psychedelic drugs have been used throughout history by different cultures as a means of altering consciousness. They are powerful tools for understanding the neurobiology of consciousness yet they have been underutilized by modern science, arguably due to political rather than scientific circumstances (Nutt et al., 2013). The majority of consciousness research has focused on states of reduced consciousness such as coma and sleep (Laureys, 2005). Indeed, consciousness has been defined as that which is lost during dreamless sleep (Tononi, 2004) but consciousness can also be studied in terms of changes in the mode or style of waking consciousness, such as is seen in the psychedelic state. Another popular model of consciousness describes it using two parameters: (1) wakefulness or arousal and (2) awareness (Laureys et al., 2009). It is recognized that these parameters have a mostly linear relationship; however, REM sleep and the vegetative state are considered anomalies, since the former involves greater awareness than would be predicted by wakefulness and the latter displays less (Laureys et al., 2009). The position of the psychedelic state in this model has never been considered before and it presents another interesting anomaly. There is no evidence of reduced wakefulness in the psychedelic state and although awareness is altered, it would be misleading to say that it is reduced. Indeed, the psychedelic state has been referred to as an "expansive" state of consciousness (Huxley, 1959). Thus, it is important to investigate what the neurobiological basis of this putative broadening of consciousness is.

One of the most popular theories of consciousness is the "information integration" theory of Tononi (2012). This proposes that consciousness depends on the presence of two key parameters: (1) information and (2) integration. *Information* is derived from information theory (Shannon and Weaver, 1949) and in the context of consciousness, refers to the potential size of the repertoire of different metastable states (Tognoli and Kelso, 2014) (or "sub-states") the mind/brain can enter over time. *Integration* refers to the capacity of the mind/brain to integrate processes into a collective whole. The parameter of *awareness* is likely to be related to the property of *information*, since the greater the repertoire of sub-states the mind can enter, and the easier it can move between these, the broader consciousness will be.

In recent years, there has been an increasing interest in human fMRI measures of resting state functional connectivity (RSFC) (Damoiseaux and Greicius, 2009). Resting state networks (RSN) can be identified using seed-based approaches (Biswal et al., 1995) and independent component analysis (ICA) (Beckmann et al., 2005). These RSNs resemble stimulus-evoked networks (Smith et al., 2009) and may be thought of as metastable substates making-up a particular (macro) state of consciousness (Carhart-Harris et al., 2014a). Thus, one way to describe the quality of a macro-state of consciousness may be to investigate the integrity and dynamics of its sub-states and how they interact with each other. One way this can be done is by looking at the internal stability (integrity) of an RSN, i.e., reflected in the strength of the coupling between its constituent nodes. For example, we have found decreased intra-RSN connectivity post-psilocybin with both fMRI (Carhart-Harris et al., 2012a) and magnetoencephalography (MEG) (Muthukumaraswamy et al., 2013), implying a general breakdown of the integrity or internal stability of RSNs under psilocybin.

Another way to address the behavior of a system's sub-states is to look at their relationship with each other, e.g., by measuring between-RSN functional connectivity or coupling. A frequently investigated RSN is the default mode network (DMN) (Raichle et al., 2001). The DMN is known to be more active during rest than during goal-directed cognition and its activity has been found to be "anti-correlated" or at least uncorrelated or orthogonal with activity in networks that are engaged during goal-directed cognition - referred to generically as "task positive networks" or TPNs. This anticorrelation is preserved under task free conditions (Fox et al., 2005), implying that it is an important feature of normal consciousness, perhaps accounting for the distinction between externally focused cognition and introspection (Carhart-Harris et al., 2012b). We recently found that the classic psychedelic drug psilocybin reduces the anticorrelation between DMN and a number of TPNs during resting conditions, and this was interpreted as a decrease in the natural distinction between externally-focused attention and introspection (Carhart-Harris et al., 2012b), which is relevant to the notion of "ego-boundaries," i.e., an agent's sense of being apart from or separate to its environment. It would be a natural extension of the above analysis to address the full gamut of between-RSN FC identified by ICA rather than just focusing on just the DMN-RSN RSFC. This was the aim of the present study.

The primary focus of the present paper is the classic psychedelic state and determining its underlying neurodynamics as measured with fMRI. However, in order to understand the psychedelic state, it is useful to compare it with other states of consciousness to see how it relates to these. Thus, the present analysis focuses on the brain effects of a classic psychedelic drug, psilocybin (the active component of magic mushrooms) and compares this with the effects of the pro-serotonergic stimulant, 3–4 methylenedioxymethamphetanine, MDMA. MDMA is a potent monoamine releaser that produces an acute euphoria in most individuals but it is not considered a classic psychedelic, as psilocybin is. Direct 5-HT$_{2A}$R stimulation is the defining pharmacological property of classic serotonergic psychedelics, but relative to classic psychedelics, MDMA has a far weaker affinity for the 5-HT$_{2A}$ receptor (Green et al., 2003). Instead, MDMA produces a more generalized, non-selective activation of monoamine receptors by increasing the concentration of their endogenous ligands in the synapse via transporter-mediated release (Green et al., 2003). The primary subjective effects of MDMA include increased positive mood, heightened sensations and prosocial sentiments and although it can produce mild visual hallucinatory phenomena, it does not alter consciousness in the same fundamental manner as classic psychedelics (Gouzoulis-Mayfrank et al., 1996).

Thus, comparing changes in RSFC under psilocybin and MDMA can enable us to isolate and identify effects that are unique to the psychedelic-induced altered state of consciousness produced by classic psychedelics such as psilocybin. Considering the previous findings of decreased intra-RSN FC and DMN-TPN anti-correlation under psilocybin (Carhart-Harris et al., 2012a,b; Muthukumaraswamy et al., 2013), we hypothesized that the normal differentiation between RSNs would be affected by psilocybin such that RSNs whose activity is usually highly correlated would show reduced RSFC under psilocybin (but not MDMA) and that networks that are normally anti-correlated would show reduced anti-correlation under psilocybin (but not MDMA). If the hypothesized effects are present under psilocybin but absent under MDMA, this will strengthen the inference that they are specifically related to psilocybin more profound effects on consciousness.

MATERIALS AND METHODS

DESIGN

Psilocybin

This is an entirely new analysis on a previously published data set (Carhart-Harris et al., 2012a,b). This was a within-subjects placebo-controlled study that was approved by a local NHS Research Ethics Committee and Research and Development department, and conducted in accordance with Good Clinical Practice guidelines. A Home Office License was obtained for storage and handling of a Schedule 1 drug. The University of Bristol sponsored the research. The research was carried out at CUBRIC, University of Cardiff.

MDMA

This is also an entirely new analysis on a previously published dataset (Carhart-Harris et al., 2014b). This was a within-subjects, double-blind, randomized, placebo-controlled study. Participants were scanned twice, 7 days apart, once after MDMA and once after placebo. The study was approved by NRES West London Research Ethics Committee, Imperial College London's Joint Compliance and Research Office (JCRO), Imperial College's Research Ethics Committee (ICREC), the Head of Imperial College's Department of Medicine, Imanova Center for Imaging Science and Imperial College London's Faculty of Medicine, and was conducted in accordance with Good Clinical Practice guidelines. A Home Office License was obtained for the storage and handling of a Schedule 1 drug and Imperial College London sponsored the research.

PARTICIPANTS

Psilocybin

Fifteen healthy subjects took part: 13 males and 2 females (mean age = 32, $SD = 8.9$). Recruitment was via word of mouth. All subjects were required to give informed consent and undergo health screens prior to enrolment. Entry criteria were: at least 21 years of age, no personal or immediate family history of a major psychiatric disorder, substance dependence, cardiovascular disease, and no history of a significant adverse response to a hallucinogenic drug. All of the subjects had used psilocybin at least once before (mean number of uses per subject = 16.4, *SD* = 27.2) but not within 6 weeks of the study.

MDMA

The original study sample comprised of 25 healthy participants (mean age = 34, *SD* = 11, 7 females) with at least 1 previous experience with MDMA. None of the participants had used MDMA for at least 7 days and other drugs for at least 48 h, and this was confirmed by a urine screen. As a conservative step to control for between-study differences in the global intensity of the subjective effects produced by the different drugs, 11 subjects who gave ratings of <50% for the intensity of MDMA's effects were excluded from the analysis. This step meant that ratings of drug effects intensity were comparable across the two studies (i.e., the mean intensity of psilocybin's subjective effects was 67 ± 19 at peak and MDMA's was 69 ± 15). An additional subject was excluded because of significant head movements (mean head motion > one voxel width). Thus, a total of 13 subjects were included in the analysis (i.e., 12 excluded). An alcohol Breathalyzer test confirmed that none of the participants had recently consumed alcohol. For the sample of 13, participants had used MDMA an average of 29 (±35) times before (range = 1–100) and the mean time since last use was 983 (±1998) days (range = 7–6570 days). Participants were screened for general health, MR-compatibility and present mental health. Screening involved routine blood tests, electrocardiogram, heart rate, blood pressure and a brief neurological exam. All subjects were deemed physically and mentally healthy at the time of study entry and none had any history of drug or alcohol dependence.

ANATOMICAL SCANS

Psilocybin

Imaging was performed on a 3T GE HDx system. Anatomical scans were performed before each functional scan. These were 3D fast spoiled gradient echo scans in an axial orientation, (1 mm isotropic voxels).

MDMA

Imaging was performed on a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) using a 32-channel phased array head coil. Anatomical reference images were acquired using the ADNI-GO recommended MPRAGE parameters (1 mm isotropic voxels).

DRUG AND SCANNING PARAMETERS

Psilocybin

All subjects underwent two 12-min eyes-closed resting-state blood oxygen–level dependent (BOLD) fMRI scans on 2 separate occasions at least 7 days apart: placebo (10 ml saline, 60-s intravenous injection) was given on 1 occasion and psilocybin (2 mg dissolved in 10 ml saline) on the other. Seven of the subjects received psilocybin in scan 1, and 8 received it in scan 2. Injections were given manually by a study doctor situated within the scanning suite. The 60-s infusions began exactly 6 min after the start of the 12-min scans. Subjective ratings were given post-scan using visual analog scales (VAS). The subjective effects of psilocybin were felt almost immediately after injection and were sustained for the duration of the scan.

MDMA

Two BOLD resting-state scans were performed during each functional scanning session (duration of functioning scanning = 60 min). The first resting-state BOLD scan took place 60 min after capsule ingestion and the second resting-state BOLD scan occurred 113 min after capsule ingestion. Peak subjective effects were reported 100 min post administration of MDMA, generally consistent with the plasma t-max of MDMA (Kolbrich et al., 2008). The order of MDMA and placebo administration was counterbalanced.

fMRI DATA ACQUISITION

Psilocybin

BOLD-weighted fMRI data were acquired using a gradient echo planar imaging sequence, 3 mm isotropic voxels, *TR* = 3000 ms, *TE* = 35 ms, field-of-view = 192 mm, 90° flip angle, 53 axial slices in each TR, parallel acceleration factor = 2, 64 × 64 acquisition matrix. The psilocybin and placebo scans for this analysis were of 5 min (1 min post infusion).

MDMA

BOLD-weighted fMRI data were acquired using a gradient echo planar imaging sequence, 3 mm isotropic voxels, *TR* = 2000 ms, *TE* = 31 ms, field-of-view = 192 mm, 80° flip angle, 36 axial slices in each TR, GRAPPA acceleration = 2, bandwidth = 2298 Hz/pixel. For each condition, MDMA and placebo, two scans were used for the analysis, each one of 6 min (performed 60 min and 113 min post-capsule ingestion)

RESTING STATE NETWORKS (RSN)

We used RSNs that were identified in Smith et al. (2009) using ICA (**Figure 1**). Ten of these components were given functional labels based on their correspondence to the BrainMap database of functional imaging studies, involving task-evoked FMRI data from nearly 30,000 human subjects. These networks were: Visual-Medial Network (VisM), Visual-Lateral Network (VisL), Visual-Occipital pole Network (VisO), Auditory Network (AUD), Sensorimotor Network (SM), Default Mode Network (DMN), Executive Control Network (ECN), Left frontoparietal Network(lFP), Right frontoparietal Network (rFP) and Cerebellar network. In addition, we used three more components from Smith et al, that we named DMN2 (an anterior DMN and ECN hybrid), Dorsal Attention Network 1 and 2 (DAN1 and DAN2). Another 6 components were identified as non-neural noise (likely generated by head motion and non-neural physiological fluctuations).

PREPROCESSING

All analyses were performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). We used the standard imaging preprocessing FSL pipeline that involved brain extraction (Smith, 2002), motion correction using MCFLIRT (Jenkinson et al., 2002), spatial smoothing (FWHM) of 5 mm (Smith and Brady, 1997) and a high-pass filter of 100 s. The scans were registered to the subjects' T1-weighted high-resolution (2 × 2 × 2 mm) anatomical scans and were then registered to the

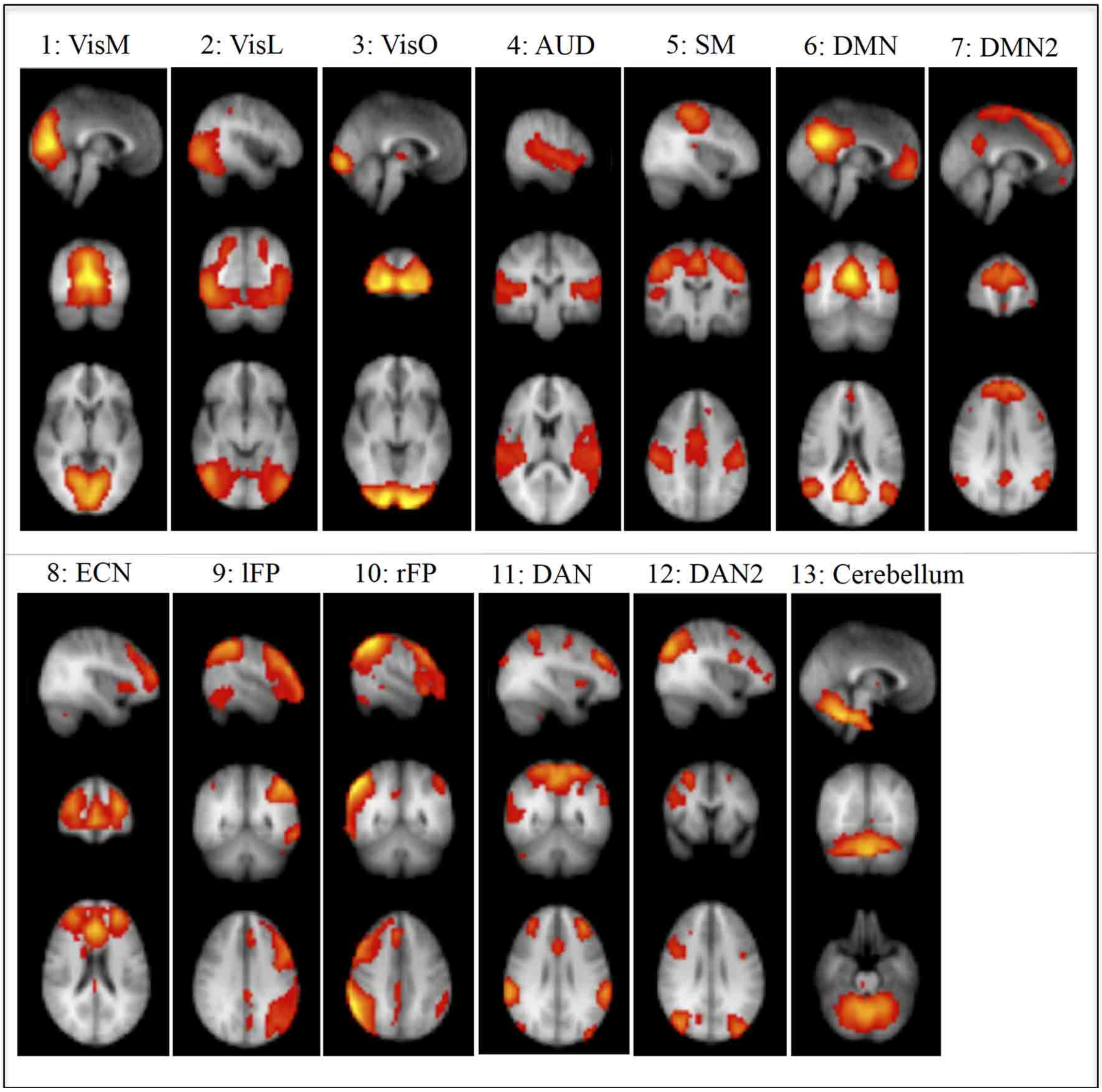

FIGURE 1 | Non-noise resting State Networks (RSN) from Smith et al., 2009: (1) Visual–Medial (VisM), (2) Visual–Lateral (VisL), (3) Visual–Occipital pole (VisO), (4) Auditory (AUD), (5) Sensorimotor (SM), (6) Default Mode Network (DMN), (7) DMN2–A hybrid of anterior DMN and Executive Control Network, (8) Executive Control Network (ECN), (9) left Frontoparietal Network (lFP), (10) right Frontoparietal Network (rFP), (11) Dorsal Attention Network (DAN), (12) DAN2, (13) Cerebellum. Ten of these components were given functional labels based on their correspondence to the BrainMap database of functional imaging studies. (RSNs 1, 2, 3, 4, 5, 6, 8, 9, 10, 13), additional networks (7, 11, 12) were labeled by the experimenters in the current study based on the regional distribution of activity.

Montreal Neurological Institute standard brain (2 × 2 × 2 mm) (Jenkinson et al., 2002). The data was resampled into 4 mm space as part of the default processing pipeline for Melodic and was done to make the analysis more computational efficient.

BETWEEN NETWORKS FUNCTIONAL CONNECTIVITY (FC)

Psilocybin

To extract time courses for each subject for each RSN and for each condition, we back-projected the components from Smith et al. (2009) into each 4D fMRI dataset using a general linear model. Specifically, we took the 20 components ICA map from Smith et al. as the set of template ICAs for the dual regression pipeline. The first step of the "dual regression" pipeline was then applied to each 4D dataset, resulting in a specific timecourse for each component for each dataset (Beckmann et al., 2009). Between-RSN coupling was presented graphically using a 13 × 13 correlation (or more strictly, regression) matrix in which the color in each square represents a beta weight or coupling strength for the corresponding RSN-RSN pair. Specifically, these weights were calculated by entering the time course for a specific RSN as a dependent variable in a general linear model, with the time course of another RSN entered as an independent variable—with this procedure repeated for each RSN pair. The mean head motion under psilocybin and its placebo condition were 0.1 ± 0.05 mm and 0.06 ± 0.015 mm, respectively ($p < 0.01$). Therefore, to further partial out non-neural noise confounds, six motion time courses (estimated from the motion correction) and motion outliers (estimated using the "fsl_motionoutlier" command implemented in FSL), as well as the time courses for 6 non-neural noise components were entered as confounds (some of this noise is driven by head motion). The model resulted in a parameter estimate or unstandardized beta weight (β) representing the strength of functional coupling between each RSN pair. The general linear model was estimated twice for each RSN pair: with each RSN as dependent variable in one model and as an independent variable in the second model. Since we were not looking at effective or directed connectivity (Friston et al., 2003), we created a symmetrical connectivity matrix by averaging together each subject's two β values for each RSN pair. For each RSN pair, three results were calculated: (a) group mean β value for the placebo condition; (b) group mean β value for the psilocybin condition; (c) Paired t-test (2-tail) for the difference between the mean β values of each condition (**Figure 2**). To correct for multiple comparisons, a false discovery rate (FDR) threshold was calculated using $q = 0.05$ and $q = 0.1$ ($N = 78$).

MDMA

The MDMA RSFC was analyzed using the same procedure described above (**Figure 2**). The only difference was that there were two resting state scans in the MDMA study, so β values

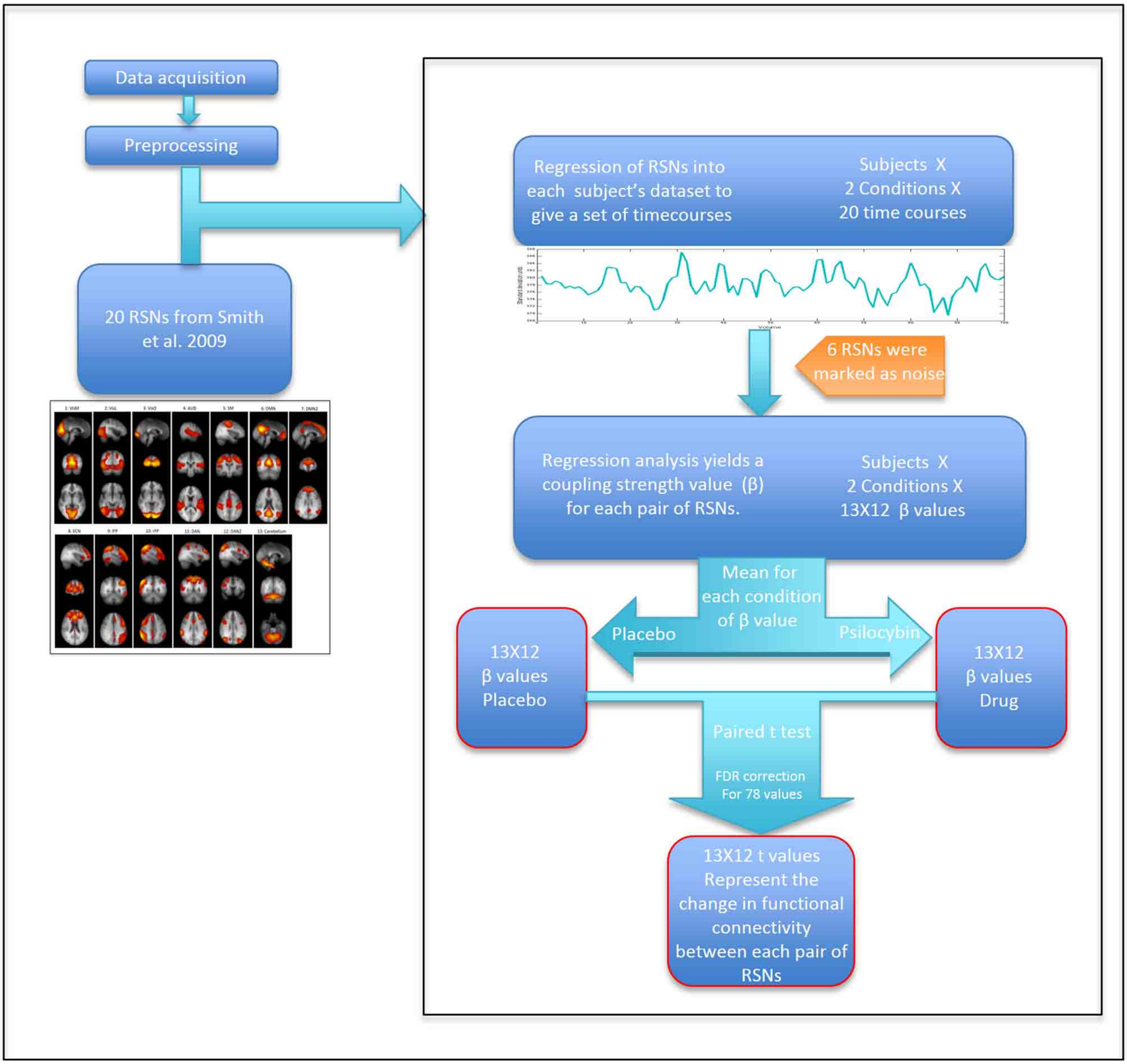

FIGURE 2 | Scheme of the analysis by steps. Calculating t-values for each RSN pair that represent the change in coupling strength between placebo and drug.

from the two scans (performed 60 min and 113 min post-capsule ingestion) were averaged together before comparing between the placebo and drug conditions. The mean head motion under MDMA and its placebo condition were 0.083 ± 0.036 mm and 0.061 ± 0.019 mm, respectively ($p = 0.047$). The same procedure to control for motion in the psilocybin analysis was used for MDMA.

RESULTS

SUBJECTIVE EFFECTS

Psilocybin

The subjective effects of psilocybin have been documented elsewhere (Carhart-Harris et al., 2011, 2012a). Briefly, the subjective effects of 2 mg psilocybin given as an intravenous injection over 60 s begin at the end of the injection period, reach a sustained peak after approximately 5 min, and subside completely after 45–60 min. Primary subjective effects include altered visual perception (e.g., hallucinated motion and geometric patterns), an altered sense of space and time, and vivified imagination. The intensity of psilocybin's global subjective effects was rated using a VAS format. The mean intensity at peak effects (5 min post-infusion) was 67% ±19.

MDMA

The subjective effects of MDMA are reported in a separate paper (Carhart-Harris et al., 2014b). At their peak, the average intensity of MDMA's global subjective effects was 69% ±15 ($n = 13$). There was no significant difference between intensity ratings under the two different drugs.

BETWEEN NETWORKS FC

Psilocybin

The coupling strengths (β) for each condition can be seen graphically in the correlation matrixes in **Figure 3** and numerically in the Supplementary material. For the placebo condition, see **Figure 3A** and Supplementary Table 1A and for the psilocybin condition see **Figure 3B** and Supplementary Table 1B. A paired t-test (2-tail) was done across subjects to compare the β values for each RSN pair in the drug and placebo (**Figure 3C** and Supplementary Table 1C). The results were corrected for multiple comparisons using FDR with $q = 0.05$ (resulting in a threshold of $p < 0.0167$) and $q = 0.1$ (resulting a threshold of $p < 0.042$). The RSN pairs that showed a significant decrease in coupling under psilocybin were: SM-VisM ($p = 0.0265$), SM-VisL ($p = 0.0051$) and SM-VisO ($p = 0.0151$). The RSN pairs that showed a significant increase in coupling were: VisM-lFP ($p = 0.0001$), VisM-DAN ($p = 0.0156$), VisM-rFP ($p = 0.0023$), VisM-DAN2 ($p = 0.0002$), VisM-Cerebellum ($p = 0.0108$), VisL-DMN ($p = 0.0046$), VisL-lFP ($p = 0.0056$), VisL-rFP ($p = 0.0031$), VisL-DAN2 ($p = 0.0142$), VisO-DAN2 ($p = 0.0256$), AUD-DMN ($p = 0.028$), AUD-ECN ($p = 0.0323$), AUD-lFP ($p = 0.0029$), AUD-rFP ($p = 0.0001$), AUD-DAN2 ($p = 0.0005$), SM-ECN ($p = 0.0105$), SM-lFP ($p = 0.022$), SM-rFP ($p = 0.0026$), SM-DAN2 ($p = 0.034$), DMN-lFP ($p = 0.0029$), DMN-DAN ($p = 0.0058$), DMN2-ECN ($p = 0.0071$) DMN2-lFP ($p = 0.0101$), DMN2-DAN ($p = 0.0005$), DMN2-DAN2 ($p = 0.0091$), ECN-lFP ($p = 0.0077$), ECN-rFP ($p = 0.0098$), lFP-DAN ($p = 0.0026$), rFP-DAN ($p = 0.0187$), and DAN-DAN2 ($p = 0.0161$).

MDMA

The same analysis as above was repeated for the MDMA condition using a q of 0.05, resulting in a threshold of $p < 0.0006$ and $q = 0.1$, resulting in a threshold of $p < 0.0012$. Only one RSN pair showed a significant change in coupling under MDMA, i.e., increased coupling between the DMN2-ECN ($p = 0.0001$).

DIFFERENCES IN MOVEMENT

Both drugs showed significant, yet relatively modest, increased head motion between conditions. The mean head motion under psilocybin and its placebo condition were 0.1 ± 0.05 mm and 0.06 ± 0.015 mm, respectively ($p < 0.01$). The mean head motion under MDMA and its placebo condition were 0.083 ± 0.036 mm and 0.061 ± 0.019 mm, respectively ($p = 0.047$). Power et al. (2012) suggest that head motion can change the results of RSFC, therefore, in the regression analysis, we added several motion confounds: six motion time courses, motion outliers [similar to the procedure of scrubbing within regression (spike regression) mentioned by Yan et al. (2013) and Satterthwaite et al. (2013)] and time courses of RSNs that were driven by motion. However, it still remains possible that the increased movement under the drugs may have caused the changes in RSFC. Hence, we investigated if there was a relationship between the change in estimated motion (mean framewise displacement) between placebo and drug and the change in coupling strength (for pairs of RSNs that showed significant differences in coupling). For most of the RSN pairs no relationship was found ($p < 0.05$). However, under psilocybin, there were significant correlations with motion in the following RSN pairs: VisM-SM ($p = 0.002$), VisL-SM ($p = 0.001$), VisO-SM ($p = 0.02$), VisL-DMN ($p = 0.03$), VisM-rFN ($p = 0.048$), VisL-rFN ($p = 0.01$), VisO-DAN2, DMN-lFN ($p = 0.001$), DMN-DAN ($p = 0.01$). For that reason, the significant results of these RSN pairs should be approached with caution.

DISCUSSION

To our knowledge, this is the first analysis to test the effects of different pharmacological agents using a standard ICA-derived template of RSNs to construct between-network functional connectivity matrixes for different drug states. This approach may have wider application, enabling researchers to determine connectivity "fingerprints" for characterizing different states of consciousness, i.e., not only those induced by pharmacological agents but sleep states and even pathological states. This will enable informed comparisons to be made between different states, potentially allowing us to categorize different states based on their connectivity profiles. Functional connectivity matrixes have been used before to differentiate between pathology states such as schizophrenia and bipolar disorder (Mamah et al., 2013) and here we suggest that they could be used more broadly to characterize states of consciousness, including those induced by psychoactive drugs.

Probably the most striking result of the present study was the marked increases in between-network RSFC under psilocybin.

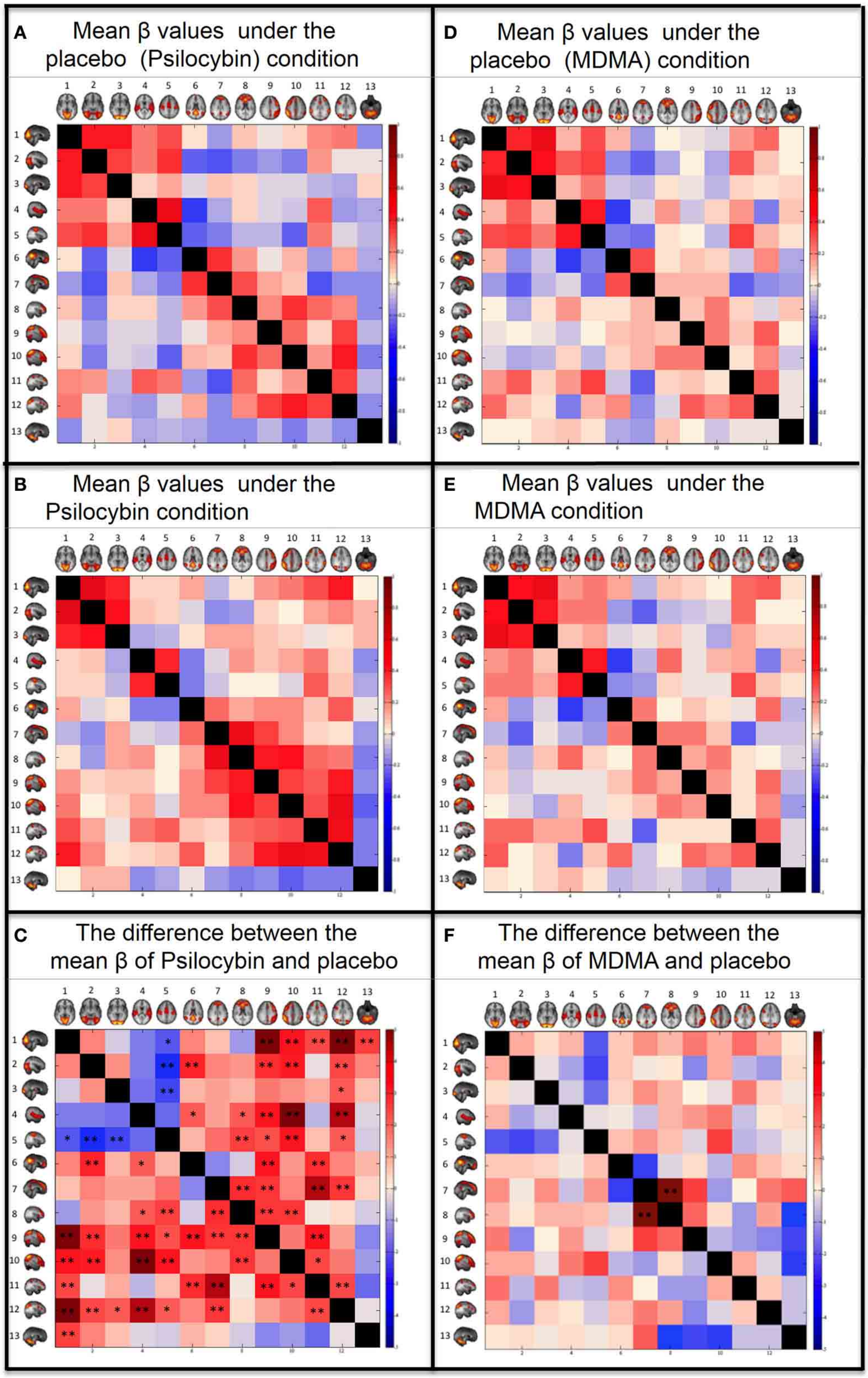

FIGURE 3 | Between networks resting state functional connectivity results. Within each matrix, each colored square represents coupling between corresponding RSN pairs with the color of the square denoting the coupling strength **(A,B,D,E)** or change in coupling strength **(C,F)** between the RSN pairs (blue, negative coupling or a decrease in coupling; red, positive coupling or an increase in coupling). The six images are: **(A)** Group mean of β values for the placebo of psilocybin condition. **(B)** Group mean of β values for *(Continued)*

FIGURE 3 | Continued
the psilocybin condition. **(C)** Paired *t*-test (2-tail) for the difference between the mean β values of psilocybin and placebo. **(D)** Group mean of β values for the placebo of MDMA condition. **(E)** Group mean of β values for the MDMA condition. **(F)** Paired *t*-test (2-tail) for the difference between the mean β values of MDMA and placebo. The networks from Smith et al. (2009) are: (1) Visual–Medial (VisM), (2) Visual–Lateral (VisL), (3) Visual–Occipital pole (VisO), (4) Auditory (AUD), (5) Sensorimotor (SM), (6) Default Mode Network (DMN), (7) DMN2–A hybrid of anterior DMN and Executive Control Network, (8) Executive Control Network (ECN), (9) left Frontoparietal Network (lFP), (10) right Frontoparietal Network (rFP), (11) Dorsal Attention Network (DAN), (12) DAN2, (13) Cerebellum. FDR correction for multiple comparison ($N = 78$) was applied on the *t*-tests: $^*0.05 < q < 0.1$. $^{**}q < 0.05$.

These increases were evident for heteromodal networks, both in terms of increased unimodal-heteromodal (e.g., AUD-rFP) and heteromodal-heteromodal network RSFC (e.g., lFP-ECN). Based on previous analyses (Carhart-Harris et al., 2012b), we had predicted that RSN pairs with weak or negative RSFC at baseline would show increased coupling post-psilocybin, and this was found (e.g., DMN-VisL). However, the increases in between-network RSFC were more fundamental than this, being evident for RSN pairs that were already positively coupled at baseline (e.g., DMN2-ECN). The increase in correlated brain activity across normally distinct brain networks was particularly true for heteromodal RSNs, where the distribution of 5-HT_{2A} receptors is known to be highest (Erritzoe et al., 2010) and 5-HT_{2A} receptor stimulation is linked to desynchronous cortical activity (Riba et al., 2002; Wood et al., 2012; Muthukumaraswamy et al., 2013) and network disintegration (Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2014a).

The pattern of increased between-network RSFC under psilocybin did not apply universally for the whole of the brain. Decreased RSFC was observed between the three visual RSNs and the sensorimotor network [these networks are known to be highly connected (Wise et al., 1997; Van Den Heuvel et al., 2008)], and there was a general trend toward decreased unimodal-unimodal network RSFC (e.g., VisM-AUD and SM-AUD showed decreased RSFC under psilocybin but this failed to survive FDR correction, see Supplementary Table 1). However these decreases can also be explained by the changes in head motion between conditions and further work is required to test whether these decreases in sensory RSN RSFC under psilocybin relate to the drug's characteristic perceptual/hallucinatory effects.

Previous neuroimaging studies with psychedelics have so far failed to reveal a simple and compelling explanation for their characteristic hallucinogenic effects (Vollenweider et al., 1997; Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013) (but see De Araujo et al., 2012) and so drug-induced visual hallucinations remain poorly understood. Under normal conditions, activity in the visual cortex is driven by and thus anchored to visual input. Moreover, activity in other networks (e.g., the DMN), concerned with other distinct functions (e.g., introspection), is often weakly or inversely coupled to visual activity (e.g., see the pale and blue colored squares for the visual-RSN pairs in **Figures 3A,D**). Thus, increased communication between the visual system and systems that are usually reserved for distinct functions may lead to erroneous perceptual associations. For example, increased DMN-visual network RSFC, may relate to an increased influence of imagination (mediated by the DMN) on visual perception (mediated by the visual networks). A similar process may occur in situations of sensory deprivation where sensory processing becomes decoupled from sensory stimulation, allowing the system to "free-wheel" with the potential for the spontaneous emergence of internally-generated percepts. Decreased cross-modality RSFC and increased unimodal to heteromodal network RSFC may be a common characteristic of such states but future studies are required to test this. For example, comparisons between the present results and changes in RSFC in the meditative state could inform these speculations.

Given reports of synesthesia-like experiences under psychedelics (e.g., participants reported that the noise of the MR scanner influenced the rate and content of their closed eye visual hallucinations Carhart-Harris et al., 2012a and see also Luke and Terhune, 2013) one may have predicted increased cross-modality communication under psilocybin rather than the decreased coupling that was observed here. However, it has yet to be determined whether synesthesia-like experiences in drug-induced altered states of consciousness are qualitatively and mechanistically related to synesthesia experienced outside of this context and it is also worth noting that increased visual to heteromodal cortical functional connectivity has been found in color-grapheme synesthesia (Dovern et al., 2012; Sinke et al., 2012) as well as in the present study.

Taking a dynamical systems theory approach to the present results, RSNs can be conceived of as "attractors," i.e., patterns of activity into which the brain tends to gravitate for short periods of time (Deco et al., 2009; Hellyer et al., 2014). A macro-state of consciousness (such as normal waking, deep sleep or the psychedelic state) may, therefore, be graphically represented as an "attractor landscape" in which the depth of "basins of attraction" (valleys in an otherwise flat 2D-plane) reflect the stability of particular RSNs or metastable "sub-states," i.e., more long lasting sub-states will have deep basins of attraction and unstable sub-states will have shallow ones. A recent paper (Kanamaru et al., 2013) has described brain function in these terms, suggesting that the shape of attractors depends on selective attention. In this particular model, high levels of acetylcholine activating muscarinic receptors were found to produce an attractor landscape with more stable sub-states. Relating this to the present results, the increased RSFC observed between different RSNs could be interpreted as a flattening of the attractor landscape, in which the basins of attraction are shallower, implying that the global system will move more easily between different metastable sub-states. A flattened (but not flat) attractor landscape would be consistent with increased "information" in the sense of the "information-integration" theory of consciousness (Tononi, 2012) since greater movement between metastable sub-states would imply that a larger number of these sub-states (or a broader "repertoire") can be entered over a given time. At a critical flatness, the size of the repertoire of metastable states will be maximal but if the landscape is too flat, information will be reduced because attractors will become too unstable. This scenario is referred to as "super-criticality" (Chialvo, 2010), and if taken to the extreme, an entirely flat landscape would imply that the system has no metastable states, or just one entirely disordered one. Future studies are required to determine whether the psychedelic state is "critical" or "super-critical" in this sense (Tagliazucchi et al., 2012; Carhart-Harris et al., 2014a). Another way these results could be perceived however, is that increased between-RSN RSFC under psilocybin is representative of a "sub-critical" system, i.e., one that is more globally synchronous and therefore ordered; however, that there were also decreases in between-RSN RSFC under psilocybin, does not support this view. We intend to follow-up this matter in order to test our hypothesis that it is specifically the *ease of transition* (or transition probability) between RSNs/metastable sub-states that is facilitated under the drug.

In contrast to the marked changes in between-network RSFC observed with psilocybin, only one RSN-pair showed a significant change in RSFC under MDMA, i.e., increased ECN-DMN2 RSFC (**Figure 3F**). This result is difficult to interpret in isolation; however, it is worth noting that ECN-DMN2 RSFC was also significantly increased under psilocybin (**Figure 3C**). MDMA is not considered a classic psychedelic, although like psilocybin, its subjective effects are known to be significantly mediated by serotonergic mechanisms (Liechti and Vollenweider, 2001; Van Wel et al., 2011). Thus, increased ECN-DMN2 RSFC may relate to a shared aspect of these drugs' subjective effects, such as their propensity to alter mood and cognition (Carhart-Harris et al., 2014b). Pre-treatment studies with selective receptor antagonists would help to inform these matters.

There is an important caveat to be addressed about the present analysis. It should be noted that the two studies from which the data was derived employed quite different methodologies (e.g., intravenous administration of psilocybin vs. oral administration of MDMA, different MR scanners and different study samples). Thus, it would be problematic to attempt to make inferences based entirely on a comparison of their relative RSFC profiles. This analysis was not intended to be a formal comparison of the brain effects of MDMA and psilocybin and if this was the intention, then a standardized methodology would need to be employed. Rather, the present analysis has focused on understanding the neural correlates of the psychedelic state as produced by the classic psychedelic, psilocybin, and the finding that MDMA had a less marked effects on between-network RSFC has merely served to emphasize that the psychedelic state rests on a particularly profound disturbance of brain function. This does not imply that MDMA's own subjective effects are unimportant or that they do not involve some (albeit more subtle) changes in between-network RSFC.

The significant change in head movement under psilocybin implies that some of the results should be interpreted with caution, in particular the decreases in coupling strength. We have used multiple ways to model motion as a possible confound but for a subset of the RSN pairs, the changes with drug correlate with the differences in mean motion. These significant correlations do not necessarily mean that motion is responsible for these changes, since intensity of drug is likely to be associated with increased movement, meaning that disambiguating the two effects is problematic for some RSN pairs. In support of this, we found a marginally significant correlation between changes in motion and changes in the subjective intensity rating ($r = 0.382$, $p = 0.08$). Future work restricting head motion in the scanner and with larger samples is necessary to be able to demonstrate that changes in these RSN pairs that correlate with motion reflect genuine brain activity or not.

In conclusion, this new analysis has used between-network functional connectivity to investigate the effects of two distinct serotonergic compounds on spontaneous brain function. It was found that psilocybin produced marked changes in between-network RSFC, generally in the direction of increased coupling between RSNs, with an additional decrease in coupling between visual and sensorimotor networks. MDMA had a notably less marked effect on between-network RSFC implying that psilocybin's more profound effects on global brain function (at least as determined by this measure) may explain its more profound effects on consciousness. The analytic methods used in this study, i.e., using ICA templates to determine functional connectivity matrixes for different drug states, may have wider application, enabling researchers to more objectively describe and potentially categorize different states of consciousness.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2014.00204/abstract

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Neurophysiological correlates of various mental perspectives

Thilo Hinterberger[1,2]*, **Milena Zlabinger**[3] **and Klaus Blaser**[4]

[1] *Section of Applied Consciousness Sciences, Department of Psychosomatic Medicine, University Medical Center Regensburg, Regensburg, Germany*
[2] *Brain, Mind and Healing Program, Samueli Institute, Alexandria, VA, USA*
[3] *Department of Psychology, University of Tübingen, Tübingen, Germany*
[4] *Center for Applied Boundary Studies, Basel, Switzerland*

Edited by:
Etzel Cardeña, Lund University, Sweden

Reviewed by:
Gerd Thomas Waldhauser, University of Konstanz, Germany
Vilfredo De Pascalis, La Sapienza University of Rome, Italy

****Correspondence:***
Thilo Hinterberger, Section of Applied Consciousness Sciences, Department of Psychosomatic Medicine, University Medical Center Regensburg, Regensburg,
Franz-Josef-Strauß-Allee 11,
Regensburg, Germany
e-mail: thilo.hinterberger@ukr.de

A common view of consciousness is that our mind presents emotions, experiences, and images in an internal mental (re-)presentation space which in a state of wakefulness is triggered by the world outside. Consciousness can be defined as the observation of this inner mental space. We propose a new model, in which the state of the conscious observer is defined by the observer's mental position and focus of attention. The mental position of the observer can either be within the mental self (intrapersonal space), in the mental outer world (extrapersonal space) or in an empathic connection, i.e., within the intrapersonal space of another person (perspective taking). The focus of attention can be directed toward the self or toward the outside world. This mental space model can help us to understand the patterns of relationships and interactions with other persons as they occur in social life. To investigate the neurophysiological correlates and discriminability of the different mental states, we conducted an EEG experiment measuring the brain activity of 16 subjects via 64 electrodes while they engaged in different mental positions (intrapersonal, extrapersonal, perspective taking) with different attentional foci (self, object). Compared to external mental locations, internal ones showed significantly increased alpha2 power, especially when the observer was focusing on an object. Alpha2 and beta2 were increased in the empathic condition compared to the extrapersonal perspective. Delta power was significantly higher when the attentional focus was directed toward an object in comparison to the participant's own self. This exploratory study demonstrates highly significant differences between various mental locations and foci, suggesting that the proposed categories of mental location and intra- and interpersonal attentional foci are not only helpful theoretical concepts but are also physiologically relevant and therefore may relate to basic brain processing mechanisms.

Keywords: mental perspectives, attentional focus, EEG, intrapersonal space, empathy

INTRODUCTION

Continuously and with increasing interest, the scientific fields of philosophy and neuroscience are concentrating on the study of the phenomenon of consciousness. Research on altered states of consciousness, meditation, sleep, and out-of-body experiences has become popular in the scientific community. However, there is still a lack of understanding the links between consciousness as a first-person experience and the variety of related psychophysiological results. One of the most challenging problems arises from the categorical incongruences between the concepts of subjective mental experience and the physiological description of the brain. Efforts to approach the problem have been made by Damasio (1999) and Metzinger (2009), among others. Physiological measurements can also be used to justify psychological concepts if their physiological correlates discriminate those concepts. The aim of the present study was to contribute to a new mental model with electrophysiological data as correlates. This model was termed Boundary-Based Awareness Model (BBAM; Blaser, 2011, 2012, 2013) and assumes a structure for the relationship between the observer and the observed mental (re-)presentation that distinguishes between various mental positions of the observer as follows: (1) the inner self model, (2) the physical world model, and (3) empathic connection with other individuals. The model further distinguishes between the corresponding attentional foci. Although the BBAM has been confirmed by two questionnaires, namely the boundary protection scale (BPS; Blaser et al., 2014b) and the interpersonal attention management inventory (IAMI; Blaser et al., 2014a), the physiological role of these mental perspectives has never been studied before. This was the focus of the study presented here. As a first step, this study is an exploratory approach that might generate hypotheses, but it was not designed to give clear evidence of the assumed underlying processes.

PHYSICAL AND MENTAL WORLD

Fundamentally, consciousness is a phenomenon that occurs in a subjective mental domain. It may be regarded as the system-immanent view of neuronal information processing. Therefore, to better understand the intriguing question of how we perceive and understand the physical world and also another person's mind, it is helpful to presume the model of an inner space of the mind and an inner self. Early on, James (1892) distinguished between different kinds of self, such as the physical self, the mental self and the spiritual self. These distinctions seem to reappear in recent concepts of self as discussed in neuroscience (Panksepp, 1998; Damasio, 1999; Gallagher, 2000; Churchland, 2002; Kelley et al., 2002; Turk et al., 2003; Vogeley and Fink, 2003; Dalgleish, 2004; Northoff and Bermpohl, 2004). In modern neuroscience and neurophilosophy, a common view is that our mind represents emotions, experiences and images in an internal mental (re-)presentation space, which in a state of wakefulness is triggered by the outside world (Damasio, 1999; Blaser, 2008; Metzinger, 2009; Hinterberger, 2011). The sensory system can be seen as the physical interface which enables us to come into contact with objects, events and even the emotional contents of other people apart from us. Sensory information becomes entangled with the current mind state, creating the present experience within an inner mental space. For example, the interaction of the mental self with the mental outside world plays a crucial role in the new understanding of schizophrenia (Taylor, 2011). However, using this model for consciousness, it should be noted that being conscious is not just related to the existence of such an inner representation. Moreover, consciousness requires an observer and therefore can be defined as the observation of this inner mental space. While the observer him/herself remains abstract, the self is represented in such a spatial model as the self-model as described by Damasio (1999) or Metzinger (2009). The self can be thought of as part of the inner representation space, more or less separated from the world model that carries those observed objects which are assessed as being separate from our own body. In fact the concept of the self involves a number of different brain functions depending on whether we speak of a biographical self, the cognitive image of the self or the self as an embodied sensory perception. In this context we do not differentiate those aspects because they all might be present to some extent when a person is asked to observe him/herself.

SELF AND OTHER

The mental self can be thought of as embedded in an interconnected fashion within the mental representation space (Damasio, 1999; Northoff et al., 2006). Thus, in analogy to the physical body in which the skin is the boundary that separates us from the outside world, a mental boundary can be attributed to the mental self. Psychotherapists already work with this model and often share a common understanding when speaking about thick and thin boundaries (Tausk, 1992). Accordingly, a protective mental boundary would mean that our mental self is clearly separated from the mental outer world, while in individuals with a blurred boundary, the self and the outer world may overlap and sometimes cannot be clearly distinguished from each other.

The outer world does not only contain more or less meaningful objects. Moreover, social life occurs in this realm, and therefore the mental world model is filled with representatives and concepts of other people one knows. This could explain why therapists often realize that people with thin boundaries sometimes have difficulties with the distinction between emotions, feelings and thoughts belonging to them and those of another person. The Boundary Protection Scale (BPS-20) is a psychometric instrument for determining the properties of an individual's mental boundary (Blaser et al., 2014b). The ability to read the mental states of a fellow human is called mentalizing (Fonagy et al., 2002; Allen et al., 2008). The neural basis of mentalizing and how we distinguish between the self and the other has been studied by many authors (Decety and Sommerville, 2003; Northoff and Bermpohl, 2004; Frith and Frith, 2006a,b; Uddin et al., 2007; Castiello et al., 2010). Special ways of understanding others are represented by compassion (Gusnard et al., 2001; Goetz et al., 2010; Klimecki et al., 2013), empathy (Singer, 2006; Lamm et al., 2007; Hooker et al., 2008; Singer and Lamm, 2009) and theory of mind (Gallese and Goldman, 1998; Vogeley, 2001; Gallagher and Frith, 2003; Völlm et al., 2006). They are, as will be described later on, expressions of different mental perspectives toward the self and the other.

CONSCIOUS OBSERVATION/MENTAL FOCUS AND LOCATION

In this model the "conscious observer" in us is neither identical with the self, nor is it a part of the world, but its mental representation can be attached to or even identified with one of them. In the spatial model of consciousness described above, at least two properties can be attributed to the conscious observer, thus defining his/her state: the mental position or location and the focus or direction of attention[1]. Those properties define the mental viewpoint or perspective.

According to our model, there are at least three places in which the observer can be located: (1) within and in connection with the mental self-construct, which we call the *intrapersonal space* or internal self-referential perspective, (2) within the outer world, free and independent in the mental space which we call the *extrapersonal space* or external perspective, and (3) *perspective taking*, i.e., an empathic connection to another person which can be either cognitive or affectively embodied (Blaser, 2008, 2012, 2013). Accordingly, the focus of attention can be directed either toward the self, i.e., the intrapersonal space, or toward the world, i.e., the extrapersonal space or another person within the extrapersonal space. Both the mental position and focus of attention define the mental perspective of a conscious observation. The combinations of the various mental locations and foci result in ten different perspectives, listed in **Table 1**. They represent the modes postulated by the BBAM (Blaser, 2011, 2012, 2013). To test the spatial attention model on another level, the authors developed a questionnaire, the IAMI. The validation of this new self-rating instrument confirms the concept of an intrapersonal space, an extrapersonal space and the extrapersonal mental space of a fellow human. The IAMI constitutes a tool for assessment of the ability to manage the various states in daily life (Blaser et al., 2014a; see Materials and Methods).

With this mental space model and its interpersonal framework we attempt to reduce mindfulness, compassion, cognitive self-perception, theory of mind, theory–theory and empathy

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[1] These properties of mental location and attentional focus in a mental space might be metaphorically related to the physical properties position and momentum in the physical space-time model. This would imply that mental location and attentional focus are complementary mental categories.

Table 1 | Overview of mental localization, attentional focus, and processing modality according to the BBAM.

No.	Mode	Mental location	Attentional focus	Processing modality (cognitive or affective)
1	IS	Intrapersonal	Own self	Affective (mindful self-centered interoception)
2	IF	Intrapersonal	Object in the outer world	Affective (mindful)
3	IP	Intrapersonal	Another person whose mental location is inside his/her intrapersonal space	Affective (compassion)
4	OS	Extrapersonal	Own self	Cognitive self-perception
5	OF	Extrapersonal	Object in the outer world	Cognitive
6	$E_{cog}F$	Perspective taking	Object in the outer world via another person whose mental location is in the outer world	Cognitive (theory of mind)
7	$E_{cog}P$	Perspective taking	Another person whose mental location is inside his/her intrapersonal space	Cognitive (theory–theory)
8	ES	Perspective taking	Own self	Affective (empathy)
9	$E_{aff}F$	Perspective taking	Object in the outer world	Affective (empathy)
10	$E_{aff}P$	Perspective taking	Another person in his/her intrapersonal space	Affective (empathy)

The first letter in the mode designation codes the mental location while the second letter codes the attentional focus. Some states are perceived more affectively while others are perceived more cognitively.
Mental locations: I, intrapersonal; O, extrapersonal; E, perspective taking (empathic). Attentional foci: S, self; F, object outside of the self; P, other person.

to a common denominator (Blaser, 2012). This novel theoretical framework weaves mental life and interpersonal dynamics together. It enables us to understand the patterns of relationships and what occurs when we come into contact with another person.

NEUROSCIENTIFIC CONCEPTS

Although we do not intend to discuss all the neuroscientific aspects of these concepts we do aim to present some neuroscientific findings relating to the proposed concepts.

The discriminability of mental foci has been shown previously in studies on self-perception, for example the involvement of cortical midline structures in self-reference as seen by neuroimaging studies (Northoff and Bermpohl, 2004).

In earlier research it could be shown that the first-person perspective and the third-person perspective (comparable with the mental locations “intrapersonal space” and “external intrapersonal space” in our model) rely on differential neural processes. For example, Vogeley et al. (2004) were able to identify different brain regions activated by observation tasks when researching mental states of the first- versus the third-person perspective), while Ruby and Decety (2001) used PET measurements to explore the cognitive and neural processing involved in agency.

Some of the modes listed in **Table 1** often occur in the resting state, i.e., while no external task that demands a large amount of resources from the brain functions is being performed. During resting conditions, a person’s mind is usually engaged in information processing, memorization, self-referential thoughts, evaluations, etc. All these tasks require the activation of so-called resting state networks in the brain. One of them is the default mode network (DMN; Raichle et al., 2001), which comprises a number of non-goal-oriented mental processing functions such as task-independent introspection or self-referential thoughts. From the literature we could not decide whether the DMN relates more to a self-directed attentional focus or an embodied self-centered mental location. Therefore, one could expect the DMN to be active during the intrapersonal modes but also in self-directed modes.

In this study we focus on the correlates with EEG data. This necessitates an introduction to some related concepts with the corresponding EEG results.

Intrapersonal space (I)

Jann et al. (2010) and Mantini et al. (2007) described EEG correlates of the resting state networks. They found that the DMN, which we would assume to be active in intrapersonal mental locations, correlated with increased frontocentral alpha1, posterior, and occipital alpha2 and parietal beta1. Delta and theta were decreased. Ward (2003) also reports that alpha could increase during attentional tasks in order to avoid distraction, and alpha has also been shown to be stronger when attention was directed toward internal mental imagery rather than external input (Cooper et al., 2003).

Extrapersonal space (O)

In contrast, the extrapersonal modes require adoption of an external viewpoint and might therefore reduce DMN activity.

Perspective taking (E)

Perspective taking or imagination of a well-known person is a memory-related task. Increased theta activity has been found to be associated with memory functions, i.e., both encoding and retrieval of information (Klimesch, 1999; Başar et al., 2000; Ward, 2003).

Attentional focus

A self-directed mental focus could also be part of the DMN (Knyazev, 2013), leading to decreased delta and theta band activity and increased frontocentral alpha1, posterior, and occipital alpha2 and parietal beta1 (Mantini et al., 2007; Jann et al., 2010).

Cognitive versus affective processing

As listed in **Table 1** some of the intrapersonal modes are attributed to emotional and affective processing, i.e., all perceptions are related to the person's own physical being. In contrast the extrapersonal modes are attributed to cognitive processing as all perceptions (of the self, of other persons or of external objects) are cognitively evaluated. Perspective taking can be cognitive (theory of mind or theory–theory), but if it occurs with an empathic attitude and emotions are involved, we treat it as affective. Electrophysiologically, cognitive processing is associated with a decrease in alpha band activity and an increase in theta activations (e.g., Ramos et al., 1993; Klimesch, 1996, 1999). Ray and Cole (1985) attributed alpha to the attentional aspect and beta waves to cognitive and emotional processing, with activation in the temporal areas for emotionally positive or negative tasks and in the parietal areas for cognitive tasks. The prefrontal sector is most directly associated with emotion (for an overview and commentary see Davidson, 2004). There is no consistent pattern of alpha activity comparing neutral and affective stimuli. Aftanas et al. (2002, 2004), for example, found an increase in posterior and anterior alpha with affective stimuli, whereas De Cesarei and Codispoti (2011) found a decrease in posterior sites. Uusberg et al. (2013) found enhanced high alpha in central and parietal areas in late event-related potentials with emotional stimuli, most prominently with aversive stimuli. Müller et al. (1999) identified the temporal areas as being associated with positive (right hemisphere) and negative (left hemisphere) emotions. Regardless of the valence they found enhanced gamma band power (30–50 Hz) at right frontal electrodes with emotional processing compared to processing of neutral pictures. Although the field of cognitive and affective neuroscience is large most studies have been performed with visual stimuli, and a clear correspondent of our tasks could not be found in the literature. This restricts the formulation of a very specific hypothesis.

More detailed relationships between these concepts and the states examined in our study will be mentioned in the section "Materials and Methods." An explicit classification of mental location, mental foci and their combinations has never been studied before. However, as these concepts overlap with well-researched concepts it can be supposed that the modes of the model presented here discriminate between each other as well.

The aim of the present study was to assess EEG pattern differences between mental location and the direction of the attentional focus. The existence of neurophysiological differences between the mental states defined in the spatial attention concept would demonstrate as a first step the neurophysiological relevance of this concept. Our hypothesis in this study was that in a guided exercise the various tasks would not only represent subjectively different states of consciousness but also show significantly different patterns on spectral EEG data. This was tested by measuring 64 channels of EEG in 16 participants who were guided through six of the mental states from **Table 1** to investigate the differences between mental locations and also between attentional foci. A more specific formulation of the hypothesis is given in the section "Materials and Methods."

MATERIALS AND METHODS

PARTICIPANTS

Sixteen healthy participants (10 female, 6 male) aged between 33 and 70 years (mean: 52 years) took part in one experimental session and gave written informed consent. All of them had previously participated in a workshop in which they had practiced the different mental states through the IAMEx as presented below. To verify that the studied sample showed no pathological conspicuity but rather increased mental abilities all participants completed the following questionnaires: the IAMI, BPS-20, Revised Symptom Check List (SCL-90R), and freiburg mindfulness inventory (FMI). The study was approved by the legal ethics committee of the University Clinic Regensburg.

STUDY DESIGN

Assessment through questionnaires

Boundary Protection Scale (BPS-20). Blaser constructed the BPS-20 to assess the ability of a person to maintain his/her personal boundaries. It consists of 20 items, six of them framed negatively, which are summed to yield a single boundary protection value. The higher this value, the worse is the boundary protection. Ratings are given on a scale from 1 (almost never) to 5 (almost always). The internal consistency of this scale was found to be 0.71 (Cronbach's alpha) in a validation study with 1,089 participants (Blaser et al., 2014b).

Interpersonal attention management inventory (IAMI). This consists of 50 items dealing with everyday life experiences leading to 10 factor items assessing the ability to control the direction of the attentional focus and the mental location. As each of the 10 subfactors is related to one of three mental locations it is possible to construct three major factors assessing the ability to manage the inner, the outer and the empathic mental perspective. Ratings are given on a scale from 1 (almost never) to 5 (almost always). The IAMI was validated in the same study as the BPS-20 involving 1,089 participants and showed an internal consistency of 0.87 (Cronbach's alpha; Blaser et al., 2014a).

Freiburg Mindfulness Inventory (FMI). Mindfulness, with its subfactors *presence* and *acceptance,* was measured using the 14-item version of the FMI (Buchheld et al., 2001; Buchheld and Walach, 2002; Walach et al., 2006). The FMI assesses self-ratings of awareness and non-judgment of present-moment experiences (Buchheld et al., 2001; Buchheld and Walach, 2002; Heidenreich et al., 2006; Walach et al., 2006; Kohls et al., 2009). Sample items are "I am open to the experience of the present moment" and "I accept unpleasant experiences." Ratings are given on a scale from 1 (no, never) to 4 (yes, always). The global FMI scale yielded an internal consistency of 0.83 (Cronbach's alpha), while the two subfactors only reached 0.71 (presence) and 0.64 (acceptance; Kohls et al., 2009). The validation study with 1,089 participants showed an internal consistency of 0.83 (Cronbach's alpha) for the FMI.

Revised Symptom Check List (SCL-90R). Psychopathological symptoms were assessed using the SCL-90R self-rating questionnaire (Franke, 2002) with 90 items focusing on 9 scales. Additionally, three global factors can be calculated, namely a Global Severity Index, the Positive Symptom Distress Index and the Positive Symptom Total. In our analysis, all of the values were transformed into normalized *t*-values with a mean of 50 and a standard deviation of 10. Cronbach's alpha was reported to be in the range between 0.75 and 0.97.

The Interpersonal Attention Management Exercise (IAMEx)

For therapeutic treatment Blaser has developed a mental exercise termed the IAMEx. The IAMEx is used to train voluntary achievement of the various states and representation modes. This exercise was practiced with all participants and comprised the main part of this study. It provided the various mental states for the neurophysiological discrimination of different mental locations, attentional foci and processing modes. For the purposes of experimental consolidation we restricted our study to the mental foci self and object. Therefore, only six of the mental perspectives taken from the list in **Table 1** were studied physiologically by EEG measurements during the instructed exercise. Explicitly, in our study the participants were guided through the states displayed in **Figure 1**, characterized as follows:

Mode IS. This involves directing the focus of one's attention at the internal from within the intrapersonal space (self-centered introspection). The bodily sensation is the experience of being present in the moment of subjective experience as it occurs (Stern, 2004). This also relates to so-called focusing, a method that enables a person to get in touch with his/her emotions physically through bodily experience (Gendlin, 1998). This is related to the theory of Damasio (1999), who coined the phrase "I feel, therefore I am."

Instruction. Try to center yourself. Perceive your breath. Are you breathing deeply or superficially, slow or fast, with the chest, with the belly or with both? There is no need for you to change anything, only to perceive. Are you aware of any feelings and do you notice bodily sensations? Where do you perceive something? Yield to it.

Mode IF. Directing the attention from the intrapersonal space to the exterior world, one is still connected to the physical body in a mindful way. To look outside from within involves a bi-focussed mode of perception, i.e., perceiving the outer world and simultaneously feeling one's own bodily sensations. This mental state is central to mindfulness-based therapy forms (Segal et al., 2002).

Instruction. Now turn your attention to the flowers (which stand on a table 3 m away from the participant). Remain self-centered and mindful. What changes occur in your bodily sensations when you perceive the plants mindfully?

Mode OS. By crossing one's own self-boundary with the location of attention from inside to outside one arrives in a cognitive mental state, disconnected from the inner world and bodily sensations; functions such as the working memory, problem solving, analyzing, and planning of processes are activated. Simultaneously, the DMN activity should be reduced. That enables cognitive self-perception, i.e., to look from the outside, from a meta-position, at one's own feelings. It is associated with the normal forms of dissociation in contrast to the pathological forms (Putnam, 1997). Previc (2009, 2011) associates distant extrapersonal states such as dreaming, hallucinations, out-of-body experiences or religious activity with ventral dopaminergic pathways.

Instruction. Imagine you're standing on a white sheet of paper which lies 4 m in front of you, looking from there to yourself sitting on the chair with the electrode cap on your head. What are you seeing? How is this for you?

Mode OF. As with mode OS the mental location is in the extrapersonal space, but the focus of attention is an object in the outer world. This is associated with cognitive control, for example as described by Herwig et al. (2007), which is important for an objective viewpoint toward an object in the outer world. The intended state does not require a self and is therefore called a "selfless"[2] state.

Instruction. Imagine you're still standing on the white sheet of paper, now looking from there to the flowers. How is it now, when you're looking from there to the flowers?

Mode EF. As with modes OS and OF the mental location is in the extrapersonal space, but the focus of attention are the thoughts of another person about an object. This is known as the theory of mind or cognitive empathy (Shamay-Tsoory et al., 2009) in the sense of thinking about the thoughts of another person (Gopnik and Wellman, 1992).

Instruction. Imagine a previously determined person now enters the room and positions herself to the left of you on a green sheet of paper. What is she thinking, when she is looking at the flowers from there? What do you guess she is thinking looking at the flowers?

Mode ES. With one's mental location in an external intrapersonal space and the focus on one's own person, one can look in an empathic way at one's own feelings. In contrast to cognitive empathy and the mirror neuron system, which displays a form of affective or emotional empathy (Shamay-Tsoory et al., 2009), for some authors this is (together with modes $E_{aff}F$ and $E_{aff}P$, see **Table 1**) the "real" form of empathy, whereas the other forms (modes IP, $E_{cog}F$ and $E_{cog}P$, see **Table 1**) are not denoted with the term "empathy" (e.g., Singer and Lamm, 2009). This can be described as looking through the emotional glasses of another person and can be achieved by asking the question "how would it be for me?" (Lamm et al., 2007).

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[2] We have used quotation marks to indicate that the term "selfless" should not be construed with its usual meaning of "altruistic."

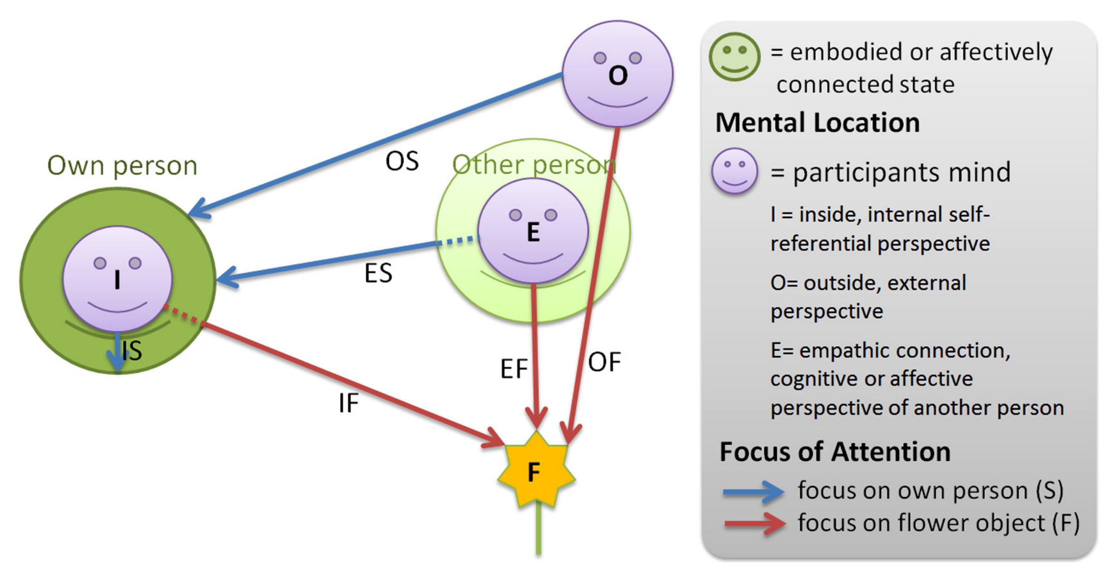

FIGURE 1 | Illustration of the 6 task conditions in this study. Participants were asked to adopt three different mental locations in which they focused either on their own body or on flowers in the room. The states are identified by two-letter acronyms describing location and focus.

Instruction. Imagine the person takes one step away from you and you take her place on the green sheet of paper and empathize with her. What is she feeling, when she looks from there at you sitting on the chair with the electrode cap? What are your bodily sensations when looking through her emotional glasses at yourself sitting there?

Experimental procedure

A sequence of nine different instructions led the participant through all states of interest within one IAMEx as listed in **Table 2**. The experimental session was subdivided into three EEG recording phases. The first phase consisted of a short reference measurement with 2 min of the participant sitting relaxed with open eyes, 2 min of sitting with closed eyes and another 2 min of reading a text from an arbitrary book. Recording phases 2 and 3 were carried out with open eyes. Each of them consisted of a guided IAMEx according to **Table 2**. After each instruction the corresponding state should be maintained for about 1 min, so the whole exercise took a bit less than 15 min including the time for the instructions. Recording phase 3 repeated phase 2 in order to increase statistical power and possibly test for retest stability. After both phases 2 and 3 the participant was asked on a self-rating scale how well he/she was able to fulfill each of the experimental tasks 2–8 in **Table 2**.

Experimental setup

All physiological data were recorded with a 72-channel QuickAmp amplifier system (BrainProducts GmbH, Munich, Germany). EEG was measured using an actively shielded 64-channel electrode cap with Ag/AgCl electrodes which were arranged according to the international 10/10 system (ANT, Netherlands). The system was grounded at the participant's shoulder. Data were recorded with a common average reference and filtered in a range from DC to 70 Hz at a sampling rate of 250 Hz and 22-bit resolution. For correction of eye movement and blink artifacts, a vertical and horizontal electrooculogram was measured by placing two electrodes above and below one eye and two electrodes on the left and right side of the eyes. Respiration rate was measured with a respiration belt and skin conductance on the second and third finger of the non-dominant hand. Additionally, an electrocardiogram (ECG) was assessed with two electrodes. In this report we only focus on the EEG data.

At least two experimenters were present. One of them (K.B.) served as instructor guiding the participants through the IAMEx. The other experimenter was monitoring the raw data during the recording and writing a time stamp protocol taking note of the start and end times, i.e., when the instruction was completed and when the next instruction was started. The participant was seated in a comfortable chair in one corner of the room. From there he/she could view a white and a green sheet of paper on the floor as well as a vase with flowers on a small board as specified in the IAMEx (see instructions above). All three objects were about 3–4 meters away from the participant and about 0.5–1.5 meters from each other.

EEG DATA ANALYSIS

EEG signal processing

The whole data analysis was performed using Matlab. After detrending the DC recorded EEG data sets all EEG channels were corrected for eye movements using a linear correction algorithm which detects eye blinks and movement events and uses those periods to determine a correction factor for each channel. The electrooculogram was multiplied by this factor and then subtracted from the EEG according to Gratton et al. (1983).

A power spectrum time series was calculated using the fast Fourier transform (FFT). FFT was applied to the windowed EEG time series, which was convolved using a Nutall window and shifted in steps of 0.5 s. A window size of 2 s was chosen for

Table 2 | Sequence of different tasks in the IAMEx.

No.	Task	Mental location	Attentional focus	Processing modality
1	Resting with eyes open	U	U	U
2	Intrapersonal mental location observing the self from within and one's own body (mindful interoception, self-centered state)	I	S	A
3	Intrapersonal mental location observing an object in the outer environment Leaving the inner boundary	I	F	A
4	Extrapersonal mental location observing the self from an outside viewpoint (cognitive self-perception)	O	S	C
5	Extrapersonal mental location, observing an object in the outer environment ("selfless" state)	O	F	C
6	Taking over the cognitive perspective of another person and observing the same object (theory of mind)	E	F	C
7	Merging with another person observing the self and physical sensations (empathic self-perception) Approaching the self and reconnecting	E	S	A
8	Intrapersonal mental location experiencing one's own physical sensations and observing the self (mindful interoception)	I	S	A
9	Resting with eyes open	U	U	U

The right columns indicate the mental location and the focus which define a task.
Location: U, undefined; I, inside; O, outside; E, perspective taking (empathic).
Focus: U, undefined; S, self or own physical sensations; F = flowers.
Processing modality: U, undefined; A, affective; C, cognitive.

calculation of the FFT frequency coefficients. This resulted in 140 FFT frequency bins from 0–70 Hz and a resolution of 0.5 Hz. To limit the influence of high-amplitude artifacts the spectral amplitudes were limited to 5 standard deviations. To obtain a measure of the power spectral density (PSD), FFT values were squared. The FFT bins were then averaged into 7 standard frequency bands: delta (1–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12 Hz), beta1, or SMR (12.5–15 Hz), beta2 (15.5–25 Hz), gamma (25.5–47 Hz), and an additional high gamma band (53–70 Hz). All data were visually inspected in a time-frequency-resolved fashion to detect periods of noise or bad signals in order to control for bad electrodes or longer periods of EMG noise or other artifacts. Short-term artifacts were controlled for by the use of medians as described below. The high gamma band was not expected to provide reliable information and therefore was only used for discussion of possible high-frequency artifacts such as muscle tension, which are normally more visible in the high frequencies. Thus, for statistical comparison only the first seven frequency bands were considered.

Epoching

Before segmentation of the data streams from the three recording sessions the PSD time trace was detrended in order to be independent from a possible sequence effect. Then, the data stream was cut into epochs according to the different task conditions, resulting in six resting state conditions (five with eyes open and one with eyes closed), one reading condition and two times the nine tasks of interest as shown in **Table 2**. For temporal averaging of the PSD time traces within each task epoch all 2 s intervals were averaged. As there were two intervals per second about 120 values were averaged in an epoch of about 1 min. In order to be robust against rare but possible high-amplitude artifacts the temporal median was used and the interquartile range served as a measure for the standard deviation which can be estimated by multiplication by 0.7413 (see Matlab function iqr). Thus, an average EEG PSD with its standard deviation was available for each task condition, electrode, frequency band and participant. Further reduction levels were achieved by averaging over all electrodes, resulting in the global band power.

In addition to the six single tasks for the analysis of locations and foci, three conditions were added with specific location only and no specific focus, i.e., both foci were merged into one epoch. Also, to analyze conditions that discriminate between the two foci only, two conditions were added in which all locations were merged. As shown in **Table 3** the unspecific or arbitrary location was indexed with an X as the first letter and the arbitrary focus was indexed with an X as the second letter. This resulted in 11 mental conditions of potential interest.

Statistical comparisons

In order to uncover the specificities of each condition it was necessary to contrast them with each other. According to our model

Table 3 | A matrix showing the indices for 11 conditions of various foci and locations.

Mental location	Attentional focus		
	Self	**Object**	**Both merged**
Intrapersonal	IS	IF	IX
Extrapersonal	OS	OF	OX
Empathic	ES	EF	EX
All merged	XS	XF	–

Location: I, intrapersonal; O, extrapersonal; E, empathic connection; X, all three locations were merged.
Focus: S, self or own physical sensations; F, flowers; X, both foci were merged.

in **Figure 1** two general types of comparisons can be distinguished, namely those comparing different locations with each other and those comparing the different foci. The location comparisons aim to distinguish between an internal, external and empathic mental position. These comparisons were made with an unspecific focus and the self- and object-oriented focus, resulting in nine comparisons [**Table 4(1)**]. The distinction between the object- and self-directed mental focus was calculated for merged mental locations and for the three specific locations [**Table 4(2)**]. An additional contrast condition was chosen which should show the difference between a "selfless" state, defined as an outside position with the attention directed toward an external object, and a self-centered state, defined as an internal mental position with self-directed awareness. The corresponding category was termed "relatedness" [**Table 4(3)**]. Finally, as some of the instructions require cognitive processes and others ask for affective and emotional involvement we decided to contrast the cognitive and affective processing modes by averaging all cognitive tasks (i.e., OS, OF, EF) and all affective tasks [i.e., IS, IF, ES; **Table 4(4)**]. Together with one additional comparison of the resting state with eyes open versus closed a list of 16 comparisons or contrasts of interest was available. As a measure of the difference between tasks within each person we chose the estimated effect size by using the formalism of Cohen's d, however, we used the median of epochs instead of the mean and an estimated standard deviation using the interquartile range.

In order to account for the differences in the fulfillment of specific tasks the effect size of each participant, task, electrode, and band was multiplied by a self-rating factor specific for each task and participant. This self-rating factor was calculated by averaging the self-ratings (1–5) over all single tasks which formed the task condition and dividing by the average across all task conditions.

Before calculation of the effect across participants the Anderson–Darling test of normal distribution was performed, showing that delta and alpha values in particular were not normally distributed. As a consequence, a Wilcoxon signed rank test was applied to the differences in effects corrected for individual task fulfillment to estimate the significances of those task comparisons.

Further considerations

Correction for multiple comparisons is not trivial as such measures are highly dependent on each other. Therefore, Bonferroni correction of significance levels would be far too conservative and wipe out most effects. The false discovery rate (FDR) adjustment method constitutes a less conservative approach. Based on the formulas of Benjamini and Hochberg (1995) and Yekutieli and Benjamini (1999), we applied FDR adjustment to the *p*-values across six frequency bands and 15 comparisons. In the results shown in **Figure 2**, all values that survived FDR adjustment at the 5% level were marked with a white dot. A pink dot marked those values with $p < 0.01$ and a green dot was used to mark marginally significant results with $p < 0.06$. Thus, the topographic mapping in **Figure 3** of the dotted fields from **Figure 2** might present reliable positive results.

Table 4 | The contrasted conditions are listed systematically.

		Foci			
		Arbitrary	***Self***	***Object***	
(1) Comparisons of locations	*Intra-extrapersonal*	IX-OX	IS-OS	IF-OF	
	Intrapersonal-empathic	IX-EX	IS-ES	IF-EF	
	Empathic-extrapersonal	EX-OX	ES-OS	EF-OF	
		Locations			
		All locations	***Inside***	***Outside***	***Empathic***
(2) Comparisons of foci	*Object-self*	XF–XS	IF–IS	OF–OS	EF–ES
(3) Relatedness	*"Selfless"-self-centered*	OF-IS			
(4) Processing mode	*Cognitive-affective*	C–A = (OS + OF + EF)–(IS + IF + ES)			

The comparisons in bold are those of special interest which formed the basis of our hypotheses.

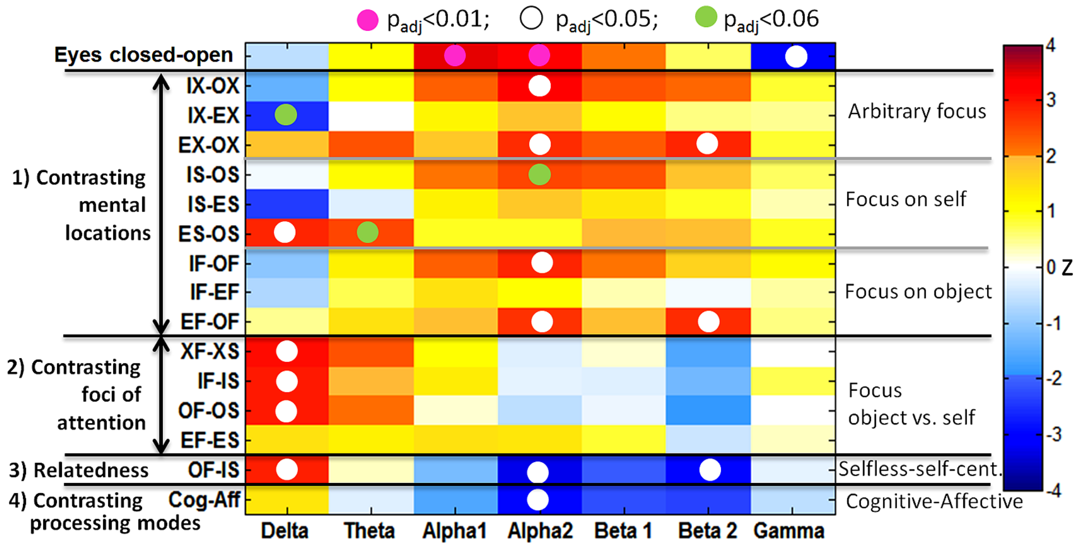

FIGURE 2 | Significances of mean differences between conditions displayed for the global band power measure. Significant contrasts are shown as red and dark-blue fields. The white dots indicate that the *z*-score remained significant ($p < 0.05$) after FDR adjustment across seven frequency bands and 16 comparisons. Pink dots were significant at $p < 0.01$, and the green dots indicate $p < 0.06$.

HYPOTHESES

(H1) On the global scale, we expected band power differences in the EEG comparing all mental tasks as shown in **Table 4**. Topographic differences were calculated for the specific comparisons shown in bold in **Table 4**. Here, we assumed that the distinct subjective states of consciousness would express themselves in discriminable topographic and spectral EEG patterns. Specifically, we hypothesized that

(H2) Different *mental locations* would present different spectral EEG patterns. Therefore, the tasks IX, OX, and EX have to be compared to each other. According to Knyazev (2013), self-referential processing should show enhanced alpha and beta oscillations and diminished theta and delta activities. The same prediction could be made when hypothesizing that OX tasks reduce DMN activity, which is active in IX tasks according to Jann et al. (2010).

The EX mode involves memory-related tasks because of the need to imagine a well-known person and therefore should exhibit increased theta waves (Ward, 2003).

(H3) Self-directed and object-directed *mental foci* should show different EEG patterns. The tasks XF and XS will be contrasted. According to Knyazev et al. (2011) extraversion (possibly similar to XF) could be predicted by increased posterior and decreased orbitofrontal theta activities. As self-referential thinking is sometimes associated with the DMN of the brain it is further hypothesized that the corresponding EEG characteristics will match those of the XS state.

(H4) *Self and other:* this is a special combination of the previous modes in which a self-concept is not involved at all and which is expected to be different to a state in which a self-concept is referenced to itself (OF-IS). Therefore, we would expect to find both the correlates of IX-OX (hypothesis 1) and the correlates of XF-XS (hypothesis 2) in this mode.

Here also, according to Knyazev (2013), during self-referential processing alpha and beta oscillations should increase, while theta and delta activities should be larger in the "selfless" state (Knyazev, 2012).

(H5) As can be seen from **Table 1** we ask whether the IAMEx also presents a discriminable difference between *cognitive* and *affective processing* modes. This is an additional hypothesis which does not directly relate to the model of focus and location but is included because of the categorization of the modes into more affective and more cognitive ones. While cognitive processing is expected to show decreased alpha and increased theta band activities, emotional processing would exhibit increased alpha and right frontal gamma band oscillations.

(H6) The confounding variables age and gender should not have a significant influence on the results.

RESULTS

PARTICIPANT CHARACTERISTICS

The results of the questionnaires were used to characterize the sample of participants. Therefore, the participants' responses to the FMI, BPS-20, and IAMI were compared with the population means taken from validation studies. Validation of the BPS-20 and IAMI included 1,089 participants, and the SCL-90R was compared with the population means published by Franke (2002). The results listed in **Table 5** reveal our participants as having higher personal boundary protection compared to the population mean ($d = -1.29$) and slightly higher individual attention management ($d = 0.46$); in particular, inner boundary management exceeded that of the normal population ($d = 0.79$). The participants also showed higher mindfulness scores ($d = 0.45$–0.72, depending on

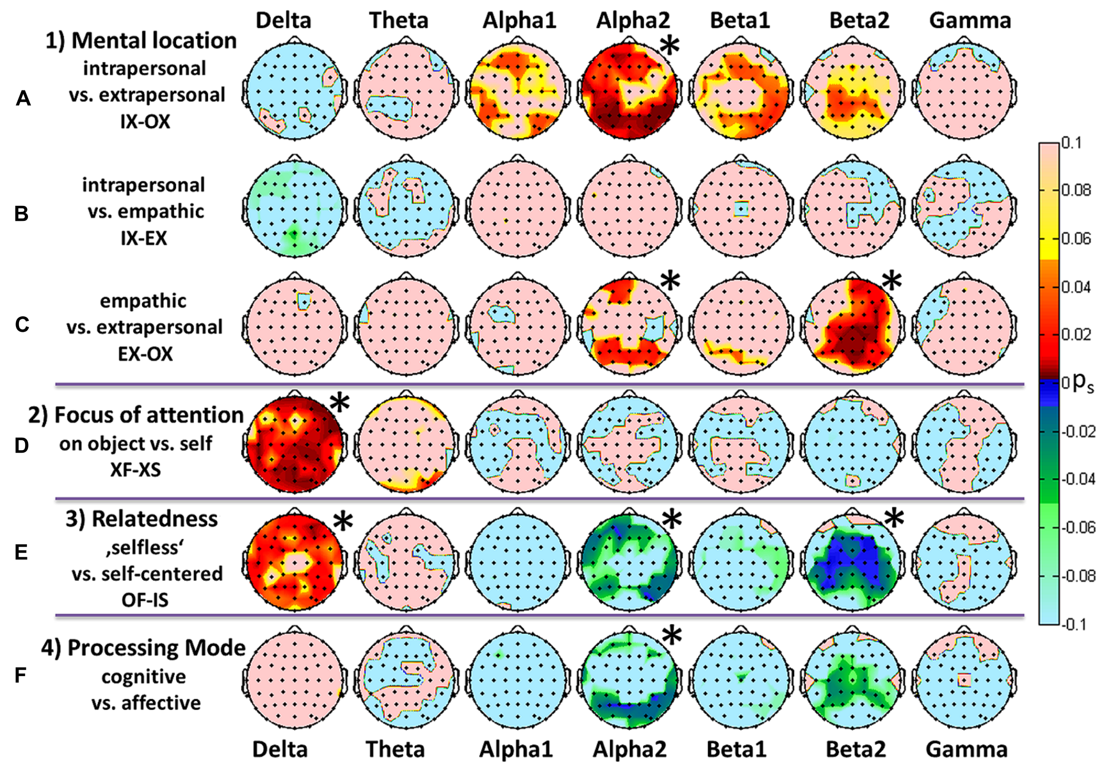

FIGURE 3 | Comparisons of the most prominent findings depicted as topographic color maps for all frequency bands. FDR-adjusted signed p-values resulting from a Wilcoxon signed rank test for 16 participants. Red areas represent a significant increase while green/blue signaling represents a significant decrease in spectral power. **(A–C)** Different mental locations with an arbitrary focus. **(D)** Comparison of attentional foci, i.e., the flowers versus self-directed, independent of the location. **(E)** Differences between a "selfless" and a self-centered mind set reflected by a change in both position and focus. **(F)** Contrast between mental processing modes. The asterisks indicate overall significance according to **Figure 2**.

the factor). Psychopathological symptoms measured with the SCL-90R were within the range of the normal population (±1 SD) in 14 of 16 participants. Altogether, our participants formed a psychologically healthy sample with a high mindfulness self-rating and increased boundary protection as well as increased attention management abilities.

Task fulfillment

The fulfillment of each task was rated by the participants on a scale from 1 to 5. On average, 6.8 of the 16 participants rated the tasks as having been fulfilled with a score of 4.5 or 5; 6.1 of 16 gave a score of 3.5 or 4; 2.5 of 16 gave a score of 2.5 or 3, and 0.6 of 16 rated task fulfillment with low scores of 1–2. A detailed list for specific tasks is shown in **Table 6**.

GLOBAL EEG DIFFERENCES

General effects

To generally test the differences between the 11 conditions across participants a non-parametrical Friedman test was applied to the spectral data of the 16 participants. Electrodes were used as blocking factor. All bands presented a highly significant effect with $F > 73$ and $p < 0.001$ except for the gamma band, which was not significant. Similarly, a Friedman test was applied to the effect sizes of the 16 comparisons between tasks with electrodes as blocking factor. All bands presented highly significant effects ($F > 400$, $p > 0.001$). This allowed for a detailed analysis, and, moreover, our global hypothesis (H1) was confirmed.

Specific global analysis

Significance values of PSD differences on a global scale (global band power) of 16 comparisons resulting from a Wilcoxon signed rank test with subsequent FDR adjustment of p-values across seven bands and 16 comparisons are illustrated in **Figure 2**. The first row shows the trivial result of an "eyes closed vs. open" contrast leading to a highly significant alpha1 ($z = 3.46$, $p_{\text{adj}} = 0.007$) and alpha2 ($z = 3.36$, $p_{\text{adj}} = 0.009$) power increase in closed eyes with a simultaneous gamma decrease ($z = -2.95$, $p_{\text{adj}} = 0.02$). This result will not be discussed further. In all other comparisons participants had their eyes open.

Mental locations. Contrasting all inside with all outside mental locations showed a significant increase in alpha2 ($z = 3.21$, $p_{\text{adj}} = 0.012$), but also in the beta band, without reaching the significance level of 0.05 after FDR adjustment. Specifically, this alpha2 increase reached significance in the object-directed contrast IF-OF ($z = 2.84$, $p_{\text{adj}} = 0.021$). There was no difference in delta power between IS and OS, but it was significantly stronger in empathic self-perception compared to cognitive self-perception (ES-OS: $z = 2.84$, $p_{\text{adj}} = 0.021$). The hypothesis (H2) of increased alpha2 was confirmed, while the

Table 5 | Results of the BPS-20, IAMI, FMI, and SCL-90R questionnaires from participants in the current study compared with the population mean.

Inventory	(Sub-) Scale	Study mean (±Std)	Population mean (±Std)*	Effect size (Cohen's d)
BPS-20	BPS	51.6 (±10.1)	62.2 (±8.2)	−1.29
IAMI	Total	186.0 (±19.0)	178.0 (±17.2)	0.46
	Inside	57.6 (±4.9)	52.5 (±6.5)	0.79
	Outside	77.9 (±8.4)	74.9 (±8.1)	0.37
	Empathic	50.4 (±9.0)	50.6 (±7.9)	−0.03
FMI	Total	42.4 (±4.0)	37.7 (±6.4)	0.62
	presence	19.0 (±1.6)	16.6 (±2.9)	0.72
	acceptance	23.4 (±3.0)	21.1 (±4.2)	0.45
SCL-90R	GSI	49.6 (±8.3)	50 (±10)	−0.03
	PSDI	46.9 (±8.1)	50 (±10)	−0.24
	PST	50.3 (±8.1)	50 (±10)	0.02

**N = 1,089 (see Blaser et al., 2014a,b). GSI, Global Severity Index; PSDI, Positive Symptom Distress Index; PST, Positive Symptom Total; STD, Standard Deviation.*

Table 6 | The average number of the 16 participants with the self-ratings for each task is listed.

Task	Fulfillment self-rating			
	$R \leq 2$	$R = 2.5$ or 3	$R = 3.5$ or 4	$R = 4.5$ or 5
IS	0	1.5	5	9.5
IF	0.5	1	6.5	8
OS	1.5	3	6	5.5
OF	0	4	6.5	5.5
EF	0	2.5	7	6.5
ES	0	3	5.5	7
IS	2	2,5	6	5.5

expected increase in beta activity did not reach significance after FDR adjustment, and decreased delta and theta could not be confirmed.

Increased alpha2 ($z = 3.67$, $p_{\text{adj}} = 0.02$) and beta band power, with a predominance of beta2 ($z = 2.79$, $p_{\text{adj}} = 0.023$), was visible in empathic connections with another person compared to the extrapersonal location (EX-OX). This effect was especially strong in the object-oriented focus EF-OF, with significantly increased alpha2 ($z = 2.69$, $p_{\text{adj}} = 0.034$) and beta2 ($z = 2.79$, $p_{\text{adj}} = 0.023$). The hypothesized increase in theta did not reach significance.

Attentional foci. Contrasting attentional foci revealed a different picture, with the strongest and highly significant differences in the delta band for the comparisons XF-XS ($z = 3.10$, $p_{\text{adj}} = 0.017$), IF-IS ($z = 2.95$, $p_{\text{adj}} = 0.019$) and OF-OS ($z = 3.00$, $p_{\text{adj}} = 0.019$). This would confirm the hypothesis (H3) of an increase in delta in the externally directed foci, which would reduce DMN activity. The change in the theta band did not reach significance after FDR adjustment, and the alpha and beta bands were not sensitive to the attentional focus as hypothesized.

Relatedness. Taking both comparisons together, i.e., foci and locations, constitutes the category relatedness. Here, an outside mental location with the focus on an external object (OF) showed increased delta band activity ($z = 2.90$, $p_{\text{adj}} = 0.021$) and decreased alpha2 ($z = -3.26$, $p_{\text{adj}} = 0.011$) and predominantly beta2 activity ($z = -2.95$, $p_{\text{adj}} = 0.019$) in contrast to an internal self-focused mental awareness (IS), as shown in the second last row of **Figure 2**. As suggested in hypothesis H4 we found a combination of the correlates of IX-OX and XF-XS with significant patterns in delta, alpha2 and beta2 bands.

Processing mode. Clear similarities were visible between the categories relatedness and the processing mode. In the latter, only the alpha2 band reached significance after correction ($z = -2.95$, $p_{\text{adj}} = 0.019$). The alpha decrease in cognitive modes could be confirmed, while a theta increase in cognitive modes and higher gamma band activities in emotional processing, as proposed in hypothesis H5, could not be found.

Influence of age and gender

Although the statistical power with 6 male subjects seems to be quite small for detecting reliable gender differences we tested for possible differences. A Kruskal–Wallis test on the global band power differences across 16 comparisons and 7 frequency bands did not show significant differences between male and female participants [$\chi^2(df = 1) = 0.6$, $p = 0.44$]. A separate analysis of each frequency band also did not reveal significant gender differences.

An ANCOVA with the confounding factor age was performed on the effect sizes of power differences between tasks for 16 comparisons and seven bands. The findings show that the overall result remains significant after considering age as a confounding factor ($F = 5.42$, $p = 0.02$). A correlation analysis using Spearman's rank correlation between age and the effects of 16 comparisons and seven frequency bands revealed no significant correlations after FDR adjustment. Therefore, it can be concluded that age does not play a significant role in this context and hypothesis H6 holds true.

TOPOGRAPHIC DIFFERENCES

Figure 3 displays topographic mappings from the three general comparisons between the three mental locations (3a–c), the general comparison of the object- versus self-directed focus (3d), the "selfless" versus self-centered states (3e) and the contrast of cognitive and affective processing (3f). A Wilcoxon signed rank test with subsequent FDR adjustment of p-values at the level of electrodes was calculated on the effects weighted with the fulfillment self-rating. The resulting p-values were multiplied by the sign of the corresponding z-values. The topographic maps thus show the significant signed p-values.

Mental locations

Comparisons of intrapersonal and extrapersonal tasks presented highly significant increases in the parieto-occipital and midfrontal and prefrontal alpha and low beta PSD. In contrast, the high beta activity revealed a significant increase in the medial-parietal region. Other frequency bands did not show any noteworthy changes. Similar but much weaker increases could be observed when contrasting empathic connectedness and the extrapersonal location for those three bands. In the high beta band the increase was shifted toward right centro-parietal regions.

Attentional foci

Completely different spectral and topographic patterns resulted from the comparisons between different foci of attention. Here, significant changes could be observed almost globally in the delta band only.

Relatedness

The alteration of mental location and attentional focus in the comparison OF-IS led to the strongest differences in PSD. A global increase in delta activity was accompanied by a decrease in the frontal and lateralized temporal and parietal alpha2 band, as well as a highly significant lateralized beta2 decrease.

Processing modes

States which required cognitive processing showed decreased activities in the posterior alpha2 and centroparietal beta2 bands.

DISCUSSION

Our results indicate that both mental locations and attentional foci showed significant characteristics in neurophysiological data measured by 64 channels of EEG. Generally, we found that the alpha2 and beta2 bands served as good indicators for (a) the distinction between intrapersonal (IX) and extrapersonal space (OX), (b) the distinction between perspective taking (empathy; (EX) and extrapersonal space (OX), (c) the distinction between "selfless" and self-centered states, and (d) the distinction between affective and cognitive processing modes. The topographic similarities suggest that those four polar categories seem to be represented by similar neural mechanisms. In contrast, the delta band served as an indicator for the distinction of attentional foci (object vs. self). In the following it is attempted to use the results for a clearer characterization of the concepts "intrapersonal," "extrapersonal," "empathic," "self-centered," "selfless," "cognitive processing," "affective processing," and "focus of attention."

MENTAL LOCATIONS

Intrapersonal (IX in Table 3)

According to the instructions in the IAMEx, both the IS and IF states represent a mindful, affective or emotional perception of either a person's own body or the environment. The intrapersonal space therefore represents a first-person perspective. In contrast to the extrapersonal space we found significantly higher alpha2 band power over frontal brain areas and lateralized parietal areas. According to Vogeley and Fink (2003) the medial prefrontal, medial parietal and lateral temporoparietal cortex is involved in the first-person perspective. The medial parietal cortex is related to the viewpoint of the observing self. This may be supported by our findings for the beta2 band. The results also fit with the findings of Knyazev (2013), who reported enhanced alpha oscillations during self-referential cognitive processing and enhanced beta activity in the postcentral gyrus while theta and delta activities were reduced in the superior frontal gyrus. However, we did not find any reduction in theta activity.

Higher left parietal alpha was also reported by Mu et al. (2008) during pain empathy compared to processing of neutral stimuli. Only small and non-significant differences in the empathic states (IF-EF) and the self-directed state were visible. Therefore, the intrapersonal space could be interpreted as a self-experiencing or even "self-empathic" process through which the world is perceived. In considerable concordance with the highly significant lateralized centroparietal alpha2 effect, the experience of self-location and hand ownership has been found to be related to bilateral sensorimotor cortices and posterior parietal alpha increases as well (Lenggenhager et al., 2011; Evans and Blanke, 2013).

Extrapersonal (OX in Table 3)

The extrapersonal space represents a cognitive construct of the world. It can also be thought of as a dissociated state which, according to Damasio (1999), is characterized by an active inhibition of emotional activity in the medial prefrontal cortex, which is essential for monitoring and modulation of emotions. In addition, decreased power in frontal and parietal beta PSD (**Figures 3A,C**) supports this theory. Those regions seem to be less activated when subjects were located mentally in the extrapersonal space, which is a cognitive space. This is in line with the findings of Gusnard et al. (2001) and Raichle et al. (2001) showing those regions to be activated during resting states.

Perspective taking (empathy; EX in Table 3)

Taking over another person's perspective is performed as a cognitive and an affective empathic connection. The affective empathic connection was found to be associated with activations in the inferior frontal gyrus (Shamay-Tsoory et al., 2009), anterior insular cortex and dorsal anterior cingulate cortex (Lamm and Singer, 2010). Unfortunately, subcortical activities are usually not visible on EEG. Lamm et al. (2007) associated activations in the right parietal cortex with the adoption of another person's perspective. This is in line with our highly significant right parietal beta2 increase in the comparison of EX and OX. These EEG findings are also supported by Baars et al. (2003), who found heightened fMRI activity in medial parietal, inferior lateral parietal and prefrontal cortical areas when participants were asked to adopt the visual perspective of another person. Findings as reported by Lamm et al. (2007) in an fMRI study showing that the left parietal cortex demonstrated higher activity in the self-perspective, whereas the right parietal cortex was associated with the adoption of another's perspective, could not be demonstrated with our method. The fact that often subcortical structures in the parietal cortex seem to distinguish between the perspective of the self and that of another person might explain the small and non-significant changes between IX and EX.

Sadaghiani et al. (2010) stated that alpha2 band activity was positively correlated with activations of the dorsal anterior cingulate cortex, anterior insula, anterior prefrontal cortex and thalamus. This is in line with the increased interoceptive awareness in IX, attributed in particular to the anterior insula. In a study by Foxe et al. (1998), enhanced alpha synchronization was also attributed to selective attention and was proposed to reflect disengaged anticipatory activities, while active anticipation reduced the alpha oscillations. This would indicate that the enhanced alpha activity in the intrapersonal location might suppress the flood of information that other perspectives would require, and the inside view would therefore be the simplest.

FOCUS OF ATTENTION

Object- versus self-directed attention

With regard to the detection of EEG correlates of self-referential processes, the in-depth review of Knyazev (2013) mentions that delta and theta oscillations (most prominently in frontal midline regions) correlate negatively with activity in the DMN. We found highly significant global delta activations in the object-directed attention task, indicating inhibition of the DMN during XF tasks. According to Knyazev (2012) higher delta activity during "selfless" states suggest that the basic homeostatic and motivational processes are rather object-related states without the necessity of a self-construct. It seems important to note that alpha2 does not seem to be sensitive to the attentional focus but is strongly responsive to the mental location.

RELATEDNESS

"Selfless" versus self-centered

As can be seen in **Figure 3**, the contrast of a "selfless" state, i.e., an object-oriented external perspective, and a "self-centered" state, i.e., a self-oriented intrapersonal perspective, displayed the most prominent differences in the delta, alpha2, and beta2 bands. The relatedness concept represents a combination of location and focus alterations, and in fact the physiological results also tend to show a combination of the results between IX-OX and XF-XS. This supports the idea that self-centeredness can be neurophysiologically separated into the aspect of intrapersonal mental connectedness and a self-directed attentional focus. The findings suggest that "selflessness" and self-centeredness might be intellectually and physiologically relevant concepts. Most of the differences are in line with the findings of other research groups. We found higher right frontotemporal delta power in "selfless" states compared to self-centered states. The OF state may also be related to a dissociated state. Dissociation has often been associated physiologically with the temporal lobe (Bob, 2003), which in our study showed increased slow waves and decreased fast frequencies compared to a self-centered state. The increased delta activity was accompanied by decreased bihemispheric frontal, central and parietal beta2 power, suggesting decreased processing in this region. Wheeler et al. (1997) reported that in some cases lesions in the right frontotemporal cortex led to the experience of cognitive detachment from the self. Interestingly, the contrast of "selfless" with self-centered shows a very similar picture, especially with regard to alpha and beta bands, to the contrast between "thoughtless emptiness" and a state of presence referred to as open monitoring as measured in a study with 30 meditators (Hinterberger et al., 2014). In fact, the state of being present in the moment with an awareness of the physical space of the body represents the IS state, while pure observation of an object from outside (the instruction in the OF state did not ask for cognitive thoughts about the object) might come close to a non-attached thoughtless state. The contrast between visual perception and self-reference is strongly visible in the left and right fronto-centro-parietal beta2 decreases. These lateralized effects could indicate visual information processing in the ventral stream, which is related to object recognition (Goodale and Milner, 1992; Brown, 2009). In contrast, an association between self-reference and activation in cortical midline structures (e.g., Northoff and Bermpohl, 2004) was not visible here.

PROCESSING MODE

Affective versus cognitive processing

In psychology and neuroscience we find a distinction between cognitive and emotional or affective processing. Damasio (1999) has summarized the findings in relation to the mechanisms of affective processing. He describes emotions as the basis for the self and the self-model. Newen and Vogeley (2007) suggest that the neural correlates of the first-person perspective are associated with the medial prefrontal and parietal cortex and the temporo-parietal junction. These are deactivated when subjects perform cognitive tasks (Raichle et al., 2001) and could represent an indicator for affective versus cognitive mental states. The affective modes IS, IF, and ES require a sensorily driven sense of body ownership, which has been found to be associated with activations in midline cortical structures (Tsakiris et al., 2010). These modes present increased beta2 power in central areas, as visible in **Figure 3F**. Decreases in parietal and occipital alpha in cognitive modes become plausible due to the fact that cognitive modes require more visual information processing while self-perception promotes the visual alpha rhythm. Our findings for the alpha2 band are in line with the cognitive reduction as reported by Klimesch (1996, 1999) and Ramos et al. (1993). Ramos et al. (1993) also found the decreased beta during cognitive tasks. The affective enhancement of posterior alpha is in line with Uusberg et al. (2013). The right frontal gamma increase as reported by Müller et al. (1999) could not be observed. Despite this close link between affective processing and the self, the distinction between affective and cognitive modes as shown in **Figure 3F** presents similar effects, albeit not as strong, to the comparison between the "selfless" and self-centered mode. The delta contrast is also less pronounced. This raises the question whether the categories self-centered versus "selfless" processing are physiologically more pronounced in the EEG and possibly more relevant in terms of brain processing than the categories cognitive versus affective.

TASK DIFFICULTY

As we were measuring objective physiological correlates of subjective mental tasks the validity of our findings depends on the actual performance of each task. We attempted to assess this individually for each task using a task fulfillment self-rating score. In this analysis we have decided to include the self-rating scores as a weighting factor in the effect sizes of each task, assuming that this would lead to results with a higher validity. Actually, the weighted results did not differ from the non-weighted results with regard to the essential findings.

The observation that the first two intrapersonal modes were more reliably achieved than the following modes supports the idea that these might reflect well-trained networks such as the DMN. Cognitive states and perspective taking might be harder to achieve as they require the performance of dual tasks, namely (a) the projection of one's own viewpoint to an external place or to an external person and (b) answering questions about the attentional focus. The fact that the final IS mode was much more difficult to achieve than the initial one suggests that task fulfillment depends on the previous task. Gundel and Wilson (1992) showed that higher task difficulty resulted in the reduction of parietal and occipital alpha activity due to the amount of visual scanning as well as an increase in theta activity in the left frontal electrodes, which they hypothesize to be associated with the amount of general mental processing. This might further support the significant parietal and occipital alpha2 increase in the contrasts IX-OX and EX-OX because the OX tasks involve multitasking situations and were reported to be the most difficult ones and therefore are expected to show reduced alpha.

LIMITATIONS OF THE STUDY

The sequence of the tasks was fixed, and therefore we do not know how well the EEG changes can be transferred to other sequences. It can be assumed that there is a significant carryover effect between tasks, which becomes visible when comparing the initial and final IS modes, as they were spectrally and topographically different. Therefore, these results may only be valid for the IAMEx sequence used here and may not be generalizable. For this, a further replication of this study concept with randomized task sequences would be necessary. Further, associations of EEG findings with fMRI results should be treated with care, and probably a LORETA analysis of our data would provide a more robust basis for such interpretations. For a replication of this study we would suggest the use of fMRI directly. Finally, the limited number of participants also calls into question the robustness of the results.

CONCLUSION

We presented a spatial model of different forms of interpersonal perception, and our results confirm the neurophysiological discriminability of three mental locations and two attentional foci. The model of interpersonal attention management which served as the basis for this study seems to provide a useful concept for research in the domain of consciousness science. Different mental perspectives such as intrapersonal positions, cognitive and affective extrapersonal positions, and empathic connectedness were consciously occupied and could be related to specific EEG patterns.

It is likely that depressive patients and patients with a clear psychiatric diagnosis but also with psychotic symptoms such as hallucinogenic experiences differ in their ability to access these different mental positions and attentional foci. We further hypothesize that people with dissociative disorders or depressive episodes have difficulties with the free choice of and transition between mental locations. A further study with a clinical sample may therefore demonstrate that such patients present smaller contrasts between the tasks of the IAMEx. The IAMEx in combination with physiological measurements could therefore serve as a diagnostic tool. The IAMEx itself could serve as an exercise for psychosomatic rehabilitation. Further, the data suggest that via the presented exercises individuals could learn to generate brainwaves in specific frequency bands at will. This suggests the possible development of a neurofeedback device to train attentional and intra- and interpersonal flexibility for therapeutic and recreational purposes. Individuals who have difficulty empathizing with others could probably also profit from these methods.

We have presented data showing the neurophysiological distinction between concepts of intrapersonal versus extrapersonal mental space, "selfless" versus self-centered mental states, and cognitive versus affective processing. All three conceptual dualities showed very similar EEG PSD patterns in their comparisons. Although the category cognitive versus affective might be the most well-known differentiation in psychology it did not present the strongest effects. The most prominent differences, in the "selfless" versus self-centered contrast, showed a combination of the results in the location- and focus-dependent contrasts. This suggests that both the mental location and the attentional focus play a fundamental role in brain processes related to the self-concept and that they could be distinguished in the present study with respect to brain oscillations. Thus, the attentional focus and the so-called mental location seem to provide physiologically relevant categories because the contrast between intrapersonal and extrapersonal location displayed significantly different EEG patterns compared to the contrast between self- and object-directed attentional focus. At this point, we would like to raise the following philosophical question: what is the relationship between the mental concept of subjective experience and the concepts or terms we use to describe the organization and function of the brain? This seems to be an important question as our mental categories are essentially responsible for the interpretation of physiological findings and thus form our picture of the mechanisms of the brain.

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Predicting the unpredictable: critical analysis and practical implications of predictive anticipatory activity

Julia A. Mossbridge[1]*, Patrizio Tressoldi[2], Jessica Utts[3], John A. Ives[4], Dean Radin[5] and Wayne B. Jonas[4]

[1] Department of Psychology, Northwestern University, Evanston, IL, USA
[2] Dipartimento di Psicologia Generale, Universita di Padova, Padova, Italy
[3] Department of Statistics, University of California at Irvine, Irvine, CA, USA
[4] Samueli Institute, Alexandria, VA, USA
[5] Consciousness Research Laboratory, Institute of Noetic Sciences, Petaluma, CA, USA

Edited by:
Etzel Cardeña, University of Lund, Sweden

Reviewed by:
Daryl J. Bem, Cornell University, USA
Douglas Miller Stokes, Freelance Writer, USA

****Correspondence:***
Julia A. Mossbridge, Department of Psychology, Northwestern University, 2029 N. Sheridan Road, Evanston, IL 60208, USA
e-mail: j-mossbridge@northwestern.edu

A recent meta-analysis of experiments from seven independent laboratories ($n = 26$) indicates that the human body can apparently detect randomly delivered stimuli occurring 1–10 s in the future (Mossbridge et al., 2012). The key observation in these studies is that human physiology appears to be able to distinguish between unpredictable dichotomous future stimuli, such as emotional vs. neutral images or sound vs. silence. This phenomenon has been called *presentiment* (as in "feeling the future"). In this paper we call it *predictive anticipatory activity* (PAA). The phenomenon is "predictive" because it can distinguish between upcoming stimuli; it is "anticipatory" because the physiological changes occur before a future event; and it is an "activity" because it involves changes in the cardiopulmonary, skin, and/or nervous systems. PAA is an unconscious phenomenon that seems to be a time-reversed reflection of the usual physiological response to a stimulus. It appears to resemble precognition (consciously knowing something is going to happen before it does), but PAA specifically refers to *unconscious physiological* reactions as opposed to *conscious premonitions*. Though it is possible that PAA underlies the conscious experience of precognition, experiments testing this idea have not produced clear results. The first part of this paper reviews the evidence for PAA and examines the two most difficult challenges for obtaining valid evidence for it: expectation bias and multiple analyses. The second part speculates on possible mechanisms and the theoretical implications of PAA for understanding physiology and consciousness. The third part examines potential practical applications.

Keywords: presentiment, predictive coding, anticipatory activity, neural prediction, temporal processing

PART 1. THE EVIDENCE FOR PREDICTIVE ANTICIPATORY ACTIVITY

Predictive anticipatory activity (PAA) is defined here as statistically reliable differences between physiological measures recorded seconds before an unpredictable emotional event occurs vs. seconds before an unpredictable neutral event occurs. An emotional or arousing event is defined as an event that activates the sympathetic nervous system; while a neutral event activates the sympathetic nervous system to a lesser degree or not at all. A colloquial definition of PAA is "sensing the future," or *presentiment* (e.g., Radin, 1997, 2004; Radin and Borges, 2009). Here we use the more descriptive term PAA to indicate that this phenomenon is *predictive* of randomly selected future events, *anticipates* these events more often than chance, and is based on *physiological activity* in the autonomic and central nervous systems. In this section, we present the evidence for this phenomenon. We then discuss its implications (Part 2) and potential applications (Part 3).

Predictive anticipatory activity is postulated to be an unconscious physiological phenomenon that may be thought of as a preview of our conscious awareness of future emotional or arousing events. A metaphor may help to provide an intuitive feel for this effect – watching a river move past a stick. The metaphor works as follows (**Figure 1**): imagine that the direction of the water's current is the conscious experience of the flow of time (temporal flow), and imagine that an intrusion in the flow (the stick) is an emotional, arousing, or otherwise important event. The largest disturbance in the water made by the intrusion is downstream (in the "forward" time direction), which is analogous to our conscious reaction to experiencing the important event. But if one examines the flow of water near the stick, one will also see a small perturbation *upstream*, anticipating the intrusion in the water downstream due to the back pressure. Similar to PAA, this upstream perturbation is a hint of things to come. It is not normally part of our conscious awareness and, as with disturbances in a flow of water, the majority of the effect of an intrusion is downstream of the intrusion.

In contrast to PAA, *precognition* may be defined as a perception or a behavior (not a physiological measure) that is influenced by future events. For example, a recent series of experiments published in the *Journal of Personality and Social Psychology* suggested that perception of a future event may influence decisions and memory in the present (Bem, 2011; also see Maier et al., in press;

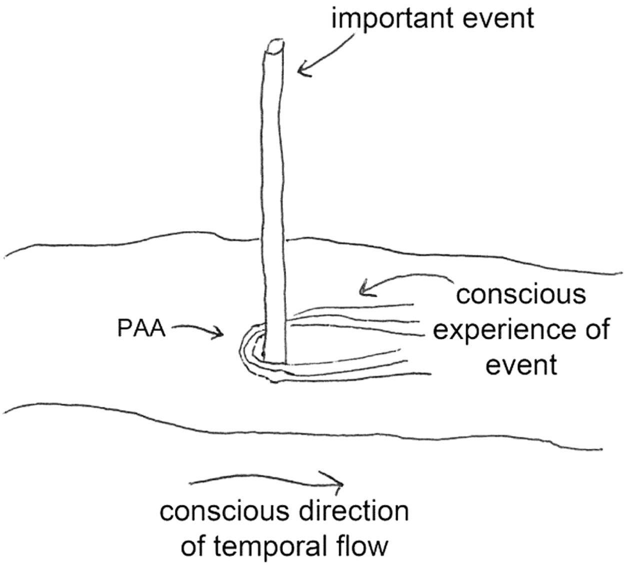

FIGURE 1 | Back-pressure perturbations from a downstream intrusion (an arousing/important event) in a stream of water may be a useful metaphor for predictive anticipatory activity (PAA). We are not normally conscious of PAA effects because downstream perturbations are much larger in magnitude.

Ritchie et al., 2012). Though it seems plausible that precognition is related to PAA, examination of that possibility is beyond the scope of this article.

Experimental tests of PAA generally use one of two designs, both of which involve a series of randomly interspersed emotional and neutral events. The most common paradigm is one in which participants passively view and/or listen to a series of stimuli that are randomized in terms of stimulus type (e.g., emotional vs. neutral). A less common paradigm is one in which participants actively guess the outcome of each in a series of future events. In both paradigms, care must be taken to ensure that a truly random series of events is generated and that participants or experimenters cannot infer the upcoming event type through usual sensory means. Physiological data (skin conductance, heart rate, respiration rate, EEG activity, etc.) are recorded continuously during the experiment (**Figure 2A**) Each trial may be assessed on a trial-by-trial basis (see Recommendations for Designing Reliable PAA Sensing Tools, below), but more typically T*pre* is evaluated by averaging it across multiple trials of similar types (**Figure 2B**; e.g., emotional vs. neutral) in the series.

More than 40 experiments investigating PAA in humans have been published over the past 36 years (including: Hartwell, 1978; Radin et al., 1995, 2011; Bierman and Radin, 1997; Radin, 1997, 2004; Don et al., 1998; Bierman, 2000; Bierman and Scholte, 2002; McDonough et al., 2002; Spottiswoode and May, 2003; McCraty et al., 2004a,b; Sartori et al., 2004; May et al., 2005; Tressoldi et al., 2005, 2009, 2011; Radin and Borges, 2009; Bradley et al., 2011).

This literature prompted a meta-analytic examination of PAA to assess the combined evidence and repeatability of the phenomenon (Mossbridge et al., 2012). The meta-analysis tested the hypothesis that the difference between physiology preceding emotional and neutral events is in the same direction as the difference after those same events; in other words, it tested the hypothesis that the pre- and post-event physiological differences have the same sign (positive or negative). Using statistically conservative methods, the analysis revealed a small but highly statistically significant effect size in support of the hypothesis [fixed effect: overall ES $= 0.21$, 95% CI $= 0.15$–0.27, $z = 6.9$, $p < 2.7 \times 10^{-12}$; random effects: overall (weighted) ES $= 0.21$, 95% CI $= 0.13$–0.29, $z = 5.3$, $p < 5.7 \times 10^{-8}$]. Higher quality studies produced a larger overall effect size and greater level of significance, indicating that lack of quality was not responsible for the significant result (Mossbridge et al., 2012)[1].

It is important to note that a meta-analysis is only as good as the data that it examines. Both questionable research practices (QRP) and physiological artifacts have the potential to produce results that mimic a PAA effect. If QRPs are sufficiently widespread, they could potentially be responsible for the highly significant meta-analytic results discussed here. Possible bias can be introduced by experimenter fraud, selective reporting, filter artifacts imposed on the raw data, multiple analyses, and anticipatory and order effects. These and other possible explanations for PAA have been critically examined and found to be lacking in explanatory power (Mossbridge et al., 2012). Here we briefly examine two of the more important criticisms of the evidence for PAA: multiple analyses and order effects, with a focus on expectation bias.

CRITICISMS OF THE EVIDENCE FOR PAA

p-Hacking

One QRP that appears to be common throughout behavioral, social and medical research is to try to create a statistically significant effect using alternative analyses when the originally planned analysis did not find a significant effect (Simmons et al., 2011). If some of the PAA researchers used this technique to produce a significant PAA result, without noting the results as *post hoc*, then a meta-analysis based on those results would have an inflated outcome. This activity, dubbed "*p*-hacking" because it involves cutting through the data in many ways to obtain a *p*-value low enough to declare statistical significance, is a concern when determining the validity of any reported experimental phenomenon. The question is whether *p*-hacking can explain the significant meta-analytic results for PAA.

To answer this question the authors performed a meta-analysis on a subset of the data. This subset consisted of studies using electrodermal activity as the measure of interest, and the meta-analysis of these studies confirmed the presence of a highly significant overall effect (Mossbridge et al., 2012). Electrodermal activity measures have fewer parameters than EEG and fMRI data, so a researcher who wished to perform *p*-hacking would have few parameter choices and thus fewer chances to get a significant effect. One critical parameter in electrodermal studies is the duration of the pre-stimulus activity under examination (T*pre*). Interestingly, within each publication and more often than not between publications, experimenters who performed multiple studies using

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[1] Another meta-analysis using Bayesian statistics and including tests of PAA as well as tests for several other non-ordinary experiences revealed similar results (Tressoldi, 2011), but because that meta-analysis was not limited to PAA alone, it is beyond the scope of this review.

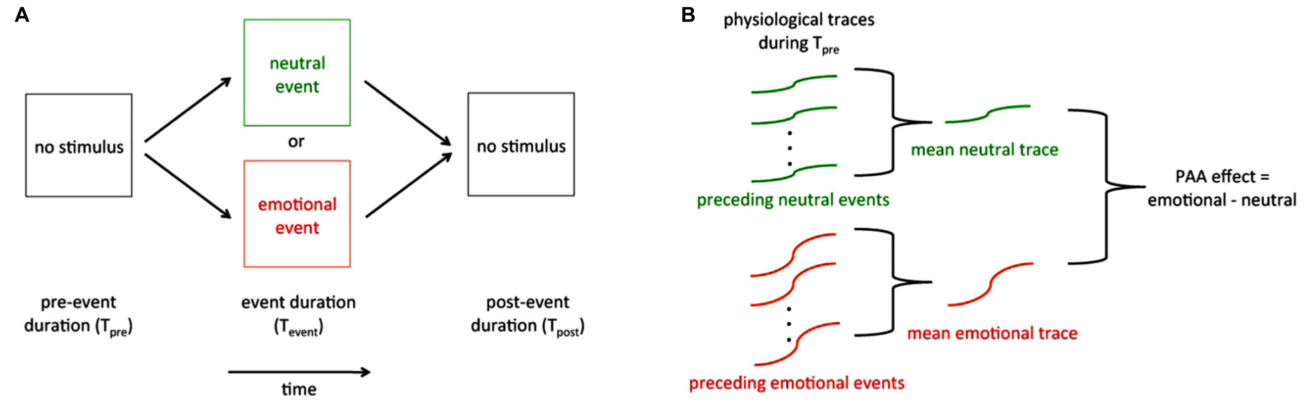

FIGURE 2 | Schematic of a generalized PAA trial and overall results. **(A)** One trial of a series of trials. The pre-event (T_{pre}), event (T_{event}), and post-event (T_{post}) durations are on the order of seconds. The physiological activities of interest are recorded continuously throughout the series of trials. **(B)** PAA effect. Data recorded during T_{pre} are baselined to a period preceding T_{pre} and are most often averaged across trials within each event type to provide an average T_{pre} response for the emotional event and an average T_{pre} response for the neutral event. The PAA effect is usually defined by the difference between these two averaged changes in T_{pre} physiology.

electrodermal activity as a measure of interest consistently used the same T*pre* duration (most often 3 s before the stimulus), even when significant results were not found (see Anticipatory Period column in Appendix table A1; Mossbridge et al., 2012). This is not behavior that is consistent with *p*-hacking strategies.

Another feature of the same PAA meta-analysis was that it tested a hypothesis that differed from any explicit hypothesis stated by the authors of the original studies. That is, for the studies included in the meta-analysis, when a hypothesis was formally stated it was of the form that there would be a statistically reliable *difference* between the pre-event physiology for an emotional upcoming event as compared to another (relatively neutral) upcoming event. The direction of this difference was usually not predicted. However, the hypothesis of the PAA meta-analysis was that the direction of the pre-event difference would explicitly mirror the direction of the post-event difference (Mossbridge et al., 2012). In other words, if the direction of the pre-event difference in a physiological measure was the same as the direction of the post-event difference in the same physiological measure, the effect size for the study was given a positive sign (in support of the hypothesis), and if the direction of the pre- and post-event differences were not the same, then the effect size was given a negative sign (in contradiction to the hypothesis). Thus, even if researchers *p*-hacked to get a significant effect in an individual study, it would not necessarily be an effect in the same direction as that tested by the meta-analysis, and therefore it would not necessarily support the hypothesis of the meta-analysis. In fact, several studies examined in the meta-analysis did show effects in directions that opposed the hypothesis of the meta-analysis itself. In this way the meta-analysis was decoupled from one possible source of *p*-hacking. Nevertheless, the cumulative results remained highly significant.

From these analyses, it appears that *p*-hacking and other forms of unreported multiple analyses are not a compelling explanation for PAA. However, it is always possible that the evidence for PAA is influenced by more subtle variations in analyses. Until there is a gold standard experiment that is replicated across laboratories using exactly the same experimental procedure, physiological measures, and statistical analyses, there remains the possibility that multiple analyses could influence the body of evidence supporting PAA. Toward this end, we recommend that all researchers who investigate PAA register their experiments in advance, at any of several registries designed for experiments examining exceptional experiences[2] or at a general experimental research registry[3].

Order effects and expectation bias

Order effects may occur in any experiment with multiple sequential trials, including PAA studies. For example, *forward priming* describes a situation in which previous events influence responses to future events. Thus, responses to the word "flower" are faster if the word is preceded by the word "tree" vs. the word "knife" (Meyer and Schvaneveldt, 1971). Psychophysiologists who wish to avoid priming effects typically use randomization methods to help ensure that it is unlikely for a majority of the participants to systematically experience the same trial order. This increases the likelihood that spurious order effects will average out over participants and will not influence the cumulative results. In addition, the greater the number of trials in any given experiment, the less likely that similar trial orders may occur. If order effects are largely responsible for PAA, there should be a significant negative correlation between study effect size and the number of trials performed. However, this is not the case (Mossbridge et al., 2012).

While order effects do not appear to be a problem in these data, expectation bias is a more subtle effect that requires closer examination. Expectation bias is related to the human propensity to expect a "tail" in a coin toss after observing a series of "head" outcomes (the gambler's fallacy). The reason expectation bias can potentially explain PAA is that a series of (randomly selected)

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[2] http://www.koestler-parapsychology.psy.ed.ac.uk/TrialRegistry.htmlxsxsxs

[3] https://osf.io/

neutral stimuli may produce a physiological shift toward excitement as the presumably imminent emotional trial approaches. In a sequence of trials with several such series of neutral events preceding emotional events, simulations suggest that the resulting physiological data could mimic a PAA effect (Dalkvist et al., 2002; Wackermann, 2002). Thus to understand the mechanisms underlying PAA, it is crucial to determine for each PAA experiment whether expectation bias was a potential explanation for the reported outcome.

There are several ways to quantify expectation bias. For example, one can examine a plot of the physiological measure of interest during T*pre* for an emotional event vs. the number of neutral trials preceding that emotional event. If expectation bias is a viable explanation for the PAA effect in a given experiment, then the activity during T*pre* for emotional events with greater numbers of neutral events preceding them will be larger than for those with fewer neutral events preceding them (Radin, 2004). Of the 26 studies examined in the recent PAA meta-analysis, 19 of them used this method or similar methods to empirically determine whether expectation bias could explain the PAA effect. None of them found that it could. Further, the overall effect size of the subset of studies that performed expectation bias analyses was greater than the effect size of the seven studies that did not perform such analyses, lending little support to the idea that expectation bias creates the PAA effect in general (Mossbridge et al., 2012). However, it is worth noting that studies revealing larger effects usually include more details about attempts to account for mundane explanations such as expectation bias, so there may be an inherent bias here.

Several statistical methods can be used to correct for expectation bias if evidence for that bias is found (e.g., Dalkvist et al., 2013). At least one of us (Mossbridge) has found an expectation bias effect in one PAA study, but because removing the bias produced a larger PAA effect, expectation was not a viable explanation. The bias was removed by discarding data from all but the first trial of the experimental session, because any significant PAA effect on the first trial could not be explained by expectations produced by preceding trials (Mossbridge et al., 2011). Importantly, this method revealed a larger PAA effect than the traditional trial-averaging method (compare Figures 1–6 in Mossbridge et al., 2012). This stronger effect could be due to the reduction of "temporal blurring" when physiological measures preceding only the first trial are examined (see Implications of PAA for Physiology and Consciousness Research, below). Based on this larger effect when only the first trial is considered, experiments are underway in which each individual performs only a single trial[4]. Despite obvious drawbacks due to the increase in inter-individual noise, and the effort involved in collecting data, this approach guarantees that expectation bias is not a viable explanation for any observed PAA effect.

The remainder of this article is based on the assumption that PAA reflects a true anticipatory prediction rather than being a physiological artifact or the result of bias and QRP. This assumption is made to allow us to explore the concept of PAA beyond the initial existential question.

TYPES OF ANTICIPATORY PHYSIOLOGICAL ACTIVITY

Three broad categories of anticipatory physiological effects are well established in neuroscience and psychophysiology: anticipation of intentional motor activity, anticipation of stimulus detection, and anticipation of a complex firing pattern. PAA may be a novel, fourth category, or it may overlap with one or more of the three established categories.

Anticipation of intentional motor activity is supported by neurophysiological evidence indicating that the neural anticipation of our conscious awareness of having a will to move occurs at least 500 ms (Libet et al., 1983; Haggard and Eimer, 1999) and as much as 10 s (Soon et al., 2008; Bode et al., 2011) before the first conscious report of the will to move. Anticipation of stimulus detection is supported by the fact that EEG alpha activity during the pre-stimulus period for trials presenting stimuli that will be detected differs from alpha activity during pre-stimulus periods preceding stimuli that will not be detected (Ergenoglu et al., 2004; Mathewson et al., 2009; Panzeri et al., 2010). The explanation here is that specific phases and/or amplitudes of neural oscillations facilitate or suppress detection of the upcoming stimulus. Also, anticipation during sleep of a complex firing pattern to be used in the future, a phenomenon dubbed "preplay," has been observed in mouse hippocampal neurons during sleep before entering a novel maze (Dragoi and Tonegawa, 2011). The firing pattern recorded during sleep has greater-than-expected similarity to the patterns recorded when the mouse eventually navigates the maze, an effect explained by the researchers with the idea that the hippocampus recycles generalizable firing patterns from its recent history to create the complex firing patterns accompanying spatial exploration. For these three categories of anticipatory effects, reasonable explanations using the usual cause-preceding-effect assumption are sufficient to explain the results. The usual causal temporal assumptions do not suffice, however, when attempting to understand PAA, because it apparently represents a statistically reliable *retrocausal* effect. In the next section we examine potential mechanism for PAA.

PART 2. POTENTIAL MECHANISMS FOR PAA AND IMPLICATIONS OF PAA

POTENTIAL MECHANISMS FOR PAA

Delayed conscious experience

One seemingly reasonable explanation for PAA is that our conscious mind is wrong about when events occur. That is, our conscious experience of events is delayed by seconds relative to some external/physical time of which we are not conscious. Meanwhile, unconscious neural processes are much less delayed relative to this external time. The explanation goes as follows: one important role of the unconscious is to assess the environment and mobilize physiological resources when it senses challenging external events. Once resources are mobilized and the body is readied, the conscious mind is presented with an ordered version of events that is necessarily temporally delayed so the conscious mind does not initiate counter-productive actions that might interfere with the preparation of physiological resources. Because challenging external events can occur at any time, the conscious mind is always receiving delayed and filtered information about sensory and motor events. Virtually all behavior is unconscious, and

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[4] Dick Bierman has also performed a slightly different protocol of the single-trial study and found a presentiment effect, but this has not been published.

conscious awareness rides on top of this activity like an unfolding and delayed story.

This *delayed conscious experience* hypothesis predicts that we should find brain areas with activity that predicts upcoming consciously perceived events seconds before they occur. As mentioned previously, outside the PAA literature, Bode et al. (2011) and Soon et al. (2008) have reported that up to 10 s before the conscious experience of a decision to produce a motor event, brain activity predicts conscious decisions. These data support the delayed conscious experience hypothesis, but do they reflect PAA?

Although PAA may seem like a sensory counterpart to the predictive coding observed in the motor system, it differs in terms of the order of events and by not involving inferred events or making a decision. In PAA experiments, the physiological and stimulus events are in the wrong order to be explained causally, and they are time-stamped by a computer (not subjectively reported by research participants). Regardless of the absolute times when these events occur, a physiological reaction occurs before the stimulus to which it seems to be linked. Thus PAA neither supports nor refutes the delayed conscious experience hypothesis, but this hypothesis is not a viable explanation for PAA.

Quantum biology

A potentially more viable way to understand PAA effects is that they might reflect an epiphenomenon associated with quantum processing in biological systems. Aharonov et al. (1964, 1988) suggested that one way to explain quantum effects is via interactions between future and past events. This idea has recently been supported by advances in quantum measurement, so-called "weak measurements," which demonstrate that observations in the future do indeed affect observations in the past (Aharonov et al., 1964, 1988; Hosten and Kwiat, 2008; Dixon et al., 2009). Further support of a similar "retrocausal" phenomenon in physics is provided by experimental verification of delayed-choice entanglement (Ma et al., 2012). Finally, because quantum effects have been shown to manifest in biological systems at physiological temperatures, e.g., in photosynthetic reactions (e.g., Scholes, 2011; Dawlaty et al., 2012; Olaya-Castro et al., 2012), it is no longer inconceivable that retrocausal quantum effects can occur in the human nervous system.

However, one problem with a quantum biological explanation for PAA is that retrocausal effects *on the order of seconds* would have to be explainable via quantum processes, and we know of no evidence so far that these effects can occur at that time scale[5]. Nevertheless, exploration into biological quantum effects is in its infancy, and most biological models have yet to entertain the consequences of retrocausation. Thus, the idea that PAA may be related to quantum effects is speculative and currently difficult to test. However, the quantum biology hypothesis demonstrates the value of anomalous phenomena in driving science forward by motivating scientists to search for novel explanations based on emerging scientific concepts. For further discussion of the philosophical and quantum mechanical arguments for time symmetry and retrocausation the reader is referred to an article on backward causation in the Stanford Encyclopedia of Philosophy[6] and to Bierman (2010).

IMPLICATIONS OF PAA FOR PHYSIOLOGY AND CONSCIOUSNESS RESEARCH

Physiology

The most mundane implication of PAA for physiologists is that the time-honored convention of establishing a baseline for physiological post-event measures by subtracting mean pre-event activity may obscure important physiological effects in two ways (Bierman and Radin, 1997; Mossbridge et al., 2012). First, by assuming that pre-event activity is equivalent between event types (without testing this assumption), PAA may be hiding in plain sight. Indeed, several re-examinations of pre-event activity reported in psychophysiology studies conducted for other purposes suggest that the PAA effect actually is present but overlooked (Bierman, 2000; Mossbridge et al., 2012). Of course, when researchers are performing a conventional psychophysiology experiment it is unlikely that they will feel the need to closely examine expectation bias or use truly random techniques to specifically rule out order bias. Thus PAA results found in data from such studies could potentially be due to these mundane explanations.

A second way that baselining data to pre-event physiological activity could obscure important physiological effects is by falsely increasing or decreasing post-event physiological differences. This can occur because pre-event activity is rarely equivalent between event types due to PAA, so subtracting these differing values can produce misleading post-event data as a result.

A more intriguing implication of PAA for those attempting to understand human physiology is that there seems to be a correlation between pre- and post-event responses, such that the magnitude of a post-event response seems to correlate with the magnitude of the corresponding pre-event response. Note that a simple correlation between pre- and post- responses is not what is being discussed here; certainly across individuals there is a strong correlation between the physiological state before and after any event, partially due to the fact that there are stronger inter-individual physiological variations than intra-individual variations. Instead, what has been observed is a correlation between the magnitude of the *change* in a physiological measure before an event and the magnitude of a *change* of that physiological measure after the event. We call this "temporal mirroring." To investigate the idea of temporal mirroring in PAA, Radin (2004) quantitatively tested temporal mirroring using independent ratings of emotionality for different stimuli and found a significant correlation between pre-stimulus response size and stimulus emotionality. In another study, men had large blood-oxygen level dependent (BOLD) post-responses to erotic images randomly distributed along with violent and neutral images, and in men the only significant PAA effect occurred for erotic but not violent images (Bierman and Scholte, 2002). Meanwhile, women in the same study had large BOLD post-responses to violent but not erotic images, which also matched their PAA effects. Others have noted similar gender effects for which post-event differences in responding mirrored pre-event

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[5] Elementary forms of coherence vanish quickly, but it is possible that coherence in living systems might be "pumped" and sustained for a relatively longer time.

[6] http://plato.stanford.edu/entries/causation-backwards/

differences (McCraty et al., 2004b; Radin and Lobach, 2007; Radin and Borges, 2009; Mossbridge et al., 2011).

Another parameter dependence suggesting temporal mirroring is the relationship between PAA effects for single-modality events (auditory or visual stimuli presented alone) vs. events that are more ecologically valid in that they incorporate multiple modalities (e.g., emotional auditory and visual stimuli presented simultaneously). Well known in the multimodal literature is the idea that responses to stimuli presented in multiple modalities are more robust than responses to each modality alone (e.g., Meredith and Stein, 1986; Meredith et al., 1987). According to the "Hypothesis of Functional Equivalence," any pre-stimulus PAA activity, if it exists, should be drawn on with same readiness as a post-stimulus response to a stimulus (Carpenter, 2012), supporting the functional value of temporal mirroring. Along these lines, in at least one report (Radin, 2004), PAA effects for events presented using multiple modalities are quantitatively larger than PAA effects for single-modality events, though several methodological differences between experiments preclude strong conclusions being drawn from these data.

Thus, it appears that the pre- and post-event physiological responses may mirror one another in size across participants (though pre-event responses are generally smaller than their post-event counterparts), implying that physiological processes are predicting either the importance of the future event to the organism or perhaps the future physiological response itself. These two interpretations may seem similar, but they have different implications for understanding the physiological mechanisms underlying PAA. The idea that PAA predicts the importance of the future event to the organism suggests that even if no physiological post-event response occurs due to some manipulation of the organism's physiology or due to a probable event not occurring, PAA would occur before a highly probable important event. In contrast, if PAA predicts an organism's future physiological response, then no PAA effect would occur if no physiological post-event response occurs. These differing interpretations of the pre-to-post-event mirroring phenomenon have important implications for applications that attempt to harness and amplify PAA, and these implications will be discussed below (see Part 3: Potential Applications of PAA Sensing Tools).

One final implication of PAA for our understanding of physiological systems is that PAA responses apparently decay with time prior to an event. If the size of a PAA response did not decay with time, one would never expect to find PAA, as arbitrarily timed future events that are important would be "temporally blurred" with arbitrarily timed future events that are not important. This is clearly not the case, as inter-trial intervals as short as 10 s have produced significant PAA effects. This does not necessarily mean that PAA effects completely vanish beyond 10 s, but it does indicate that there is some decay of PAA with time preceding the event. Thus, the physiological mechanisms underlying PAA are temporally localized in relation to each event[7].

Consciousness

A major implication of PAA for our understanding of consciousness is that there must be a necessity for PAA to remain non-conscious most of the time. That is, for most people at most times there is a clear difference between the forward temporal flow of information and experience of which we are aware and a seemingly symmetric flow of information within the non-conscious portions of our experience, as evidenced by the existence of PAA. Why should this be the case? If some part of our nervous system can obtain information about events seconds in the future, would we not have evolved to make this information conscious?

One answer to this question is that the information is not conscious because most of the time it is not useful, like the majority of information that is processed unconsciously. Under this assumption, the mirroring of future physiological states by our unconscious physiological processes is just a side effect of how physiological systems (and in a more general sense the unfolding of events in time) work. The idea is that there has to be a physiological post-event response to produce the PAA prediction of that response, so there is then no point to being consciously aware of PAA effects as the event will occur in short order and there may be nothing we can do to stop it.

A seemingly paradoxical PAA experiment called a "bilking experiment" is one in which a participant's PAA response is used to avoid a future emotional event that presumably caused the PAA response to occur in the first place. If such a PAA response can be shown to exist when there is no accompanying future emotional event, this would invalidate the idea that PAA requires a post-stimulus response and would support the idea that PAA predicts probable vs. actual events. One of us (Tressoldi et al., 2013) has preliminary data that support this idea. However, such bilking experiments are in their infancy, making it difficult to draw conclusions.

Another answer to "Why aren't we conscious of PAA?" is that the conscious mind is not especially skilled at making quick decisions. Unconscious processing is increasingly being recognized as a powerful resource that provides the results of its calculations to conscious awareness for further use and elaboration (e.g., Kahneman, 2011). Converging evidence suggests that unconscious processing can result in learning and decision making that betters, or at least matches, those resulting from conscious processing (e.g., De Houwer et al., 1997; Dijksterhuis et al., 2006; Strick et al., 2011; Voss et al., 2012; Atas et al., 2013; Hassin, 2013). Thus, it might be evolutionarily advantageous for unconscious processing to assess upcoming events, filter them, mobilize resources, and only then inform conscious awareness (see *Potential Mechanisms for PAA* and *Delayed Conscious Experience*, above).

PART 3. POTENTIAL APPLICATIONS OF PAA SENSING TOOLS

Assuming we can understand PAA well enough to amplify and characterize it for a given event of interest, the potential uses of PAA-sensing tools (PAASTs) largely depend on the delay between the PAA signal and the event of interest. Potential applications also depend on whether the PAA is caused by the high a priori probability of an emotional event or is the result of an actual and unavoidable emotional event.

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[7] The temporal issue might be related to the boundary conditions of each trial. In other words, the backward temporal information flow could end with the presentation of the stimulus. This could potentially be tested by delaying feedback over multiple trials, some of which are a long sequence of emotional targets, and some of which are a long sequence of calm targets.

Applications that could benefit from a few seconds advance notice may include: slamming on the brakes of a vehicle to prevent a crash, taking cover in advance of an explosion, or in general orchestrating quick movements to effect a fortuitous result within a few seconds. Applications requiring 10s of seconds might include: course corrections for vehicles, preparing to move out of a location, locating a hiding spot and then hiding there, preparing for a medical emergency, communicating information verbally, or in general, orchestrating more complex chains of action.

POTENTIAL ROADBLOCKS TO DESIGNING RELIABLE PAA SENSING TOOLS

How does one amplify and characterize PAA for an event of interest so that one can determine the practical temporal window of usability for a PAAST? The amplification and characterization process itself could present several difficulties, which we speculate about here (see Recommendations for Designing Reliable PAA Sensing Tools, below, for potential solutions to these problems).

One critical problem to overcome during the characterization process is that when a PAAST is used outside of the laboratory, many events occur beyond the event of interest. For instance, one potentially life-saving application of PAASTs could be to predict the detonation of an improvised explosive device (IED). A PAAST device, when working perfectly, would emit an alert 10–20 s before the detonation of an IED, providing time to avoid the device or take cover. When working well, the PAAST device should not be triggered by emotional events such as an individual soldier's phone call from a friend or a near miss in a firefight. The specific physiological PAA "signature" of a soldier to the IED detonation must be isolated.

When the signal is characterized and is being amplified, time course is likely critical. Any "temporal blurring" that might occur due to an overlap in physiological responses either before or after the IED detonation must be minimized. For example, if a soldier goes into a simulation where he will be faced with 20 IED detonations in a short time period, a temporal blurring of his or her physiology may occur because responses to later detonations will include responses to previous detonations.

A third potential roadblock is that in the process of characterizing and amplifying PAA to a simulated IED detonation, the event itself may become uninteresting, producing small post-event physiological responses. If the post-event physiological response is small, this would likely reduce the size of the matching PAA response (see Physiology, above). Thus a soldier must be kept engaged and the simulated IED detonation must maintain its emotional and cognitive impact value.

Finally, it is important to address a perceived paradox that seems like a potential stumbling block, but may not be. The paradox goes like this: if PAA is a reflection of the future physiological state of an individual, and the actions taken once a PAA alert is given change the physiological state of that person, the PAA alert may not work in the first place. Imagine this scenario (**Figure 3A**): a PAAST gives a soldier an IED alert. The soldier takes cover away from a nearby trash heap but hears the sound of the subsequent explosion of the IED. The soldier has a typical post-detonation emotional response, which is what produced the PAA alert. Now imagine

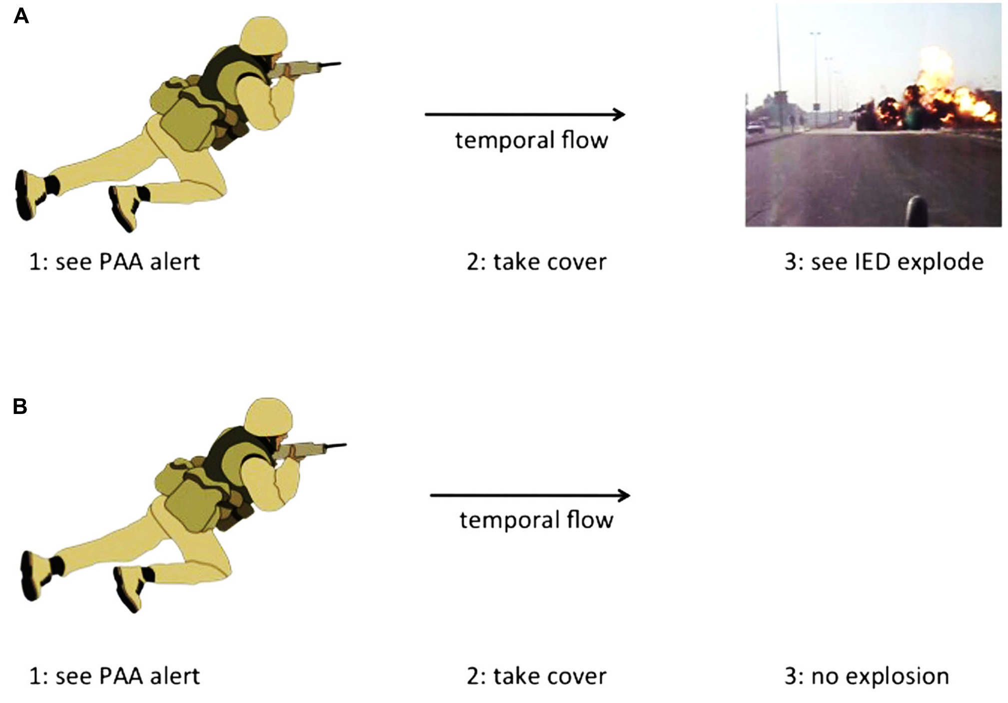

FIGURE 3 | Schematic illustrating two possibilities for the operation of a PAA-sensing tool. (A) A soldier sees the PAA alert, takes cover, and sees the IED explosion from a safe location. **(B)** A soldier sees the PAA alert, takes cover, and does not see or hear the IED explosion. Note that in either case, injury was avoided, even though the second case seems theoretically paradoxical (see text for details).

this paradoxical scenario (**Figure 3B**): a PAAST gives a soldier an IED alert. The soldier hides in a tank and puts on headphones. The soldier does not have a typical post-detonation emotional response, so there could not have been a PAA alert. However, there was a PAA alert. How could this work? If the second scenario can occur, it means one of two things: (1) that PAA does not reflect the future physiological state of the individual, or (2) that a non-typical post-detonation response is still an emotional response to saving one's own life and so can still produce PAA. The PAAST still saved the soldier's life, regardless of how it worked (see above for Potential Mechanisms for PAA and Implications of PAA). There may be a theoretical paradox here[8], but perhaps not a practical one.

RECOMMENDATIONS FOR DESIGNING RELIABLE PAA-SENSING TOOLS

Recommendations for designing reliable PAASTs are speculative, as they are based on results from studies varying broadly in their events of interests, methodology, and participants. However, here we make an attempt to outline best practices, as they would currently be defined, for designing a reliable PAAST.

The first step in designing any PAAST would seem to be finding the time course of the decay of PAA for the event of interest. Again, taking the example of IED detonation, once this delay is known, the optimal inter-detonation interval to produce the most reliable PAA effect will become apparent, and the usefulness of that delay can be assessed for the application. Thus, one critical initial experiment would be to use variations in the inter-detonation interval to determine the extent to which the PAA effect can be amplified by reducing temporal blurring with respect to the PAA response (see *Implications of PAA for Physiology and Consciousness Research* and *Physiology*, above).

After finding the critical delay for the IED detonation event across a group of soldiers, the next step would be to characterize the specific physiological "tell" or signature of each soldier who will be using the PAAST. What are the respiration, temperature, blood volume, skin conductance, EEG, and heart rate signatures for each soldier? Obtaining this information would require exposing each soldier to multiple simulated experiences with IED detonations. Based on the little knowledge we have about PAA, these simulation protocols should share several characteristics. To ensure the robust emotional responses that produce reliable PAA, each simulated IED detonation should include at least auditory and visual information, with somatosensory and olfactory cues where possible. To reduce the influence of responses to previous events (temporal blurring) and to ensure continued strong responses after the upcoming event that seem to produce strong PAA (temporal mirroring), delays between simulated detonations should be relatively long (on the order of minutes or hours) and randomly timed. To ensure the generalizability of the PAA signature across multiple situations, detonations should occur in differing scenarios. Because the device must distinguish PAA to IED detonations from emotional responses to other events, events causing emotional responses (but that are not IED detonations) should be intermixed within the series of IED detonations. Finally, to ensure the continued autonomic responses to the IED detonation, any decrement in the post-stimulus response should be monitored and the simulation stopped at this point and resumed again when the post-stimulus response is robust.

During the entire simulation time, the soldier should be moving and behaving in a life-like environment while physiological data are being recorded continuously. Once enough simulated IED detonations are recorded (likely 30–60), the data from multiple physiological systems preceding each detonation can be analyzed on a trial-by-trial basis using non-linear machine-learning methods to find the characteristic PAA for that soldier. The reason we suggest automated learning is that non-linear, complex relationships between physiological variables and their time courses could exist that allow a fuller characterization of PAA. Along this line of thinking, one of us (Mossbridge) has preliminary data showing that such algorithms may be able to use EEG activity to determine the correct response to an upcoming random event (pressing the left or right mouse key as a correct response to an unpredictable event) on a trial-by-trial basis with above 75% accuracy in ¾ of untrained individuals[9]. We note that without the use of machine learning, finding the combination of electrodes and time points that would produce this predictive effect would have been difficult.

Characterizing the PAA for each soldier could be time consuming, and one possible way to reduce this investment is to screen soldiers to find those who have particularly reliable PAA effects, then characterize PAA to simulated IED explosions in only those soldiers. These PAA-sensitive soldiers could then use the resulting personalized PAAST as "a canary in the coal mine" for their whole team. Another possible time-saving method might be to run multiple soldiers on the IED simulation, then combine their data to characterize a generalized PAA to the simulated IED detonations that can be applied to soldiers who were not tested in the simulated environment. The reliability of this method, of course, would depend on the physiological similarity between the soldiers from whom the data were obtained and those in the field. One possible way to bridge this difference would be to use a generic PAAST on multiple soldiers in combat, so that, for instance, if three of four soldiers have their PAAST activated, all four soldiers would take cover. Assuming an algorithm combining the soldiers' data would not alert the soldiers when only one soldier has a PAA response, this kind of generic physiological profile/multiple-user approach could potentially also reduce the chance of false alarms and increase the likelihood of avoiding real danger.

SUMMARY AND CONCLUSIONS

In summary we have made the following points in this article.

- PAA, the predictive physiological anticipation of a truly randomly selected and thus unpredictable future event, has been under investigation for more than three decades, and a recent conservative meta-analysis suggests that the phenomenon is real.
- Neither QRP, expectation bias, nor physiological artifacts seem to be able to explain PAA.

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[8] If PAA predicts probable rather than actual futures, there would be no paradox.

[9] For study results from the registered analysis, see http://www.koestler-parapsychology.psy.ed.ac.uk/Documents/Study_Results_1004.pdf. Note that because the final analysis producing a significant effect was exploratory rather than confirmatory, these results should be replicated before any strong conclusions are drawn.

- The mechanisms underlying PAA are not yet clear, but two viable yet difficult-to-test hypotheses are that quantum processes are involved in human physiology or that they reflect fundamental time symmetries inherent in the physical world.
- The evidence indicates that there is a temporal mirroring between pre- and post-event physiological events, so that the nature of the post-event physiological response is a reflection of the characteristics of the PAA for that event.
- Temporal blurring, in which closely overlapped emotional events may confuse or minimize both post-event responses and PAA before the event, may be a critical factor in isolating and amplifying PAA.
- The principles of temporal mirroring and temporal blurring both guide the recommendations for designing reliable PAASTs.
- Future research with multiple stimulus modalities, long inter-trial intervals, multiple individuals simultaneously exposed to the same stimulus, and machine-learning techniques will advance our understanding of the nature of PAA and allow a better harnessing of the delay before future events unfold.

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Retro-priming, priming, and double testing: psi and replication in a test–retest design

Thomas Rabeyron *

LPPL, Psychology Department, University of Nantes, Nantes, France

Edited by:
Etzel Cardeña, University of Lund, Sweden

Reviewed by:
Julia Mossbridge, Northwestern University, USA
Daryl J. Bem, Cornell University (Retired), USA

***Correspondence:**
Thomas Rabeyron, Psychology Department, Chemin de la Censive du Tertre, 44000 Nantes, France
e-mail: thomas.rabeyron@univ-nantes.fr

Numerous experiments have been conducted in recent years on anomalous retroactive influences on cognition and affect (Bem, 2010), yet more data are needed to understand these processes precisely. For this purpose, we carried out an initial retro-priming study in which the response times of 162 participants were measured (Rabeyron and Watt, 2010). In the current paper, we present the results of a second study in which we selected those participants who demonstrated the strongest retro-priming effect during the first study, in order to see if we could replicate this effect and therefore select high scoring participants. An additional objective was to try to find correlations between psychological characteristics (anomalous experiences, mental health, mental boundaries, trauma, negative life events) and retro-priming results for the high scoring participants. The retro-priming effect was also compared with performance on a classical priming task. Twenty-eight participants returned to the laboratory for this new study. The results, for the whole group, on the retro-priming task, were negative and non-significant ($es = -0.25$, ns) and the results were significant on the priming task ($es = 0.63$, $p < 0.1$). We obtained overall negative effects on retro-priming results for all the sub-groups (students, male, female). Ten participants were found to have positive results on the two retro-priming studies, but no specific psychological variables were found for these participants compared to the others. Several hypotheses are considered in explaining these results, and the author provide some final thoughts concerning psi and replicability.

Keywords: retro-priming, priming, anomalous experiences, precognition, PSI, replicability, methodology

INTRODUCTION

Non-ordinary mental expressions are frequently associated with altered states of consciousness (Cardeña et al., 2014) and potential specific interactions between mind and reality that are currently not explained by known physical or biological mechanisms, called *psi*. Although numerous studies have been conducted in order to prove the existence of these interactions (Radin, 2006; Tressoldi, 2011) or explain them using a more classical approach (Holt et al., 2012), the results of this research and its interpretations are still a topic of debate in the scientific community (Alcock et al., 2003).

Psi has been extensively studied during the last twenty years, most notably through the use of ganzfeld research (Bem and Honorton, 1994). In a typical ganzfeld study, a "sender" (situated in a shielded room) tries to influence a "receiver" (situated in the "ganzfeld" that is supposed to improve psi perceptions) in order to help him to visualize a target—usually a short movie. The receiver then has to choose between several movies (the target and three decoys), indicating which one was "sent." This protocol has been replicated dozens of times and has produced significant and controversial results concerning the reliability of the effect observed (Milton and Wiseman, 1999; Bem et al., 2001; Storm and Ertel, 2001, 2002; Wackermann et al., 2008; Storm et al., 2010; Williams, 2011).

The details of this controversy will not be examined here; rather, we will note that one of the main difficulties in ganzfeld research, and more generally with what are called "free choice settings" (Storm et al., 2010), is that participants have to freely describe what they are thinking and feeling during the session. The participants and experimenters generally have difficulty in discriminating between the participant's imagination and supposedly "real" psi information. The latter could indeed be unconscious, and the description of the target would then be a mix of potential psi information perceived unconsciously and associations coming from several unconscious levels of mental functioning. This could explain the difficulty in obtaining stronger effect sizes in ganzfeld experiments.

This kind of observation has led to the development of the "presentiment paradigm," in which experimenters test unconscious responses (Radin, 1997). Such an effect could be more reliable than usual conscious responses. In a basic presentiment experiment, participants' reactions are measured *before* they see neutral, violent, or erotic pictures (Radin, 2004). Researchers have thus, obtained small but significant differences in the intensity of reactions before the stimulus. The same kind of protocol has been carried out in different settings, for example, using sounds instead of pictures (May et al., 2005) or using image-priming, with smiling and angry faces (De Boer and Bierman, 2006). A recent meta-analysis produced significant results from presentiment experiments (Mossbridge et al., 2012).

Bem (2010) has more recently developed several paradigms concerning anomalous retroactive influence on cognition and affect, in an attempt to replicate this effect more globally and facilitate the replication process amongst several laboratories. One of these paradigms is a backward priming set-up called "retro-priming." In a classical priming experiment, the participant's reaction is measured after he or she has seen the prime. In a retro-priming experiment, as in presentiment research, the participant's response time is measured not after but *before* the prime. The participant has to push a button to indicate if a picture is positive or negative. Then, the participant sees a prime that is a positive or a negative word. Response time is measured to find out if participants were influenced by the prime they saw after the picture.

In order to try to replicate this effect, we first carried out a retro-priming experiment in which we looked for correlations between anomalous experiences, psychological variables (mental health, mental boundaries, trauma, negative life events) and retro-priming results (Rabeyron and Watt, 2010). These results (see **Table 1**) were non-significant on the whole population ($n = 162$), but we obtained a slightly positive significant effect on the student population ($n = 112$; $r = 0.17$; $p < 0.05$), close to the effect size reported by Bem ($d = 0.20$) (2010). More surprisingly, we also obtained a strong effect with male participants ($n = 45$; $r = 0.41$; $p < 0.01$).

Bem's results gave rise to debates concerning methodological and experimental aspects in the field of psychology that go beyond the existence of psi (Lebel and Peters, 2011; Miller, 2011; Rouder and Morey, 2011; Wagenmakers et al., 2011; Pashler and Harris, 2012). Incidentally, psi research has historically been the source of such methodological and statistical questions (Rhine et al., 1966). Bem's paper spawned numerous attempts to replicate it (see e.g., Galak et al., 2012; Bem et al., submitted) and reflections on the difficulty of direct replications in psychology (Ritchie et al., 2012). This aspect has been associated more generally with debates concerning the "decline effect" in science (Schooler, 2011) and a potential "replication crisis" (Stroebe and Strack, 2014) especially in the fields of psychology and medical sciences (De Winter and Happee, 2013). Several researchers have proposed that large numbers of research findings could be false (Ioannidis, 2005), for a number of reasons, such as insufficient statistical power or questionable research practices (Simmons et al., 2011; Bakker et al., 2012; Francis, 2012).

Replicability in psi research is also a well-argued topic, and has led some researchers to argue that psi is actually different from the already familiar classical physical effects. One proponent of this kind of theory is Walter von Lucadou, with his Model of Pragmatic Information (MPI) (Lucadou, 1995), which is associated more generally with General or Weak Quantum Theory (Atmanspacher et al., 2002). These theories suppose that exact replication of a psi effect would eliminate or change this effect because psi would correspond to a "non-local correlation" that could not be used to predict results; this is called the "non-transmission" axiom (Lucadou and Romer, 2007). More recently, Dick Bierman (2008) proposed the Consciousness Induced Restoration of Time-Symmetry (CIRTS), in which problems of reproducibility are seen as the consequence of time paradoxes. These kinds of theories have fundamental implications and are at the core of numerous current debates in the field.

Last but not least, another difficulty encountered in psi research is the purported need to use high scoring participants for example, better results have been obtained with selected participants in ganzfeld studies (Storm et al., 2010); Some researchers think that only a small proportion of the population could produce consistently high scoring results (McMoneagle, 2000) and that it is possible to select participants using a test and re-test set up (Ertel, 2005, 2013). From this point of view, the difficulty in obtaining a reliable effect comes from the need to pre-select the participants, which is rarely done. Is it possible to select the high scoring psi subjects with a retro-priming experimental set-up? And can we find a psychological profile corresponding to these subjects?

In the present study, we tried to deal with several of these aspects. We decided to select the high scoring participants from the first retro-priming experiment (that is, those who had shown a strong retro-priming effect) and ask them to perform the retro-priming experiment again. If the high scorers in the first study did so by chance alone, then in the second study their performance would tend to regress to the mean (Mee and Chua, 1991), but if a genuine psi effect, with a sufficient effect size, was the cause of their high scoring in the first study, then they would tend to continue to score well on the re-test. We also tried to replicate the *post-hoc* findings from the first study, that is, the significant results with students and male participants, and find common psychological characteristics and a specific profile amongst the high scoring participants from both experiments.

Table 1 | Experiment 1 retro-priming and priming results.

Group	*N*	Retro-priming *t*	Retro-priming *es*	Priming *t*	Priming *es*
Whole group	155	1.32	0.11	8.06	0.65***
Student group	112	1.77	0.17*	7.44	0.70***
Male group	45	2.73	0.41**	2.73	0.41**
Female group	110	0.07	0.01	6.69	0.64***

**P < 0.05; **P < 0.01; ***P < 0.001.*

METHODS

PARTICIPANTS

For the first experiment, 162 participants were recruited: 31 from a general population volunteer panel in Edinburgh University Psychology Department, 114 students from Edinburgh University's intranet website and 17 other participants from advertisements in shops and several internet websites. There were more females (71.6%) than males in the whole group. The median age was 28.64 years (range = 16—76). After the analysis of the first experiment's results, the participants with the most positive results on the psi task (which meant that their retro-priming results—the total logarithm response time of incongruent minus congruent trials—were more than 0.05; this applied to 39 participants, 23% of the whole group) were invited to a second study. Twenty-eight participants responded positively to our request and came back to the laboratory. There were more females (64.29%) than males (10 males and 18 females) and the median age was 26.07 years (range = 18—76).

RETRO-PRIMING EXPERIMENT

The psi task was a retroactive priming task devised by Bem (2008), as described further below. The computer used was a Dell Optiplex 745, running Windows XP. The program used for the psi task was designed by Daryl Bem at Cornell University with REAL basic. It was a slightly different version of the software than the one used by Bem (2008); this version used pictures as primes instead of words. We used a Windows version of this software, using an algorithm to generate a random sequence of numbers.

This psi task was a precognitive experiment in which the response time of participants was measured in order to see if they would be influenced by a prime (a picture) that they would see not before but *after* a word. Participants were shown a word on each of 64 trials and were asked to press one of two keys on the keyboard as quickly as they could, in order to indicate whether the word was pleasant or unpleasant. The participant's response time in making this judgment was the major dependent variable, and the difference in mean response times between incongruent and congruent trials was the index of a priming effect, with positive differences denoting faster responses to congruent trials. The first 32 trials constituted the retroactive priming procedure, and participants were told that a picture would be flashed on the screen just after they made their decision. In this condition, when the participant has a positive result, it appears as though he or she has been "influenced" by the picture seen after the word. A participant who is very permeable to psi information is expected therefore to obtain a very positive score. The remaining 32 trials constituted the standard "forward" priming procedure, and participants were told that from this point on, the flashed picture would appear before rather than after they made their response. The standard priming condition was used to allow us to compare psi results with a classical priming effect, and also to see if we would find correlations between priming results and other variables.

Response times shorter than 250 ms or longer than 2500 ms were regarded as outliers and were excluded from the data analysis, as were trials on which the participant made an error in judging the picture to be pleasant or unpleasant. Finally, because response-time data were positively skewed, all response times were log-transformed prior to being combined and analyzed. Shown below is the time sequence of events for Forward Priming and Retroactive Priming trials, respectively.

FORWARD PRIMING TRIAL

Stimulus	Fixation spot	Picture (prime)	Blank	Word	Starry sky
Time (ms)	1000	150	150	Response time	2000

RETROACTIVE PRIMING TRIAL

Stimulus	Fixation spot	Word	Blank	Picture (prime)	Blank	Starry sky
Time (ms)	1000	Response time	300	500[1]	1000	2000

PROCEDURE

Two months after the first experiment, the participants who had been selected received an email asking them to participate in the experiment for a second time at the Psychology building. When they came back to the laboratory, it was explained by the principal investigator (the same than in the first study: Thomas Rabeyron, male, 29, open to the existence of psi), that they had been selected for this second study because of their high score in the first study. They were then invited to participate again in the task they had already completed during the first study. Finally, they were briefly interviewed about items they had marked as being true on the *Anomalous Experience Inventory* during the first study (Gallagher et al., 1994). They were also asked if anomalous experiences were important in their life. This short interview lasted an average of 10 min. Participants were given £5 in appreciation of their time and effort and they were told they would receive global and personal results by email when all the data had been analyzed. The study was approved by the Department of Psychology's ethics panel.

RESULTS

FIRST EXPERIMENT

The results of the first experiment are available in **Table 1** and, as already mentioned, can be found in a more detailed analysis in a previous paper (Rabeyron and Watt, 2010). During this first study, the results on the retro-priming task were non-significant ($t = 1.32$, $df = 154$, $p = 0.09$, $es = 0.11$) while the results on the priming task were significant ($t = 8.06$, $df = 154$. $p < 0.001$, $es = 0.65$). We then decided to create several groups during a *post-hoc* analysis, using sex and population as variables. We found that the student group had significant results on retro-priming and we found a negative correlation on the whole group between age and psi results, which could have explained the non-significant retro-priming results in the whole population. We also found an unpredicted and strong effect size in the male group ($n = 45$; $r = 0.41$; $p < 0.01$).

SECOND EXPERIMENT

The 28 participants who agreed to come back for the second experiment had obtained very significant results on the retro-priming task ($t = 10.99$, $df = 27$, $es = 2.08$) during the first study. Their results for the second experiment are available in **Table 2**.

Table 2 | Experiment 2 retro-priming and priming results.

Group		Retro-priming		Priming	
	N	***t***	***r***	***t***	***r***
Whole group	28	−1.35	−0.25	3.35	0.63**
Student group	21	−1.39	−0.30	3.08	0.67*
Male group	10	−0.56	−0.18	4.30	1.36**
Female group	18	−1.23	−0.29	1.73	0.41

$^{*}P < 0.05$; $^{**}P < 0.01$.

During this second study, analyses on the whole group ($n = 28$) demonstrated negative and non-significant results on

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[1] The prime is displayed longer in the retro-priming trials because the prime appears after a blank screen and it might be missed if it appeared too briefly. The aim is also to enhance in this way the potential retro-priming effect.

the retro-priming task ($t = -1.35$, $df = 27$, *ns*, $es = -0.25$) and the results were significant on the priming task ($t = 3.35$, $df = 27$, $p < 0.01$, $es = 0.63$). For the student group ($n = 21$), the results were also negative and non-significant on the retro-priming task ($t = -1.39$, $df = 20$, *ns*, $es = -0.30$), but significant on the priming task ($t = 3.08$, $df = 20$, $p < 0.05$, $es = 0.67$). Again, for the male group ($n = 10$), the results were negative and non-significant for the retro-priming task ($t = -0.56$, $df = 9$, *ns*, $es = -0.18$) but significant for the priming task ($t = 4.30$, $df = 9$, $p < 0.01$, $es = 1.36$). Finally, for the female group ($n = 18$), there was a negative and non-significant effect on the retro-priming task ($t = -1.23$, $df = 17$, *ns*, $es = -0.30$) and there was no significant effect on the priming task ($t = 1.73$, $df = 17$, *ns*, $es = 0.41$). Overall, we found a significant negative correlation between the retro-priming results of the first and second studies ($r = -0.46$, $p < 0.05$) and a positive but non-significant correlation between the priming results of the first and second studies ($r = 0.19$, *ns*). The correlation between the priming and retro-priming results was non-significant ($r = -0.045$, *ns*).

PSYCHOLOGICAL PROFILES OF THE BEST PARTICIPANTS

Ten participants were found to have positive results (that is, showing a retro-priming effect) on the two retro-priming studies. Group comparisons between these 10 participants (six male and four female; mean age = 27.6 years) and the other 152 participants did not demonstrate significant differences on the psychological characteristics already used in the first study; that is, paranormal experiences ($U = 609$, ns, two-tailed), mental boundaries ($U = 651.5$, *ns*, two-tailed), mental health ($U = 679.5$, *ns*, two-tailed), childhood trauma ($U = 492.5$, *ns*, two-tailed) or negative life events ($U = 521.5$, *ns*, two-tailed).

From the interviews conducted with participants after the second study, it appeared that the highest scoring participant was a young female student in law who was very interested in the paranormal and who mentioned she was aware of events before they happen on some occasions. Among the 10 highest scoring participants, 5 (50%) said they have had precognitive experiences in the past. They had a range of beliefs concerning the paranormal, with some of them describing themselves as "believers" and others as "skeptics."

DISCUSSION

RETRO-PRIMING AND REPLICABILITY

While we had nearly significant results during the first study (Rabeyron and Watt, 2010), and more precisely a significant retro-priming effect size for the student group ($r = 0.17$), close to the one reported by Bem ($d = 0.25$) (2010), the results of this second study were non-significant. We also obtained overall negative effects on retro-priming results for all the groups (male, female, student, whole) and did not manage to replicate the strong effect size obtained ($r = 0.41$) with male participants in the first study. In previous research concerning psi (Ertel, 2005) some authors have suggested that psi effects could be reliable enough to maintain significant results in test–retest settings but we didn't manage to obtain such results in our retro-priming studies.

In terms of explaining this, we first need to take into account the potential impact of the regression to the mean effect (Mee and Chua, 1991; Kahneman, 2011)[2]. When best participants are selected during a first measurement, they will tend, by chance alone, to be close to the average during a second measurement. The more the results of the first measurement are the consequence of chance alone, the more the regression to the mean effect will be important. This effect would naturally lead to a decrease of the effect size in the second study, which is the case in our data. We used the technique proposed in Barnett et al. (2005) in order to evaluate the regression to the mean effect (rtme) on the results of the first study, and obtained a rtme = 0.15. The retro-priming results of the second study were still non-significant even when we took into account this regression to the mean effect ($r = -0.10$). These non-significant results would rather support a skeptical interpretation of psi data (Alcock, 2003; Wiseman, 2010; Wagenmakers et al., 2011).

These non-significant results could also be the consequence of a setting that was slightly different from that used in Bem's studies: we used pictures, rather than words, as primes, and we cannot know what impact (if any) this change had on the results, or if there was a habituation effect between the two studies. Additionally, we do not know if the fact that participants were told they had positive results on the first psi study had a potential negative impact on their results.

Finally, concerning the selection of high scoring participants, we did not find a typical psychological profile (for anomalous experiences, mental boundaries, mental health and childhood trauma, and negative life events) of the high scoring participants (that is, the 10 participants who had significant results for both studies). We note that half of the selected subjects described having had precognitive experiences in the past, but this qualitative analysis would need to be confirmed in future studies and is difficult to evaluate without a group control comparison.

PRIMING, PSI RESEARCH, AND REPLICABILITY

The priming results from the first and the second studies showed a small and non-significant correlation ($r = 0.19$, *ns*), which echoes a recent paper by Cesario (2014) concerning the difficulty encountered in the replication of the priming effect. He explains:

> "When researchers do not get the "right" combinations of variables, the failures end up in the file drawer. Indeed, this might be what is meant when researchers talk about having "insight" or "intuition" in conducting priming experiments in which they cannot verbalize why they made a decision but knew to make it" (p. 44).

It seems that the replicability difficulties we encountered here concern not only our retro-priming results, but also our priming results. They also contribute more globally to current debates, mentioned in the introduction, on replicability and the decline effect (Schooler, 2011; Francis, 2012). We might ask, then, what are the origins of these difficulties, and are they the same as the

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[2] Comparatively, classical priming results have not been influenced by the regression to the mean effect: the high scoring participants were selected only on their retro-priming results for the second study and not on their priming results. This could explain why the results of priming results were quite similar between the first ($r = 0.65$) and the second study ($r = 0.63$).

ones encountered more globally in the field of psychology? Are they the consequence of variations in the way replications are conducted (Simmons et al., 2011) and do we need to use new statistics (as proposed notably by Cumming, 2014)?

Along similar lines, Cesario's thoughts on the "insight" or "intuition" involved in conducting research and specifically on replicability difficulty have also been a regular topic in psi research (Kennedy, 2003, 2004, 2013; Etzold, 2006; Hyman, 2010). Some psi researchers have thus, proposed the idea that the replication of a psi effect would actually, in some conditions, *suppress* it and may even cause *negative results*. Indeed, we obtained a negative and significant correlation between the results of the first and second studies ($r = -0.46$, $p < 0.05$). We cannot draw firm conclusions concerning this effect because it may partly be due to the regression to the mean effect, as already mentioned, and from an Occam's razor point of view it would of course be more pertinent to view it as evidence of the absence of psi. But this kind of decline effect is not only a topic of debate in psychology (Schooler, 2011) but is also extremely common in psi research: Bierman (1980) describes it as "negative reliability," Beloff (1994) speaks about psi as being "actively evasive," Pallikari and Boller (1997) mention a "balancing effect" between positive and negative replication and Hansen (2001) has proposed a broader theory called "the trickster" to explain these kind of negative results.

We could consider these explanations as kind of "auto-immune" responses from psi researchers when they obtain negative results. Nevertheless, on carefully examining the data, patterns are often noticed that are difficult to explain by chance alone (Lucadou and Romer, 2007), and some theorists have tried to take these strange variations into account in explaining their results. Thus, the MPI (Lucadou, 1995), associated more generally with General or Weak Quantum Theory (Atmanspacher et al., 2002; Filk and Römer, 2011), predicts such sign inversion if researchers attempt to replicate psi effects, and these kinds of results have already been obtained in numerous previous experiments (Lucadou and Romer, 2007). From the MPI perspective, psi effects are considered as "non-local correlations" that share several characteristics, from a metaphoric point of view, with entanglement correlations at a quantum level. These correlations would be produced in systems with an organizational closure (a concept introduced notably by Varela et al., 1974 concerning the way a system is organized) and a psi experiment could be an example of this kind of system. Several parameters (such as "documentation" and "motivation" for example) could increase or decrease the organizational closure of a system and consequently produce (or not) a psi effect.

From this perspective, in our first study (which was already a replication of Bem's studies), we would have obtained a "displacement effect" with a strong and unexpected effect on the male population. Then, in the second study, we tried to use the retro-priming effect to transmit and extract information (a prediction of this effect) from the system (the experiment) which would suppress the effect that we wanted to replicate (especially the strong effect size with male participants). Consequently, as predicted by the MPI, we would have obtained in the second study a sign inversion and a disappearance of the initial *post-hoc* finding, which means more precisely that we had enough motivation to produce psi but the sign had to change in order to allow the expression of a psi effect without breaking the "non-transmission axiom" (NT-Axiom) (Lucadou and Romer, 2007). Of course, this interpretation is only a *post-hoc* analysis, but (Lucadou and Romer, 2007) proposes several ways of testing these kind of processes. More recently, Bierman (2008) also proposed a general model, the CIRTS, in which decline effects are explained as a consequence of the time paradox. In CIRTS, psi effects are seen as a fundamental ability of consciousness to partially restore time-symmetry. The retro-priming effect could be a consequence of such a principle, which more generally could have implications for the global and coherent synchrony of brain processes. Bierman predicted more precisely that any attempt to increase the effect size in a presentiment experiment, as in our retro-priming research, would fail because of these subtle time paradoxes that could be studied and tested with several experimental set-ups (Bierman, 2008).

The data we have obtained here does not allow us to draw conclusions concerning the relevance of these different models, but these results echo previous patterns frequently reported in research aiming for the replication of psi processes. New insights with regards to psi and retro-priming should take these hypotheses into account. If they were to be true, they could indeed have important implications for experimental and methodological psychological design. Future research should focus on improving the reliability and replicability of retro-priming studies (with, for example, the use of prospective meta-analysis, see, e.g., Kennedy, 2013) and priming studies (Cesario, 2014). It should also aim to develop theoretical models that allow empirical predictions, as proposed by Lucadou and Romer (2007) and Bierman (2008), in order to demonstrate if these patterns are mere cognitive illusions or if they are a real aspect of supposed psi effects.

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Anomalous experiences, psi and functional neuroimaging

David J. Acunzo[1], Renaud Evrard[2] and Thomas Rabeyron[3]*

[1] School of Informatics, Institute for Adaptive and Neural Computation, University of Edinburgh, UK
[2] SULISOM, Psychology Department, University of Strasbourg, Strasbourg, France
[3] LPPL, Psychology Department, University of Nantes, Nantes, France
*Correspondence: thomas.rabeyron@univ-nantes.fr

Edited by:
Etzel Cardeña, University of Lund, Sweden

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John A. Palmer, Rhine Research Center, USA

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Over the past decade, there has been increasing scientific interest in anomalous experiences. These can be defined as "uncommon experience[s] [...] that, although [they] may be experienced by a significant number of persons [...], [are] believed to deviate from ordinary experience or from the usually accepted explanation of reality according to Western mainstream science" (Cardeña et al., 2014). This scientific interest has led to important contributions toward the understanding of several aspects of these experiences (Brugger and Mohr, 2008). One of the most controversial hypotheses associated with anomalous experiences is the *psi hypothesis*, which states that anomalous experiences sometimes imply forms of interactions falling outside currently known biological and physical mechanisms (Bem and Honorton, 1994). Thus, far, small but persistent effects are frequently reported in experiments testing the psi hypothesis (Radin, 2006), while no consensus has been reached concerning their explanation (Alcock et al., 2003).

Research testing the psi hypothesis has occasionally generated a great deal of interest and controversy. The most recent example is Bem's series of precognition experiments (Bem, 2011), which triggered important methodological questionings on the validity of the frequentist approach (Miller, 2011; Rouder and Morey, 2011; Wagenmakers et al., 2011), widely used in experimental sciences. Bem's paper was followed by an attempt of replication (Ritchie et al., 2012a), which resulted in reflections on the difficulty in publishing direct replications in psychology (Ritchie et al., 2012b). This debate, still ongoing, has shown how research about anomalous experiences can stimulate cutting-edge discussions on scientific methodology. This heuristic value of anomalous experiences has a history even in the infancy of cognitive neuroscience with the German neurologist Hans Berger, inventor of electroencephalography and the first person to describe different brain waves, having previously had a telepathic experience with his sister which made him obsessed by the idea of how his mind could have carried such a signal (Berger, 1940).

More recently, attempts to test the psi hypothesis and find its neural correlates have been carried out using functional neuroimaging. The rationale behind these experiments is that if psi-related processes are indeed present in the brain, even unconsciously, they should be observable using functional neuroimaging. An example of such a study would be to test whether the brain activity of Participant A would be influenced when Participant B, situated in another isolated room, intends to send information to or simply concentrate on Participant A. Various types of hypothetical phenomena have already been examined, including forms of telepathy (Standish et al., 2003; Richards et al., 2005; Moulton and Kosslyn, 2008; Venkatasubramanian et al., 2008), distant intentionality (Achterberg et al., 2005), and precognition (Bierman and Scholte, 2002; Moulton and Kosslyn, 2008). All these six studies but one (Moulton and Kosslyn, 2008) reported results consistent with the psi hypothesis.

Unfortunately, several of these studies suffer from methodological weaknesses that could account for the reported effects. Listing these flaws may contribute to the improvement of the research in this field. These methodological weaknesses can be grouped into four categories:

1. *Counter-balancing* across participants is routinely used in experimental psychology and cognitive sciences to avoid systematic biases due to experimental conditions specific to one or several participants. In Venkatasubramanian et al. (2008), the receiver and the sender were presented green and red-colored stars to indicate the onset of telepathy and control trials, respectively. It is therefore not possible to know whether the difference in brain activity between the two conditions is due to the nature of the trial (telepathy vs. control) or to the difference in the color of the stimulus indicating trial onset. To disentangle this potential confound, the reverse cue association has to be given for half of the trials—or half of the participants, if their number is sufficient.
2. *Trial order randomization* prevents biases that could be caused by the particular order of the trial conditions. Such biases can be caused by participants detecting a certain pattern (e.g., repetitions or alternations), leading to expectations and thus detectable neural signatures that could bias the results. Habituation, leading to different brain activity between the beginning and the end of the experiment may also bias the results. To counter-balance the potential biases produced by a particular sequence—even if it was generated randomly—each participant should be given a distinct series of randomly-ordered trials. Unfortunately, proper

randomization was not met in four of the six studies: In Venkatasubramanian et al. (2008) no randomization was used at all, while in Standish et al. (2003) and Richards et al. (2005) the duration of the trials was randomized, but not their order. Moreover, in the Venkatasubramanian study, the target picture was freely chosen and drawn with a pen by one investigator used as the "sender." A randomized target selection from a prepared set of images would have been preferable. Humans are indeed inherently biased in their attempts to generate random targets (Brugger and Taylor, 2003). Besides, a randomization would have prevented potential correlations between the target imagined by the "sender" and the guess of the "receiver" due to their potential interaction or common immediate past experience before the experiment.

3. *Information shielding*: All normal mechanisms have to be excluded for correlations between the source (e.g., a "sender" or healer) and the participant's brain activity to be considered as psi (see e.g., Alcock et al., 2003). However, some reports showed weaknesses on this crucial point. In Achterberg et al. (2005), the healer's task is to influence from a distance the participant lying inside the scanner. In this study, the same healer was used for three different participants while the same sequence (i.e., the order of control and active sessions) was used. Consequently, this particular healer knew in advance this sequence, and it is not specified whether contact between the healer and the participants was prevented. In the Venkatasubramanian et al. (2008) study, the authors used the same target image for the only two participants whilst no information concerning a possible interaction between them was provided, potentially leading to the same problem.
4. *Small sample size*, i.e., too small a number of participants and/or trials per participant, was also a weakness of several studies (Standish et al., 2003; Richards et al., 2005; Venkatasubramanian et al., 2008). As underpowered studies most often miss existing effects (leading to false negatives), reported positive results have a low probability to reflect a true effect (see e.g., Button et al., 2013). Furthermore, with too few participants, proper counter-balancing is difficult and the risk of confounds is greater.

Two studies (Bierman and Scholte, 2002; Moulton and Kosslyn, 2008), however, appear methodologically sound. Both explored various potential sources of artifacts that could account for their respective significant results. Bierman and Scholte (2002) could not find any classical explanation for the significant effects observed. Moulton and Kosslyn (2008), on the other hand, concluded that their results constituted "the strongest evidence yet obtained against the existence of (psi)" despite the logical difficulties in proving a negative existential proposition (Whitehead and Russell, 1910–1913). Additionally, despite the many precautions taken by the experimenters, a subtle bias was still found in one participant's data, indicating that the design could potentially be flawed.

Finally, none of the studies addressed the issue of the confined and noisy environment inside the scanner tube that tends to make participants uncomfortable. As this problem is currently unavoidable, the participants could be prompted about their comfort or relaxation level and their answers used as a covariate in the analysis.

Testing the psi hypothesis using neuroimaging is an important topic as it may help to shed some light on the nature of anomalous experiences (Watt and Irwin, 2010; Krippner and Friedman, 2010b), on altered states of consciousness (Krippner and Friedman, 2010a; Cardeña and Winkelman, 2011) and more generally on potential methodological problems in the field of psychology and neurosciences (Watt, 2005). Nevertheless, in our opinion, no firm conclusions concerning the psi hypothesis can be made on the basis of this corpus of functional neuroimaging data, and more methodologically sound results need to be generated.

AUTHOR CONTRIBUTIONS

All authors contributed extensively to the work presented in this paper.

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