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Neurophysiologic Correlates to Sensory and Cognitive Processing in Altered States of Consciousness

A Dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Neurosciences

by

Baruch Rael Cahn

Committee in charge:

Mark Geyer, Chair
John Polich, Co-Chair
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2007

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University of California, San Diego

2007

DEDICATION

I dedicate this thesis in loving memory to my sister Lotus Blossom Cahn who passed away in 2005 from cancer of the thymus. May the love she brought to all those whose lives she touched live on through us and reach out to the world we inhabit.

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Chapter 4, in part, is in preparation for submission for publication with Franz Vollenweider as co-author. The dissertation author is the primary investigator and author of this paper.

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ABSTRACT OF THE DISSERTATION

Neurophysiologic Correlates to Sensory and Cognitive Processing in Altered States of Consciousness

by

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Doctor of Philosophy in Neurosciences

University of California, San Diego 2007

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Research is presented on the altered sensory and cognitive processing as assessed by event-related potential analysis of electroencephalographic data during states of meditation in long-term meditators and due to the effects of psilocybin, a naturally occurring serotonin receptor agonist with hallucinogenic properties. The literature on the neurophysiologic correlates to meditation are reviewed. In a passive auditory oddball paradigm rare tones and distracters are shown to evoke increased sensory processing as indexed by increases in the amplitudes of the N1 and P2 event-related potential components. The distracter stimuli are shown to evoke a later P3a component and

increases in frontal theta power associated with attentional engagement. Meditation causes a significant reduction in the P3a amplitude and frontal theta power to distracting stimuli implying the disengagement of attentional networks from ongoing sensory processing.

Psilocybin is shown to cause enhanced early sensory processing of visual stimuli as indexed by the P1 component. This psilocybin-induced alteration is shown to be especially prominent in the brain's response to distracting stimuli in a visual target detection paradigm. Psilocybin is also shown to decrease intermediate object-recognition processing as indexed by the N170 event-related potential. While N170 amplitude is increased due to the perception of illusory contours, psilocybin induces a brain state where fewer additional resources are recruited to the perception of illusory contours. Later P3 amplitudes associated with detection and response-related processing as well as distracter processing are shown to be significantly reduced by psilocybin, supporting the notion that attentional networks are disengaged from ongoing sensory processing. Psilocybin inhibits the increase in frontal theta activity associated with the perception of illusory contours and visual distracters, adding further support to the model of meditation-induced attentional disengagement. A preliminary model of psilocybin-induced changes in neurophysiology and integrative comments on the significance of the similarities and differences between the effects of meditation and psilocybin on the brain's attentional systems are provided.

INTRODUCTION

Research on the neurophysiologic basis of altered states of consciousness is still in its infancy. There is a paucity of modern research on the brain correlates to the administration of hallucinogens. The many early publications on the electroencephalographic (EEG) alterations due to hallucinogens are relatively uninformative as they relied on methods of analysis such as the subjective ratings of wave forms. The general findings indicated that increases in relative predominance of faster activity and lower amplitudes of EEG were seen with both psilocybin (Oughourlian, Rougeul, & Verdeaux, 1971; Rynearson, Wilson, & Bickford, 1968; K. Thatcher, Wiederholt, & Fischer, 1971), and LSD (Bachini, Villar, Prieto, & Garcia Austt, 1965; Schwarz, Sem-Jacobsen, & Petersen, 1956; Shagass, 1966), but without quantitative analysis this data can not be meaningfully integrated into present knowledge of EEG dynamics. Research on the effects of meditation is somewhat more advanced, but also at an early stage of development (see chapter 1 for a review of the literature). The aim of the current thesis work was to begin to chart some of the key markers of altered states of consciousness as induced by both meditation and psilocybin using electroencephalographic techniques.

The motivation for the current studies was the attempt to characterize the brain states associated with specific states of consciousness as a way of beginning to map the brain markers associated with the altered states and traits of consciousness encountered in meditative practices as well as hallucinogen-related altered states. It was hypothesized

that there might be some commonalities and likely also many differences to such states of consciousness, based on the nature of the subjective reports generated in response to experiences in and with these altered states.

The serotonin 1a/2a receptor agonist psilocybin has been reported to induce unitive states of consciousness and mystical experiences, most famously in Walter Pahnke's "Good Friday" experiment with theological students at Harvard (Pahnke, 1969; Pahnke & Richards, 1966). Subsequent phenomenological categorization of the "mystical experiences" encountered in psychedelic sessions revealed nine commonalities to these experiences: Unity, experience of objectivity, transcendences of space and time, sense of sacredness, deeply felt positive mood, paradoxicality, alleged ineffability, transiency, and subsequent positive changes in attitude and/or behavior (Pahnke, 1969).

More recent work by Adolf Dittrich and colleagues (A. Dittrich, 1998; A. Dittrich, von Arx, S., Staub, S., 1985) has further refined the measurement and dimensionality encountered in altered states of consciousness due to diverse inducers including drugs, sensory deprivation or overload, meditation, hyperventilation, and other extreme physical practices. The outcome of this work has been the development of the Aussergewohnlicher Psychischer Zustand (APZ) rating scale, the most recent English version of which is now referred to as the 5-D Altered States of Consciousness questionnaire or "5D-ASC." The statistical factor analysis evaluation of the experience of thousands of individuals undergoing altered states of consciousness has resulted in five dimensions which are assessed quantitatively by the 5D-ASC (A. Dittrich, von Arx, S., Staub, S., 1985).

The first dimension, Oceanic Boundlessness, measures characteristics commonly associated with reports of mystical states of unity (reminiscent of the nine characteristics of this type of experience explicated by Pahnke) including a positive basic mood ranging from heightened feelings to sublime happiness or grandiosity. The second dimension, Anxious Ego Dissolution, measures thought disorder, ego disintegration, loss of autonomy and self-control variously associated with arousal, anxiety, and paranoid feelings of being endangered. The third dimension, Visionary Restructuralization, refers to visual illusions, hallucinations, synaesthesias, and changes in the meaning of various percepts. More recently, systematic work by Vollenweider's group in Zurich using the 5-D ASC has demonstrated that reliable increases in all of the scales including the positively felt dimension of Oceanic Boundlessness after ingestion of the 5 HT1a/2a agonist psilocybin, even in laboratory conditions rich with brain imaging intervention and cognitive testing.

In the experiments described herein the neurophysiologic correlates of the sensory and cognitive processing of stimuli is explored. The experiment with Vipassana meditation focused on auditory processing and those with psilocybin focused on visual processing, with some paradigmatic overlap in the types of cognitive processing engaged by these two sensory modalities. The focus is on presentating the data generated by these investigations, with some preliminary hypotheses proposed regarding the meaning of these data. It is hoped that by establishing some findings with regards to changes in sensory and cognitive processing and their possible associations with aspects of the reported altered state of consciousness this work will contribute to a fuller understanding

of the basic neural underpinnings of altered states and consciousness generally. This in turn may generate insight into the neurobiology of the subjective sense of unity and boundarilessness sometimes encountered through both meditation and the use of hallucinogens, although the epistemological meaning of such experiences are likely to prove much more resistant to scientific investigation.

CHAPTER 1

Meditation States and Traits: EEG, ERP, and Neuroimaging Studies

Abstract

Neuroelectric and imaging studies of meditation are reviewed. Electroencephalographic (EEG) measures indicate an overall slowing subsequent to meditation, with increases in theta and alpha activation related to greater proficiency of practice. Sensory evoked potential (EP) assessment of concentrative meditation yields larger amplitude and shorter latency for some components and forms of practice. Cognitive event-related potential (ERP) evaluation of meditation suggests that practice changes attentional allocation. Neuroimaging studies indicate increased regional cerebral blood flow measures during meditation. These and some of the EEG effects from meditative practice appear to be generated by anterior cingulate cortex and dorsolateral prefrontal areas. Neurophysiologic meditative state and trait effects are variable but beginning to demonstrate consistent outcomes and promising directions for research and clinical applications. Psychological and clinical effects of meditation are summarized, integrated, and discussed with respect to neuroimaging data.

Overview and Definitions

Electroencephalographic (EEG) studies of meditative states have been conducted for almost 50 years, but no clear consensus about the underlying neurophysiologic changes

from meditation practice has emerged. Sensory evoked potential (EP) and cognitive event-related potential (ERP) assessments of meditative practice also reflect variegated results. Some reliable meditation-related EEG frequency effects for theta and alpha activity, as well as EEG coherence and ERP component changes have been observed. Positron emission tomography (PET) and functional magnetic imaging (fMRI) studies are beginning to refine the neuroelectric data by suggesting possible neural loci for meditation effects, although how and where such practice may alter the central nervous system have not yet been well characterized. The present paper reviews and summarizes the neuroelectric results in conjunction with neuroimaging findings. Toward this end, (1) meditation terms and effects are defined, (2) the results of neuroelectric meditation studies are collated, and (3) the findings are related to other neuroimaging reports.

The word meditation is used to describe practices that self-regulate the body and mind, thereby affecting mental events by engaging a specific attentional set. These practices are a subset of those used to induce relaxation and/or altered states such as hypnosis, progressive relaxation, and trance induction techniques (Vaitl et al., 2005). Given that regulation of attention is the central commonality across the many divergent methods (R. J. Davidson & Goleman, 1977), meditative styles can be usefully classified into two types—*mindfulness* and *concentrative* depending on how the attentional processes are directed. Most meditative lie somewhere on a continuum between the poles of these two general methods (Andresen, 2000; D. H. Shapiro & Walsh, 1984; B. A. Wallace, 1999). However, meditative traditions often do not characterize themselves according to this schema but rather place more emphasis on the benefits from the

practice. Mindfulness practices involve allowing any thoughts, feelings, or sensations to arise, while maintaining a specific attentional stance: awareness of the phenomenal field as an attentive and non-attached observer without judgment or analysis. Examples include Zen, Vipassana, and the western adaptation to Mindfulness Meditation (Kabat-Zinn, 2003). Concentrative meditational techniques involve focusing on specific mental or sensory activity: a repeated sound, an imagined image, or specific body sensations such as the breath. Examples include forms of Yogic meditation and the Buddhist Samatha meditation focus on the sensation of breath. Transcendental Meditation (TM) fits somewhat within the concentrative forms as practice centers on the repetition of a mantra, but the method places a primary emphasis on absence of concentrative effort and the development of a witnessing, thought-free "transcendental awareness." The mantra is thought to eventually occupy awareness during meditative practice without concentrative effort, thereby possibly distinguishing the technique from other concentrative practices (Mahesh Yogi, 1963; Travis et al., 2002). However, the development of a transcending observer's perspective on their mental contents is an implicit or explicit goal of most meditative traditions (Goleman, 1996; Kabat-Zinn, 1990; Walsh, 1982). This distinction, if more thoroughly assessed across meditative traditions, might evolve as a second dimension for the state space into which different techniques could be categorized usefully.

Although these perspectives make it difficult to classify a given meditative practice as purely mindfulness or concentrative meditation, the two styles overlap in their approach toward similar goals. The former requires the maintenance of attention in a state

of open perceptivity, and the latter requires narrowing of attentional focus. Mindfulness-based practices tend to encourage a continual return to an attentive set that is characterized by open, non-judgmental awareness of the sensory and cognitive fields and include a meta-awareness or observation of the ongoing contents of thought. Concentrative techniques incorporate mindfulness by allowing other thoughts and sensations to arise and pass without clinging to them and bringing attention back to a specific object of concentrative awareness to develop an internal "witnessing observer." Thus, the methods used to elicit specific states differ across practices, but the results similarly produce reported trait changes in self-experience—eliciting shift towards expanded experience of self not centered on the individual's body schema and mental contents (Mahesh Yogi, 1963; Naranjo & Ornstein, 1971; Ornstein, 1972; B. A. Wallace, 1999; West, 1987).

An early theoretical model for understanding the neurophysiology of meditative states and traits employed a continuum of autonomic arousal from parasympathetic (trophotropic) to sympathetic (ergotrophic) dominance (Fischer, 1971; Gellhorn & Kiely, 1972). Mystical experiences of consciousness can be considered related to ergotrophic states similar to those seen in psychiatric disturbance, ecstatic ritual, or hallucinogenic drug intoxication, but they also can be elicited through trophotropic meditative practice by means of a hypothetical rebound effect (Fischer, 1971). This framework has utility in reconciling the neurophysiologic arousal of peak experiences in meditative states with the more commonly observed hypoarousal of meditative practice (J. M. Davidson, 1976). However, broad and encompassing statements about "the neurophysiology of meditation"

are as yet unrealistic, as brain differences among meditative practices have not been well established (Dunn, Hartigan, & Mikulas, 1999; Lazar et al., 2003; Lehmann et al., 2001; Lou et al., 1999; Lutz, Greischar, Ricard, Converse, & Davidson, 2003). Some progress has been made to identify structure-function central nervous system relationships of meditative states and traits (Travis & Wallace, 1999), with changes in arousal and attentional state involved in meditation also related to hypnosis (Holroyd, 2003; Otani, 2003), drowsiness, sleep, and unconsciousness (Austin, 1998).

Meditation States and Traits

Measurement of the brain response to meditative practice is based on the premise that different conscious states are accompanied by different neurophysiologic states and reports that meditation practice induces distinct states and traits of consciousness. *State* refers to the altered sensory, cognitive, and self-referential awareness that can arise during meditation practice, whereas *trait* refers to the lasting changes in these dimensions that persist in the meditator irrespective of being actively engaged in meditation (Austin, 1998; D. H. Shapiro & Walsh, 1984; West, 1987). Regular meditation practice can produce relatively short-term states as well as long-term changes in traits.

State changes from the meditative and religious traditions are reported to include a deep sense of calm peacefulness, cessation or slowing of the mind's internal dialog, experiences of perceptual clarity and conscious awareness merging completely with the object of meditation, regardless of whether a mantra, image, or the whole of phenomenal experience is the focal point (D. P. Brown, 1977; B. A. Wallace, 1999; West, 1987). A

common experience of many meditative practices is a metacognitive shift in the relationship between thoughts and feelings—they come to be observed as arising phenomena instead of occupying full attention (B. A. Wallace, 1999; West, 1987). Also possible are "peak experiences" that are characterized by blissful absorption into the present moment (Samadhi, nirvana, oneness, etc.), with different traditions using specific names to describe the resulting ineffable states (Forman, 1990; Goleman, 1996; Mahesh Yogi, 1963; Wilber, 1977) that are affected by the extent of practice (Travis, Tecce, Arenander, & Wallace, 2002; B. A. Wallace, 1999). Although such peak/mystical states spurred the evolution of different meditation traditions the practice is centered on trait effects (Dalai Lama & Cutler, 1998; Goleman, 1996, 2003; Kwon, Hahm, & Rhi, 1996; West, 1987), since peak experiences can occur under circumstances unrelated to meditation (James, 1902; Maslow, 1964).

Trait changes from long-term meditation include a deepened sense of calmness, increased sense of comfort, heightened awareness of the sensory field, and a shift in the relationship to thoughts, feelings, and experience of self. States of awareness sometimes referred to as "the witness" or "transcendental experience" are also claimed to ensue over time. This experience consists of content-less awareness that is independent of mental activities, can be present during deep sleep, and produces the perception of an altered self-identity wherein the separation perceived between the observer and the observed grows ever fainter (Austin, 2000; Forman, 1990; Travis, Tecce, Arenander, & Wallace, 2002; West, 1987). As the perceived lack of separation develops, the sense of self seems

to shift from mental thought centered in the body to an impersonal *beingness*. This awareness is related to the essential emptiness of a separate and isolated self-identity.

Studies to date have not been optimally designed to assess both meditation state and trait effects, in part because of the administrative challenge, difficulty in defining appropriate control groups/conditions, and complications arising from the synergistic association between meditative states and traits (Goleman, 1996; Travis, Arenander, & DuBois, 2004b; Walsh, 1980; Wilber, 1977). Meditators consistently evince a witnessing awareness stance to their emotional and cognitive fields through their meditative practice and therefore cannot disengage this metacognitive shift. Hence, an observed "state" of meditation in a meditator may be a deeper reflection of the "trait" and may be observed in a meditator told to keep the mind busy with thoughts instead of meditating (Goleman, 1996; Mahesh Yogi, 1963). Moreover, non-meditators simply cannot keep themselves in a state of physical immobility for the long lengths of time trained meditators can exhibit, thereby making comparisons with the prolonged meditative state of a meditator practically impossible. Attempts to assess state versus trait effects have largely ignored these issues and employed protocols that omit counterbalancing of meditation vs. non-meditation states, minimized the duration of non-meditation simulations (Aftanas & Golocheikine, 2002; Hebert & Lehmann, 1977; Kwon, Hahm, & Rhi, 1996; R. K. Wallace, 1970), or only compared meditators and controls at rest to measure "trait" effects (R. J. Davidson et al., 2003; Travis, Tecce, Arenander, & Wallace, 2002; Travis, Tecce, & Guttman, 2000).

The developing field of neurophenomenology emphasizes the need to define the underlying neurophysiologic correlates of conscious states and internal experience (Delacour, 1997; Gallagher, 1997; Jack & Roepstorff, 2002; Jack & Shallice, 2001; Lutz, Lachaux, Martinerie, & Varela, 2002; McIntosh, Fitzpatrick, & Friston, 2001; Varela, 1996). The goal is to use first-person reports to correlate internal experience with brain activity to guide neuroimaging analysis. For example, studies of TM states have begun to incorporate protocol methodology that marks the neurophysiologic data with repeated reports from meditative subjects to inform the neurophenomenological correlation (L. I. Mason et al., 1997; Travis, 2001; Travis & Pearson, 1999; Travis & Wallace, 1997); similar efforts are used for neuroimaging of hypnosis states (Rainville & Price, 2003). Collaborations between members of meditative traditions and neuroscientists have begun to distill the range of phenomenological changes from long-term contemplative practice (Goleman, 2003; L. I. Mason et al., 1997; Rapgay, Rinpoche, & Jessum, 2000; Travis, Arenander, & DuBois, 2004b). This approach is a necessary step to avoid the confound of meditation self-selection characteristics underlying the observed effects (Schuman, 1980; D. H. Shapiro & Walsh, 1984; West, 1980a), with trait measured using longitudinal prospective studies of meditative practice compared to non-meditating controls (R. J. Davidson et al., 2003).

One common parameter of internal experience secondary to meditative practices is the expansiveness in the experience of self, which includes agency, autobiographical memory-referencing, and psychiatric/drug-induced changes in self-experience and depersonalization phenomena (Farrer et al., 2003; Farrer & Frith, 2002; Kircher & David,

2003; MacDonald & Paus, 2003; Mathew et al., 1999; Sierra, Lopera, Lambert, Phillips, & David, 2002; Simeon et al., 2000; Vollenweider, 1998; Vollenweider & Geyer, 2001a; Vollenweider et al., 1997). However, neurophysiologic studies of the altered self-experience from meditative practice are largely absent because of the difficulty in quantifying self-experience. Psychometric state and trait measures have been constructed (A. Dittrich, 1998; Friedman, 1983; Friedman & MacDonald, 1997), and some studies have begun use this approach to amplify meditation central nervous system findings (Lehmann et al., 2001; Travis, Arenander, & DuBois, 2004b; Travis, Tecce, Arenander, & Wallace, 2002).

EEG and Meditation

Continuous EEG

The EEG signal generated by alpha (8-12 Hz) activity was first described by Hans Berger in 1929 with the demonstration that closing the eyes decreased sensory input and increased alpha power over the occipital scalp (Berger, 1929). EEG studies have used these methods to limn the neurophysiologic changes that occur in meditation. Although the neuroelectric correlates of meditative altered consciousness states are not yet firmly established, the primary findings have implicated increases in theta and alpha band power and decreases in overall frequency (for reviews, see (Andresen, 2000; J. M. Davidson, 1976; Delmonte, 1984b; Fenwick, 1987; Pagano & Warrenburg, 1983; Schuman, 1980; D. H. Shapiro, 1980; D. H. Shapiro & Walsh, 1984; Shimokochi, 1996; West, 1979, 1980a; Woolfolk, 1975).

The association between alpha changes and cortical activation has been assessed with combined EEG and fMRI/PET studies, with increased alpha power related to decreased blood flow in inferior frontal, cingulate, superior temporal, and occipital cortices (Goldman, Stern, Engel, & Cohen, 2002; Sadato et al., 1998). Stimulation of the sensory systems or by attentional focusing is associated with decreases in alpha power from the corresponding sensory area as well (Basar, Schurmann, Basar-Eroglu, & Karakas, 1997; E. Niedermeyer, Lopes da Silva F.H., 1999; Schurmann & Basar, 2001). Results suggest a positive correlation between thalamic activity and alpha power at some but not all locations (Schreckenberger et al., 2004). Although an integrated model of the neural generators for alpha and other frequencies has not yet been established (Basar, Basar-Eroglu, Karakas, & Schurmann, 2001; E. Niedermeyer, 1997; E. Niedermeyer, Lopes da Silva F.H., 1999), alpha appears to be a dynamic signal with diverse properties that is sensitive to stimulus presentation and expectation (Schurrmann & Başar, 2001; Steriade, 2000).

Table 1 summarizes the findings from EEG meditation studies. Alpha power increases are often observed when meditators are evaluated during meditating compared to control conditions (Aftanas & Golocheikine, 2001; Anand, 1961; Arambula, Peper, Kawakami, & Gibney, 2001; Banquet, 1973; Deepak, Manchanda, & Maheshwari, 1994; Dunn, Hartigan, & Mikulas, 1999; Echenhofer, Coombs, & Samten, 1992; Ghista et al., 1976; Kamei et al., 2000; Kasamatsu & Hirai, 1966; Khare & Nigam, 2000; M. S. Lee et al., 1997; Litscher, Wenzel, Niederwieser, & Schwarz, 2001; Saletu, 1987; Taneli & Krahne, 1987; R. K. Wallace, 1970; R. K. Wallace, Benson, & Wilson, 1971; Wenger &

Bagchi, 1961), and this band is stronger at rest in meditators compared to non-meditator controls (Aftanas & Golocheikine, 2001; Corby, Roth, Zarcone, & Kopell, 1978; Deepak, Manchanda, & Maheshwari, 1994; Elson, Hauri, & Cunis, 1977; Kasamatsu & Hirai, 1966; Khare & Nigam, 2000; Satyanarayana, Rajeswari, Rani, Krishna, & Rao, 1992; Travis, 1991; Travis, Tecce, Arenander, & Wallace, 2002)—findings that suggest both state and trait alpha changes emerge from meditation practice (Delmonte, 1984a; Fenwick, 1987; West, 1980a). This outcome has been related to early biofeedback studies in which greater levels of alpha activity were found to be correlated with lower levels of anxiety and feelings of calm and positive affect (B. B. Brown, 1970a, 1970b; Hardt & Kamiya, 1978; Kamiya, 1969). However, subsequent reports suggested that the apparent increased alpha trait effect could be correlated with relaxation and selection bias for those who choose to meditate or stay with the practice, and not all meditation studies show an alpha state effect (Aftanas & Golocheikine, 2001; Benson, Malhotra, Goldman, Jacobs, & Hopkins, 1990; Drennen & O'Reilly, 1986; Hebert & Lehmann, 1977; Gregg D. Jacobs, Benson, & Friedman, 1996; Kwon, Hahm, & Rhi, 1996; Pagano & Warrenburg, 1983; Schuman, 1980; Travis & Wallace, 1999). In sum, alpha power increases are associated with relaxation, which is observed in some individuals when meditating compared to baseline (Morse, Martin, Furst, & Dubin, 1977).

Chapter 1 Table 1. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Das & Gastaut (1957)	Kriya Yoga	7	Advanced Yogic meditators Rest → meditation → rest	State: Alpha activity decrease, frequency increase; Samadhi with increased amplitude fast beta activity; no alpha blocking to stimuli; resting alpha with increased amplitude and wider distribution after meditation vs. before Trait: NA
Wenger & Bagchi (1961)	Yoga	14	Rest vs. meditation	State: Alpha activity increase, no alpha blocking Trait: NA
Anand et al. (1961)	Raj Yoga	6	Rest vs. meditation	State: Increased alpha power during Samadhi; no alpha blocking to visual, auditory, or painful stimuli during meditation Trait: High alpha amplitude at rest, beginners with higher alpha showed greater zeal to continue
Kasamatsu & Hirai (1966)	Zen	70	Meditators vs. controls EEG during eyes open rest or meditation	State: Increased alpha amplitude → decreased alpha frequency → alpha activity spreading frontally → theta bursts (→ alpha persists in eyes open rest state), non-habituating alpha blocking Trait: Increased alpha amplitude

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Wallace (1970)	TM	15	Rest vs. meditation Some photic and auditory stimuli	State: Decreased alpha frequency and increased in alpha amplitude; alpha blocking with no habituation Trait: NA
Wallace et al. (1971)	TM	36	Rest vs. meditation	State: Increased Alpha (8-10 Hz) amplitude, some subjects with theta bursts Trait: NA
Banquet (1973)	TM	24	Rest vs. meditation, with repeated sessions Some photic and auditory stimuli	State: Decreased alpha frequency → theta activity in some subjects; deep meditation states with generalized fast frequencies at 20 and 40 Hz, persistent alpha activity after meditation, no alpha blocking, no statistics Trait: None reported
Williams & West (1975)	TM	19	Photic stimulation during rest	State: NA Trait: More early alpha induction, less alpha blocking during rest session; maintenance of low-arousal state without progression towards sleep
Younger et al. (1975)	TM	8	Meditation—4 sessions per subject	State: 40% in sleep Stages I or II (range 0-70%) Trait: NA
Tebecis (1975)	TM, Self-Hypnosis	42	Rest → meditation/self hypnosis, meditation/self-hypnosis → rest	State: None Trait: Higher theta power in meditators and self-hypnosis

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Tebecis (1975)	TM, Self-Hypnosis	42	Rest → meditation/self hypnosis, meditation/self-hypnosis → rest	State: None Trait: Higher theta power in meditators and self-hypnosis
Pagano et al. (1976)	TM	5	Napping vs. meditation, 5 conditions each subject	State: 40% time in meditation met criteria for sleep Stages II-IV Trait: NA
Ghista et al. (1976)	Ananda Marga	5	Before, during, and after meditation	State: Increases in alpha and theta power Trait: NA
Bennett & Trinder (1977)	TM	32	Meditators vs. controls, each subject had 2 analytic tasks and 2 spatial tasks, tasks and meditation/relaxation order counterbalanced	State: Trend towards less variation in asymmetry during meditation compared to control subject relaxation; only alpha asymmetry assessed Trait: Greater left asymmetry on analytical tasks; right asymmetry on spatial tasks
Hebert & Lehmann (1977)	TM	13 2	Meditators vs. controls Rest→meditation→rest	State: Frontal-central theta bursts more common during meditation, associated with peaceful "drifting", not drowsy Trait: More theta burst subjects (30% compared to 0%)
Morse et al. (1977)	TM, hypnosis, Progressive Relaxation	48	Randomized order induction of various relaxation states	State: All relaxation methods induced equal alpha in some but not all participants Trait: None reported

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Fenwick et al. (1977)	TM	10	Rest → meditate → rest	State: Theta bursts in some subjects, meditation indistinguishable from stage onset sleep; meditation appeared as drowsiness that does not descend to sleep as in rest periods Trait: NA
Elson et al. (1977)	Ananda Marga Yoga	22	Rest → meditate → rest	State: Non-descending alpha-theta (Stage I-like) controls descend to Stage II during relaxation, increased alpha-theta in eyes open rest after meditation; very advanced practitioner in non-descending alpha-theta with eyes open had highest theta Trait: Higher alpha-theta power
Corby et al. (1978)	Ananda Marga Yoga	30	LTM vs. STM vs. controls Rest → breath-focus → mantra	State: Theta power proportional to proficiency, experts with lowest percents of "sleep scores" during meditation or relaxation Trait: Higher theta and alpha power
Warrenburg et al. (1980)	TM, Progressive Relaxation	27	LTM vs. PR vs. controls	State: None Trait: Increased theta
Lehrer et al. (1980)	Passive meditation	32	Novices with 5 week passive meditation vs. progressive relaxation vs. controls; tones	State: Increased frontal alpha after auditory stimulation Trait: NA

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Stigsby et al. (1981)	TM	26	Meditators vs. controls Rest vs. meditation vs. sleep onset	State: Decreased mean frequency in left frontal area, intra- and inter-hemispheric values stable, alpha/theta power for TM was between wakefulness and drowsiness and remained stable Trait: Slower mean frequency in meditators (1 Hz)
Becker & Shapiro (1981)	TM, Zen, Yoga	50	Different groups vs. "attend" and "ignore" controls	State: No effect of meditation on alpha blocking Trait: NA
Dillbeck & Bronson (1981)	TM	15	Beginning meditators, longitudinal study: 2 weeks of relaxation vs. 2 weeks TM	State: Increase in frontal alpha coherence Trait: NA
Orme-Johnson & Haynes (1981)	TM	22	Meditators vs. controls at rest	State: NA Trait: Increased alpha coherence
Farrow & Hebert (1982)	TM	1	Advanced TM meditator	State: Increased alpha power and coherence during reported thought-free "pure conscious experiences" Trait: NA
Pagano & Warrenburg (1983)	TM	48	LTM vs. STM vs. Progressive Relaxation Practitioners (PR) vs. controls Rest → meditation → PR → rest	State: Increased theta, decreased alpha, no hemispheric asymmetry Trait: Increased theta in long-term practitioners

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Persinger (1984)	TM	1	Case-study	State: During TM practice peak experience accompanied by right temporal lobe delta-wave-dominant seizure Trait: NA
Badawi et al. (1984)	TM	115	Meditation with subjective reports	State: Thought-free respiratory suspension with increased delta, theta, alpha, and beta coherence; increased theta power Trait: NA
Dillbeck & Vesely, (1986)	TM	22	EEG during a cognitive learning task	State: NA Trait: Increased alpha coherence
Heide (1987)	TM	34	Meditators vs. controls Tones presented	State: No changes in alpha blocking or habituation Trait: NA
Taneli and Krahne (1987)	TM	10	Repeated rest and meditation recordings, subjective reports	State: Increased alpha amplitude Trait: NA
Saletu (1987)	TM	4	Experienced meditators Rest → meditation	State: Increased alpha and theta power Trait: NA
Ikemi, (1988)	"Self Regulation Method"	12	Before vs. during SRM vs. during drowsiness, novices	State: Increased theta power, decreased beta power Trait: NA
Zhang et al. (1988)	Qi-gong	32	LTM vs. STM vs. controls Rest → meditation	State: LTM increased alpha power frontally and decreased occipitally, decreased alpha frequency Trait: Not reported
Gaylord et al. (1989)	TM	83	TM vs. PR vs. controls Longitudinal study, novices	State: Increased alpha and theta coherence Trait: None

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Jacobs & Lubar (1989)	Autogenic Training	28	Longitudinal 7 weeks Relaxed listening to radio vs. autogenic training	State: With training increased theta power, increased percent theta power (35%), decreased alpha power (41%) Trait: None observed
Benson et al. (1990)	Tibetan Buddhist "gTum-mo" (heat-generating)	3	Comparative study of rest meditation, stabilization meditation, g Tum-mo	State: Increased beta activity, greater asymmetries (right-sided), increased finger and toe temperature of up to 8.3 °C Trait: NA
Travis et al. (1991)	TM	20	LTM vs. STM	State: NA Trait: Increased alpha power and alpha coherence at rest
Satyanarayana et al. (1992)	Santhi Kriya Yoga meditation	8	Before and after meditation on training days 1, 10, 20, 30	State: None Trait: Increased occipital and prefrontal alpha power
Echenhofer et al. (1992)	Tibetan Buddhism	6	LTM vs. STM meditation → rest	State: Increased theta-alpha (6-12 Hz) power Trait: None reported
Deepak et al. (1994)	Mantra	20	Epileptic patients in 1-year clinical trial using EEG	State: Patients, no effects, LTM increased alpha Trait: Increased alpha with decreased seizure frequency
Pan et al. (1994)	Concentrative Qi-gong vs. non-concentrative Qi-gong	73	Two groups of Qi-gong meditators vs. controls, Rest→meditation	State: Concentrative Qi-gong associated with increased frontal midline theta activity Trait: None reported

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Jacobs et al. (1996)	Relaxation Response (mantra-based)	20	Novices guided meditation tape vs. listening to talk radio	State: Decreased frontal beta power Trait: NA
Kwon et al. (1996)	Traditional Korean meditation	11	Rest → meditation → rest	State: Variable—6 subjects with signs of drowsiness, 5 subjects with highly individual patterns Trait: NA
Mason et al. (1997)	TM	31	LTM vs. STM vs. controls, sleep records	State: NA Trait: Increased 6-10 Hz spectral power in Stage III/IV sleep with increased meditation and reports of awareness during sleep
Lee et al. (1997)	Qi-Gong	13	Rest→ meditation	State: Increased alpha power Trait: NA
Travis & Wallace (1999)	TM	20	10 min rest and meditation counterbalanced order	State: Increased intra-hemispheric frontal/central- and inter-hemispheric frontal alpha (8-10 Hz) coherence Trait: NA
Dunn et al. (1999)	Breath-focused Concentrative vs. Mindfulness	10	Relaxation and 2 meditation conditions counterbalanced, each practiced for 15 min	State: Meditation vs. relaxation—increased beta and posterior alpha, decreased delta and theta power; mindfulness vs. concentrative meditation—increased anterior theta, central-posterior alpha, and beta power Trait: NA

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Kamei et al. (2000)	Yoga	8	Rest → Yoga with postures → Yogic breathing → Yogic meditation	State: Increased alpha power and decreased serum cortisol, inverse correlation between alpha power and cortisol levels Trait: NA
Khare & Nigam (2000)	Yogic Meditation, TM	40	Yogic vs. TM meditators vs. controls, rest → meditation	State: Increased alpha power and coherence Trait: Increased alpha power
Arambula et al. (2001)	Kundalini Yoga	1	Rest → meditation → rest	State: Increased alpha power (P4-O2 electrodes) Trait: NA
Litscher (2001)	Qi-gong	2	"Qi-gong masters", meditation → mentally recite poem	State: Increased alpha power Trait: NA
Travis (2001)	TM	30	Meditation with periodic bell rings eliciting subjective reports	State: Increased theta-alpha (6-12 Hz) power and anterior-posterior coherence with pure conscious experiences Trait: NA
Lehmann et al. (2001)	Tibetan Buddhist practices	1	5 different meditative practices in succession for 2 min, with each then repeated	State: Different gamma (35-44 Hz) power increases associated with each practice Trait: NA
Travis et al. (2002)	TM	51	LTM vs. STM vs. controls recorded during cognitive task	State: NA Trait: Increased theta-alpha (6-10 Hz) power and increased frontal coherence across all bands during cognitive CNV task

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Aftanas & Golocheikine (2001, 2002, 2003)	Sahaja Yoga	27	STM vs. LTM Rest → meditation	State: Increased theta and alpha power (frontal-central), increased theta coherence, decreased dimensional complexity Trait: Decreased alpha frequency, increased theta/alpha power
Davidson et al. (2003)	Mindfulness Based Stress Reduction	32	Before and after meditation training intervention, EEG at rest and to emotional films	State: NA Trait: Leftward shift of frontal asymmetry
Lutz et al. (2003)	Tibetan Buddhist	11	LTM vs. controls Rest → meditation → rest → meditation	State: Increased gamma power, different gamma coherence patterns among practices Trait: None reported
Hebert & Tan (2004)	TM	30	LTM vs. controls	State: NA Trait: Increase in anterior-posterior alpha coherence
Faber et al. (2004)	Zen	1	Repeated measures, 4 days with one control and 3 meditation scans	State: Increased theta coherence, decreased gamma coherence except increased gamma coherence temporally Trait: NA
Lutz et al. (2004)	Tibetan Buddhist non-referential love/ compassion	18	LTM vs. controls Rest → meditation → rest → meditation	State: Increased gamma power ratio, increased absolute gamma power, increased gamma synchrony Trait: Increased gamma power ratio correlated with length of meditative training
Murata et al. (2004)	Zen	22	Novice meditators	State: Increased frontal alpha coherence Trait: NA

Chapter 1 Table 1 continued. Summary of Meditation Studies Using Electroencephalographic (EEG) Methods

	Meditation Type	N	Experimental Design	Findings
Takahashi et al. (2005)	Zen	20	Novice meditators	State: Increased frontal theta and low alpha Trait: NA
Aftanas & Golocheikine (2005)	Sahaja Yoga	50	LTM vs. controls	State: NA Trait: Increased theta and low alpha power at rest, decreased left hemispheric laterality in temporo-parietal areas at rest, decreased induction of frontal gamma synchrony to aversive movie viewing

Note: LTM=long-term meditators, STM=short-term meditators, PR=Progressive Relaxation, TM=Transcendental Meditation, NA=not applicable

What is much less clear is whether and how meditation practices produce increased alpha beyond that obtained from reducing general arousal, which may become apparent only when fine-grained topographic mapping is combined with other neuroimaging methods. Studies employing counterbalanced control relaxation conditions consistently have found a lack of alpha power increases or even decreases comparing relaxation to meditation for both TM and Yogic meditation (Corby, Roth, Zarcone, & Kopell, 1978; Hebert & Lehmann, 1977; G.D. Jacobs & Lubar, 1989; Lehrer, Schoicket, Carrington, & Woolfolk, 1980; Lehrer, Woolfolk, Rooney, McCann, & Carrington, 1983; Lou et al., 1999; Pagano & Warrenburg, 1983; Tebecis, 1975; Travis & Wallace, 1999). However, some forms of meditation may affect alpha selectively as a highly accomplished Kundalini Yoga meditator was reported to produce a five-fold increase in alpha *during* meditative practice, with only moderate increases in theta found *after* the meditation period (Arambula, Peper, Kawakami, & Gibney, 2001). Further, advanced Qi-gong meditators but not beginners increased alpha power selectively over frontal cortex, with decreases in alpha power over occipital cortex and concomitant decreases in peak alpha frequency observed (J. Z. Zhang, Li, & He, 1988).

Meditation appears to affect the EEG frequency distribution within the alpha band as both a state and trait effect, with a state-related alpha band slowing observed in conjunction with increases in power (Banquet, 1973; Hirai, 1974; Kasamatsu & Hirai, 1966; Taneli & Krahne, 1987). A group of epileptics who were taught a Yogic concentrative meditation and assessed at baseline compared to practicing regularly for one year demonstrated a decrease in the 1-8 Hz and an increase in 8-12 Hz band (Deepak,

Manchanda, & Maheshwari, 1994). TM meditators produced an overall 1 Hz slower mean frequency relative to controls (Stigsby, Rodenberg, & Moth, 1981), and a 0.8 Hz trait-related alpha frequency difference between novices and long-term Sahaja Yoga meditators of the same age was observed (Aftanas & Golocheikine, 2001).

A number of reports have suggested that increased theta (4-8 Hz) rather than increases in alpha power during meditation may be a specific state effect of meditative practice (Aftanas & Golocheikine, 2001, 2002; Anand, 1961; Banquet, 1973; Corby, Roth, Zarcone, & Kopell, 1978; Elson, Hauri, & Cunis, 1977; Fenwick et al., 1977; Hebert & Lehmann, 1977; Hirai, 1974; G.D. Jacobs & Lubar, 1989; Pagano & Warrenburg, 1983; Travis, Tecce, Arenander, & Wallace, 2002; R. K. Wallace, Benson, & Wilson, 1971; Warrenburg, Pagano, Woods, & Hlastala, 1980). Some studies of Yogic meditative practice found increases in theta to be associated with proficiency in meditative technique (Aftanas & Golocheikine, 2001; Corby, Roth, Zarcone, & Kopell, 1978; Elson, Hauri, & Cunis, 1977; Kasamatsu & Hirai, 1966), and early investigations with Zen meditation indicate theta increases to be characteristic of only the more advanced practitioners (Kasamatsu & Hirai, 1966). Long-term meditators relative to non-meditator controls exhibit trait higher theta and alpha power—perhaps related to the specific meditative technique and a slower baseline EEG frequency (Andresen, 2000; J. M. Davidson, 1976; Delmonte, 1984a; Jevning, Wallace, & Beidebach, 1992; Schuman, 1980; West, 1979, 1980a; Woolfolk, 1975). However, self-selection effects cannot be ruled out, as EEG slowing is a typical finding for both state and trait meditation effects (Corby, Roth, Zarcone, & Kopell, 1978; Elson, Hauri, & Cunis, 1977; J. Z. Zhang, Li, &

He, 1988). In addition, there are some findings of alpha power decreases instead of increases for meditators (G.D. Jacobs & Lubar, 1989; Pagano & Warrenburg, 1983), with other suggestions of no systematic EEG change related to meditation state (Kwon, Hahm, & Rhi, 1996; Tebecis, 1975; Travis & Wallace, 1999). This variability may stem from technical environments that impair relaxation or focus before or during a meditative session as well as subject-experimenter interactions and expectation influences during psychophysiological recordings (Cuthbert, Kristeller, Simons, Hodes, & Lang, 1981; Delmonte, 1985).

Theta power increases for meditative practice have been widely reported (Aftanas & Golocheikine, 2001; Ghista et al., 1976; Kasamatsu & Hirai, 1966; Kasamatsu et al., 1957; Lehmann et al., 2001; Lou et al., 1999; Pagano & Warrenburg, 1983; Schacter, 1977; Tebecis, 1975; R. K. Wallace, 1970; West, 1980b). Increased frontal midline theta power during meditation also has been observed (Aftanas & Golocheikine, 2002; Hebert & Lehmann, 1977; Kubota et al., 2001; Pan, Zhang, & Xia, 1994), although a similar activation occurs in non-meditation-related studies of sustained attention (A. S. Gevins, M. E. Smith, L. McEvoy, & D. Yu, 1997; Ishii et al., 1999). Attempting to relate the frontal midline theta to the concentrative aspect of meditational practices, Qi-gong practitioners of two different forms were assayed. One form of Qi-gong is a concentration-based practice, and the other is more mindfulness-based (Pan, Zhang, & Xia, 1994). Even though the level of expertise in the two groups was equal, the concentrative Qi-Gong technique produced frontal midline theta activity in practitioners, while the other more passive form did not. Although mindfulness-based practices have

been assessed with EEG less often than concentrative practices, a comparative study found mindfulness meditation produced greater frontal theta than concentrative meditation (Dunn, Hartigan, & Mikulas, 1999). This is an odd outcome given the presumed association between frontal theta and focused concentration. Moreover, novice meditators were assessed and global theta was shown to be higher during resting relaxation than either of the two meditative conditions thereby implicating drowsiness as the source of the theta activity in this study.

Frontal midline theta activity is generated by anterior cingulate cortex, medial prefrontal cortex, and/or dorsolateral prefrontal cortex (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Ishii et al., 1999). This activity is correlated with attention-demanding tasks (A. Gevins, M. E. Smith, L. McEvoy, & D. Yu, 1997; Kubota et al., 2001), and subjects exhibiting greater theta activity tend to have lower state and trait anxiety scores (Inanaga, 1998). Hence, increased frontal theta for both state and trait effects in meditation is associated with reported decreases in anxiety level resulting from practice (D. H. Shapiro, 1980; West, 1987)—a finding that may be associated with the feelings of peace or blissfulness and low thought content that have been correlated with theta burst occurrence (Aftanas & Golocheikine, 2001; Hebert & Lehmann, 1977). Hypnotic states also appear associated to frontal midline theta and anterior cingulate cortex activation (Holroyd, 2003; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Rainville, Hofbauer, Bushnell, Duncan, & Price, 2002; Rainville et al., 1999), which has been observed during autonomic self-regulation as assessed by galvanic skin response biofeedback (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001, 2002). The

scalp topography of the theta meditation effect is an important issue (e.g., Gevins et al., 1997), since most early reports employed only a few parietal or occipital electrodes so that claims for frontal midline theta may be unwarranted. Indeed, assessment of a relaxation-focused Yogic Nidra meditation with 16 electrodes found increases in theta power for all electrodes suggesting that this type of practice may produce generalized rather than frontal-specific theta activity increases (Lou et al., 1999).

EEG coherence refers to the squared cross-correlation between EEG power from two scalp locations within a frequency band and indexes the functional co-variation of activity among different cortical areas (Gevins, Bressler et al., 1989; Gevins, Cutillo et al., 1989; Nunez et al., 1999; Nunez et al., 1997; R. W. Thatcher, Krause, & Hrybyk, 1986). Increased alpha-theta range coherence among recording sites has been observed intra- and inter-hemispherically for state effects during meditation (Aftanas & Golocheikine, 2001; Badawi, Wallace, Orme-Johnson, & Rouzere, 1984; Dillbeck & Bronson, 1981; Faber, Lehmann, Gianotti, Kaelin, & Pascual-Marqui, 2004; Farrow & Hebert, 1982; Gaylord, Orme-Johnson, & Travis, 1989; Hebert & Tan, 2004; Travis, 2001; Travis & Pearson, 1999; Travis & Wallace, 1999), with similar trait effects found in long-term meditators at rest or engaged in cognitive tasks (Dillbeck & Vesely, 1986; Hebert & Tan, 2004; Orme-Johnson & Haynes, 1981; Travis, 1991; Travis, Tecce, Arenander, & Wallace, 2002). Interpreting coherence requires consideration of methodological issues; false positives from different electrode configurations may color the interpretation of early coherence reports (Fenwick, 1987; Shaw, 1984).

EEG measures of phasic states during meditation have been described across studies, but the lack of a standardized phenomenological description compounds the problem: One mediator's "ecstasy" may not have much in common with another's "pure conscious event", "bliss," or "absolute unitary being" (d'Aquili & Newberg, 2000; Newberg et al., 2001). Some assessments of meditators in subjectively-reported deep states of meditation found alpha desynchronization with fast beta rhythms predominant (Anand, 1961; Banquet, 1973; Das & Gastaut, 1957; Elson, 1979; Elson, Hauri, & Cunis, 1977; Lo, Huang, & Chang, 2003). Other investigations have found increased activity in the temporal lobes for absorptive states of meditative ecstasy (Persinger, 1983, 1984). These activity patterns are similar to temporal lobe epilepsy and reports of profound ecstasy, and spiritual, mystical, or religious experience from seizures (Asheim Hansen & Brodtkorb, 2003; Cirignotta, Todesco, & Lugaresi, 1980; Dewhurst & Beard, 1970; Foote-Smith & Smith, 1996; Persinger, 1993). Given the infrequent number of ecstatic states assayed, temporal involvement in peak experiences may occur, but the evidence is unclear.

Studies of TM have indicated increases of alpha coherence and respiratory suspension during episodes of thoughtless awareness or "transcendent experiences" (Badawi, Wallace, Orme-Johnson, & Rouzere, 1984; Farrow & Hebert, 1982; Travis, 2001; Travis & Pearson, 1999). A report of Yogic meditation found respiratory suspension but no observable EEG changes for the experience of "near Samadhi" (Corby, Roth, Zarcone, & Kopell, 1978). These discrepancies may originate from the focus on affectively neutral "pure consciousness" events and "thoughtless awareness" as the main

phenomenological correlate in the TM studies, whereas the assayed Yogic states were characterized by blissful affect and unity of awareness (Travis & Pearson, 1999).

Although meditative practice can influence EEG measures, how meditation affects cognitive states and alters central nervous system traits is unclear. Some techniques may change alpha power as a trait effect towards the beginning of meditation training (Aftanas & Golocheikine, 2003; Deepak, Manchanda, & Maheshwari, 1994; Elson, 1979; Elson, Hauri, & Cunis, 1977; Glueck & Stroebel, 1975; Khare & Nigam, 2000; Satyanarayana, Rajeswari, Rani, Krishna, & Rao, 1992; Stigsby, Rodenberg, & Moth, 1981; Travis, 1991; Travis, Tecce, Arenander, & Wallace, 2002; Vassiliadis, 1973). As baseline alpha levels equilibrate at higher power, theta power and/or theta-alpha coherence state effects might be manifested (Aftanas & Golocheikine, 2001; Corby, Roth, Zarcone, & Kopell, 1978; Travis & Wallace, 1999). A major limitation to date is the lack of sufficient topographic information, since most studies have employed relatively few recording sites with little consistency of location (frontal, parietal, temporal, or occipital). Evaluation of different meditation techniques to characterize possible attentional and psychological set variation also is needed (R. J. Davidson & Goleman, 1977).

Lateralized EEG Measures

Following early theories of hemispheric specialization, the hypothesis developed that meditation practice was associated with right hemispheric activity (Ornstein, 1972; West, 1987). State effects sometimes have been found: right-relative-to-left hemisphere decreases in alpha activity for meditators meditating compared to resting (Ehrlichman & Wiener, 1980; Fenwick, 1987). Trait effects were observed suggesting that meditators

compared to non-meditators demonstrated greater lateralized EEG alpha for hemispheric analytical vs. spatial discrimination tasks (Bennett & Trinder, 1977). Further, an assessment of lateralization trait differences in long-term Sahaja Yoga meditators compared to controls found no hemispheric lateralization in the meditator group and right greater than left hemispheric power over temporal and parietal cortices, suggesting relatively greater left-sided activation, in the control group (Aftanas & Golocheikine, 2005). However, no general difference in hemispheric functioning has been found during meditation (Bennett & Trinder, 1977; Pagano & Warrenburg, 1983; Schuman, 1980). A randomized control trial involving an eight-week training course in mindfulness meditation produced increases in right-sided alpha power at baseline and in response to emotion-inducing stimuli—an effect that was strongest at the medial central (C3 and C4) lateral recording sites (R. J. Davidson et al., 2003). Antibody titers to a flu shot also increased in the meditation group relative to controls, and the titer increase found correlated with the degree of leftward lateralization observed in hemispheric cortical activity (R. J. Davidson et al., 2003; Smith, 2004; Travis & Arenander, 2004).

These outcomes may reflect the relative activation of left and right prefrontal cortices, which indexes emotional tone and motivation such that left-greater-than-right alpha power is associated with greater right frontal hemisphere activation (Coan & Allen, 2004; R. J. Davidson, 1988, 2003). In this framework, appetitive and approach-oriented emotional styles are characterized by a left-over-right prefrontal cortical activity, whereas avoidance and withdrawal-oriented styles are characterized by right-over-left prefrontal cortical dominance (R. J. Davidson, 1992; R. J. Davidson, Ekman, Saron, Senulis, &

Friesen, 1990; R. J. Davidson & Irwin, 1999). Normal variation of positive versus negative affective states suggests left dominance for happier states and traits, with left-over-right frontal hemispheric dominance primarily related to the approach-withdrawal spectrum of emotion and motivation (R. J. Davidson, Jackson, & Kalin, 2000; Harmon-Jones, 2004; Harmon-Jones & Allen, 1998; R. E. Wheeler, Davidson, & Tomarken, 1993). In sum, meditation practice may alter the fundamental electrical balance between the cerebral hemispheres to modulate individual differences in affective experience, with additional studies warranted to assess this possibility.

Sleep and Meditation

After initial papers advocating a "fourth" state of consciousness originating from TM (R. K. Wallace, 1970; R. K. Wallace, Benson, & Wilson, 1971), several EEG meditation studies reported sleep-like stages during meditation with increased alpha and then theta power (Pagano, Rose, Stivers, & Warrenburg, 1976; Younger, Adriance, & Berger, 1975). Subsequent studies also seemed to suggest that meditation was a physiological twilight condition between waking and sleep, although this viewpoint did little to explain meditation state other than to indicate that it is not waking or sleeping as normally experienced (Fenwick et al., 1977; P. Williams & West, 1975). However, the ability to stay suspended between normal sleep and waking influenced meditation state assessment, with EEG differences found between meditation, baseline, and sleep (Corby, Roth, Zarcone, & Kopell, 1978; Elson, Hauri, & Cunis, 1977; Stigsby, Rodenberg, & Moth, 1981; P. Williams & West, 1975). These results contributed to the perspective that meditation training affects conscious awareness at a level similar to sleep Stage I, with

marked increased alpha-theta power and a suspension of hypnagogic effects in a manner not reported by non-meditators (Elson, Hauri, & Cunis, 1977; Fenwick, 1987; Fenwick et al., 1977; Schuman, 1980; Stigsby, Rodenberg, & Moth, 1981; Tebecis, 1975; Young & Taylor, 1998). Meditators may stay suspended in a physiological state similar to the brief period of Stage I where theta predominates before transitioning to Stage II in normals; such an explanation may account for increased theta levels observed in proficient meditators (Elson, Hauri, & Cunis, 1977).

Early reports attempted to distinguish between meditative state and Stage I sleep by presenting auditory stimuli and found that during meditation theta desynchronization occurred, whereas during Stage I sleep alpha activity was induced (Banquet, 1973; Kasamatsu & Hirai, 1966). Differential EEG band patterns are observed in meditation compared to Stage I sleep: Meditation-related increases in theta are accompanied by stable or increased alpha power (Lou et al., 1999), whereas the increased theta power in sleep Stage I is accompanied by about a 50% decrease in alpha power (Rechtschaffen & Kales, 1968). Relative to relaxed but alert wakefulness, alpha coherence decreases are observed in drowsiness (Cantero, Atienza, Salas, & Gomez, 1999). In contrast, increases in theta and alpha coherence above baseline resting wakefulness are commonly found during meditation, further dissociating meditation from drowsiness and early sleep stages (Aftanas & Golocheikine, 2003; Faber, Lehmann, Gianotti, Kaelin, & Pascual-Marqui, 2004; Travis, 1991; Travis, Tecce, Arenander, & Wallace, 2002; Travis & Wallace, 1999). Increases in overall cerebral blood flow during meditation have been observed, whereas decreases are characteristic of sleep (Jevning, Anand, Biedebach, & Fernando,

1996). This outcome may be related to findings of increased melatonin levels in meditators at baseline, and increased levels in meditators during sleep on nights after meditating (Harinath et al., 2004; Solberg et al., 2004; Tooley, Armstrong, Norman, & Sali, 2000). Taken together, the results support subjective reports that meditation and sleep are *not* equivalent states (Aftanas & Golocheikine, 2001; Banquet & Sailhan, 1974; Corby, Roth, Zarcone, & Kopell, 1978; Delmonte, 1984b; Hebert & Lehmann, 1977; Ikemi, 1988; Levine, 1976; Naveen & Telles, 2003; Paty, Brenot, Tignol, & Bourgeois, 1978; Stigsby, Rodenberg, & Moth, 1981).

The effects of meditation on sleep also have been assessed. An early study comparing sleep in TM meditators to controls reported higher levels of alpha activity for the meditators during sleep Stages III and IV (Banquet & Sailhan, 1974). Accomplished TM meditators who reported maintaining witnessing awareness throughout their sleep cycles demonstrated greater amounts of fast theta and slow alpha (6-10 Hz) power during sleep Stages III-IV (when such activity is at a minimum) relative to controls. Long-term meditators not reporting awareness throughout the sleep cycle also exhibited increased theta and alpha activity during deep sleep but of smaller amplitude (L. I. Mason et al., 1997). These findings have been hypothesized to reflect the development of a "transcendental consciousness" that persists during waking, dreaming, and deep sleep. Meditation experience may therefore produce neurophysiologic changes during sleep that correspond to a progression along a continuum from being totally unconscious to totally conscious during deep sleep (Varela, 1997).

Alpha Blocking and Alpha Habituation

An initial conceptualization of meditation effects proposed that "de-automization" was induced, such that each stimulus occurrence was perceived as "fresh" under mindfulness, open-awareness meditative states relative to rest conditions (Deikman, 1966; Kasamatsu & Hirai, 1966). A possible measure of this process is EEG alpha blocking, which is defined as a decrease in ongoing alpha (8-12 Hz) power when comparing pre-stimulus to post-stimulus activity. Prototypical alpha blocking occurs when alpha power is reduced after closed eyes are opened and is most pronounced in the occipital cortex reflecting the association between alpha activity and decreases in cortical processing (Basar, Schurmann, Basar-Eroglu, & Karakas, 1997; E. Niedermeyer, 1997). Alpha blocking also is observed when a series of discrete stimuli are presented, such that small alpha power decreases are obtained between pre- and post-stimulus alpha activity. This effect habituates over the course of a stimulus train after 10-20 stimuli, and an absence of alpha decrement from stimulus presentations is typical (Barlow, 1985; Morrell, 1966). In addition, increased alpha activity is induced when normal subjects are aroused from drowsiness or sleep by stimuli (E. Niedermeyer, 1997).

Field recordings of meditating Indian Yogis found no alpha blocking in response to both auditory and physical stimuli such as the hands placed into ice water (Anand, 1961; Das & Gastaut, 1957; Wenger & Bagchi, 1961). However, subsequent studies of Japanese Zen monks reported alpha blocking to auditory stimuli that did not habituate (Hirai, 1974; Kasamatsu & Hirai, 1966). Similar early studies of TM practitioners while meditating yielded conflicting results, with one finding an absence of alpha blocking and another indicating that most subjects demonstrated no alpha blocking habituation to

auditory stimuli (Banquet, 1973; R. K. Wallace, 1970). Both Zen and TM meditators, however, produced theta activity during meditation that was associated with states of consciousness different than those observed for drowsiness, as auditory stimuli produced a general EEG desynchronization compared to the alpha induction found in drowsy non-meditator controls (Blake & Gerard, 1937; Morrell, 1966). These early findings suggest that specific meditation practices might produce EEG measures that reflect baseline levels, stimulus reactivity, and brain state differences.

EEG studies of meditation in response to stimuli have attempted to characterize state and trait effects for alpha reactivity. Long-term TM meditators were instructed to "just rest" with eyes closed as photic stimulator light flashes were presented (Williams & West, 1975). The major findings for meditators compared to controls were: (1) alpha activity during the pre-stimulus interval was greater, (2) alpha induction occurred earlier with more regularity, and (3) alpha blocking continued throughout the stimulus train—i.e., less habituation was observed. These results suggested that the TM subjects in a resting state demonstrated substantially less EEG shifting along the wake-drowsy continuum. A subsequent study assessed TM, Zen, and Yoga mantra meditation techniques in advanced practitioners, with separate non-meditator "attend" and "ignore" control groups included (Becker & Shapiro, 1981). The attend group was told to "pay strong attention" to each click, notice all of its sound qualities and subtleties, and count the number of clicks; the ignore group was told, "try not to let the clicks disturb your relaxed state." Pre- and post-stimulus amplitude measures indicated comparable alpha blocking and habituation among groups. Another study of TM meditators likewise found

no effects of meditation on alpha blocking (Heide, 1986). Thus, comparison of well-defined meditating and appropriate non-meditating controls failed to produce the previously reported findings on alpha blocking and habituation to auditory stimuli.

Variation in meditation experience, recording environments, and methodological details may have contributed to the differences between the initial field and later laboratory findings. The early studies demonstrating that Yogic (towards the extreme of concentrative-based) practice was characterized by the absence of alpha blocking, and Zen (towards the extreme of mindfulness-based) practice was characterized by a lack of alpha blocking habituation. These outcomes are consistent with the reported subjective states of being deeply immersed and removed from sensory experience during Yogic practices, even while being more present to the ongoing moment-to-moment sensory experiences during Zen. Hence, literature reviews that highlight different meditative techniques have accepted the differential effects for the two techniques as fact (Andresen, 2000; Jevning, Wallace, & Beidebach, 1992; West, 1980a; Woolfolk, 1975). The lack of replication for these effects may reflect an absence of adequate control conditions or the challenge in finding sufficiently trained meditators (Becker & Shapiro, 1981).

Additional early meditation studies have shown relatively increased alpha power after aversive stimuli. Comparison of meditation intervention and a progressive relaxation training intervention in controls found greater frontal alpha power in response to loud stimuli for the meditation group (Lehrer, Schoicket, Carrington, & Woolfolk, 1980). In experiments with affectively arousing name-calling, highly experienced Zen practitioners showed no alpha blocking (Kinoshita, 1975). Subsequent assessment of

highly experienced Tibetan Buddhist monks indicate that dramatically reduced alpha blocking could occur, as an accomplished monk engaged in an "open awareness" meditative technique yielded a complete lack of startle response—a finding consistent with a possible underlying lack of alpha blocking (Goleman, 2003). In sum, the effects of different meditative practices and induced states on EEG alpha responsiveness to stimuli are still unclear with respect to both state and trait effects.

Advanced EEG Meditation Studies

Specificity of neuroelectric measures in meditation has been increased by assessment of EEG coherency and high frequency gamma band (30-80 Hz) in attempts to characterize mechanisms of conscious awareness and perceptual "binding" (Croft, Williams, Haenschel, & Gruzelier, 2002; Engel & Singer, 2001; Llinas & Ribary, 1993; Meador, Ray, Echauz, Loring, & Vachtsevanos, 2002; Rodriguez et al., 1999; Sauve, 1999; Sewards & Sewards, 2001; Uchida et al., 2000). The low resolution electromagnetic tomography algorithm (LORETA) of EEG signals selects the smoothest of all possible three-dimensional current distributions to localize scalp signals in a manner compatible to fMRI localization obtained in conjunction with simultaneous EEG and intra-cranial measurements (Lantz et al., 1997; Pascual-Marqui, Michel, & Lehmann, 1994; Vitacco, Brandeis, Pascual-Marqui, & Martin, 2002). A single highly experienced meditation teacher was evaluated using LORETA across four meditative states—visualization, mantra, self-dissolution, and self-reconstruction—in a case study with repeated elicitation of the meditative states but no resting condition (Lehmann et al.,

2001). Gamma activity was the only band demonstrating differential spatial distributions for the various meditations, with gamma power increased during the visualization and verbalization meditations in the right posterior occipital and left central/temporal regions, respectively. Increased gamma activity also was observed during the self-dissolution meditation in the right superior frontal gyrus—a brain area linked to an altered sense of self from cannabinoid-induced depersonalization and cognitive self-detachment from lesions (Mathew et al., 1999; B. L. Miller et al., 2001). These findings are consistent with right frontal involvement in the experience of agency, self-awareness, and self-referenced memory (Keenan, Nelson, O'Connor, & Pascual-Leone, 2001; Keenan, Wheeler, Gallup, & Pascual-Leone, 2000; M. A. Wheeler, Stuss, & Tulving, 1997).

Highly experienced Tibetan Buddhist meditators and novices who practiced the method for just one week were compared while engaged in three separate techniques: one-pointed concentration on an object, attention without object, and a state of non-referential love and compassion (Lutz, Greischar, Ricard, Converse, & Davidson, 2003). Large increases in 40 Hz gamma power were recorded in the meditators for the meditative compared to the rest state. Different synchrony patterns between the two groups and among the meditative states were observed that imply changes in both state and trait effects in the gamma band. Another study of advanced Tibetan Buddhist meditators using ambiguous bi-stable visual stimuli found different effects for concentrative compared to compassion meditation, thereby supporting the idea that these forms of practice lead to distinct mind-brain states (Carter et al., 2005). For the non-referential love state, some meditators demonstrated greater average gamma than alpha

power over frontal areas during meditation, with an absence of similar spectral changes found in the non-meditator controls. Further, the ratio of gamma to theta power was larger in the meditators at baseline, with increases observed during the meditative practice. A significant increase in gamma synchrony also was found in the meditator but not the control group during meditation. These findings indicate that at least for meditative practices involving affective regulation, gamma activity may play a prominent role.

Sahaja Yoga meditators with daily practice for five years were evaluated in comparison to a group with less than six months of experience (Aftanas & Golocheikine, 2001, 2002, 2003). The long-term meditators relative to novices exhibited slower mean frequency and greater theta/alpha power at rest, widespread increases in theta and early alpha power, and enhanced theta coherence at frontal/central locations. Theta coherency was most pronounced in the left frontal pole, and the theta power increases correlated positively with self-reported blissful affect and negatively with thought appearance rates. As EEG frequencies for long-term meditators were slowed, alpha frequency was defined individually with early alpha at 5.6-7.5 Hz, which most previous studies would have attributed to theta activity. To date, this is the only meditation study to define individual alpha frequencies prior to analysis, and the results may help account for the variegated previous findings. Decreased chaotic dimensional complexity over midline frontal and central cortical regions also was observed and may reflect decreased information processing mediated by frontal mid-line theta exerting an inhibitory influence on the normally automatic processing of association cortices. A related report assessing trait

effects found that long-term Sahaja Yoga meditators differed from controls in their lack of frontal gamma power increases to emotionally aversive movie clips (Aftanas & Golocheikine, 2005). These findings are intriguing as it has long been claimed that one of the primary benefits from meditative training is greater emotional stability for challenging life events (Kabat-Zinn, 1990).

Conclusions from EEG Meditation Studies

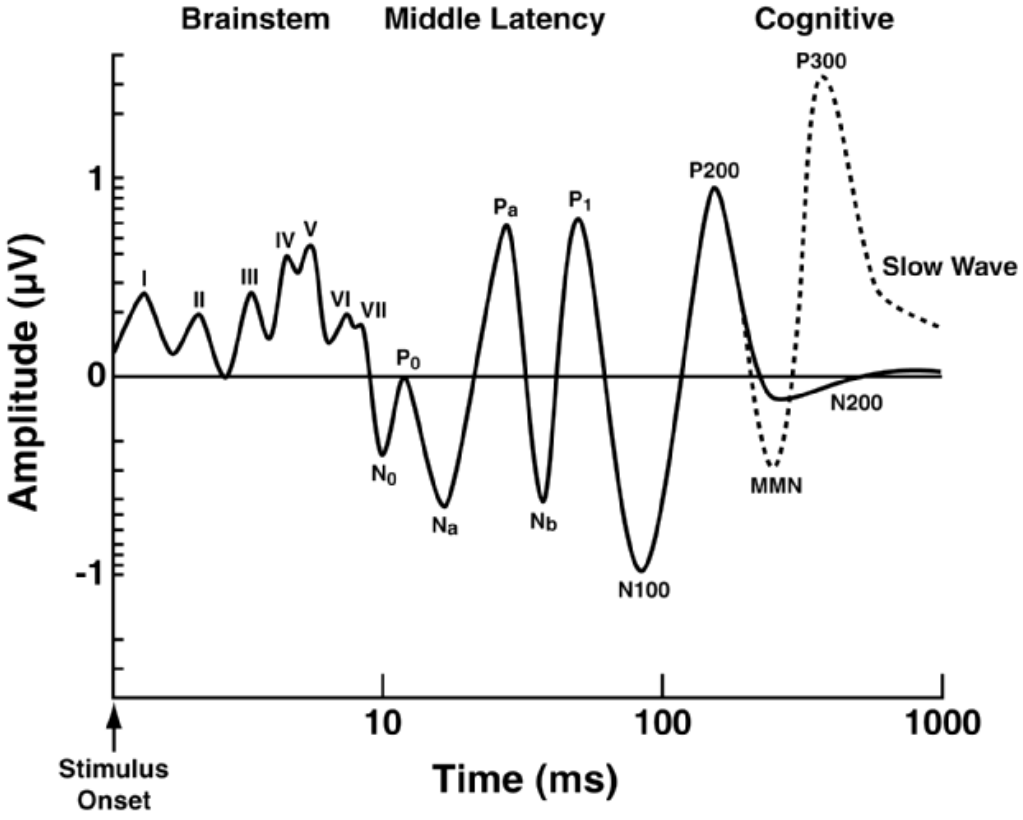
It is difficult to draw specific inferences from these studies other than theta and alpha band activity seem affected by meditation (state), which may alter the long-term neuroelectric profile (trait). The effects suggest that meditation practice is related to increased power in theta and alpha bands and decreased frequency at least in the alpha band, with overall slowing and alteration of coherence and gamma effects. Several factors could contribute to the observed variability: (1) The word "meditation" includes many different techniques, and the specific practices may lead to different state and trait changes. (2) Within a specific meditation tradition subjects can vary in their degree of meditative practice, and their self-selection for participating in EEG studies could affect state and especially trait measurement outcomes—i.e., how constitutional variables such as affective valence, introversion vs. extroversion, and anxiety level affect these measures is unknown. (3) Neurophysiologic markers of meditative states could alter baseline EEG patterns, such that clear within-group meditation effects are obscured—e.g., overall large spectral power would mask pre- vs. post-meditation state changes. (4) How EEG measures might be affected by meditator age has not been determined, despite the

neuroelectric changes that occur from early to middle age adulthood in humans (Polich, 1997). (5) Methodological difficulties limit the generalizability of early recordings and analysis, especially when stimuli were used to elicit different alpha activity levels.

ERPs and Meditation

Figure 1 schematically illustrates brain potentials that can be elicited after a stimulus is presented. EPs are evoked automatically with repetitive sensory stimulation, whereas ERPs are elicited with cognitive task processing (Picton & Hillyard, 1974; Picton, Hillyard, Krausz, & Galambos, 1974). Auditory stimuli produce the auditory brainstem response and middle latency response. The longer latency auditory evoked potentials are thought to reflect the activation of primary auditory cortex (Polich & Starr, 1983; Wood & Wolpaw, 1982). Visual and somatosensory sensory EPs also can be evoked, with standard clinical procedures now well defined (Chiappa, 1996). The P300 component is usually elicited by assigning subjects a stimulus discrimination task and can be obtained across modalities (Bashore & van der Molen, 1991; Donchin, 1981; R. Johnson, Jr., 1988; Picton, 1992; Picton & Hillyard, 1974; Polich, 2003, 2004; Pritchard, 1981).

1.



Chapter 1 Figure 1 legend. Schematic illustration of evoked and event-related brain potentials from auditory stimuli. Logarithmic scales for amplitude and latency are used for illustrative purposes only. From "Human Auditory Evoked Potentials. I: Evaluation of Components," by T.W. Picton, S.A. Hillyard, H.I. Drausz, and R. Galambos, 1974, *Electroencephalography and Clinical Neurophysiology, 36,* p. 181. Copyright 1974 by Elsevier Scientific Publishing Company. Adapted with permission.

Chapter 1 Table 2. Summary of Meditation Studies Using Evoked Potential (EP) or Event-Related Potential (ERP) Methods

Reference	Meditation Type	N	Experimental Design	EP/ERPs	Findings
Paty et al. (1978)	TM	25	Meditators vs. controls, before vs. after meditation/relaxation	CNV	State: Increased CNV amplitude after meditation, decreased amplitude after sleep-like relaxation control period Trait: NA
Barwood et al. (1978)	TM	8	Before, during, and after meditation; sleeping	AEP	State: Nonsignificant decrease in N1 latency during meditation Trait: NA
Corby et al. (1978)	Tantric Yoga "Ananda Marga"	30	LTM vs. STM vs. controls, before vs. breath-focused vs. mantra meditation	EEG, passive auditory oddball	State: No findings; all groups showed equivalent decreases in component amplitudes across sessions Trait: NA
Banquet & Lesévre (1980)	Yoga	20	Meditators vs. controls, before vs. after meditation or rest	Visual oddball	State: After meditation, increased P300 amplitude; after rest, decreased P300 amplitude Trait: shorter RT, fewer mistakes, increased N120 and P200 amplitudes
McEvoy et al. (1980)	"TM-Siddhi"	5	Meditators vs. controls, before vs. after meditation	ABR	State: Wave V latency increased at 45-50 dB and decreased at 60-70 dB; intensity/latency relationship increased in slope from 45-70 dB, Central transmission time (Wave V-Wave I) increased at 50 dB Trait: NA

Chapter 1 Table 2 continued. Summary of Meditation Studies Using Evoked Potential or Event-Related Potential Methods

Reference	Meditation Type	N	Experimental Design	EP/ERPs	Findings
Becker & Shapiro (1981)	TM, Zen, Yoga	50	Different meditation groups; "attend," and "ignore" control groups	AEP and EEG	State: AEP, no effect of meditation on average N1, P2, P3, early larger N1 amplitude that habituated to the mean in Yoga and TM groups Trait: NA
Ikemi, (1988)	"Self Regulation Method" (SRM)	12	Before vs. during SRM vs. during drowsiness, beginning meditators	CNV	State: During SRM, decreased CNV amplitude, error rate; during drowsiness, decreased CNV amplitude, increased RT, error rate Trait: NA
Goddard (1989)	TM	26	Elderly meditators vs. elderly controls	Auditory and visual oddball	State: NA Trait: Visual P300 latencies shorter in meditators, no auditory P300 effects
Liu et al. (1990)	Qi-gong	21	Before, during, and after meditation	ABR, MLR, AEP	State: ABR Waves I through V amplitudes increased, MLR Na-Pa amplitude decrease; AEP P2 amplitude decrease Trait: NA
Cranson et al. (1990)	TM	39	LTM vs. STM vs. controls	Auditory oddball	State: NA Trait: P300 latency inversely correlated with length of meditation practice: none>short>long
Goddard (1992)	TM	32	Elderly meditators vs. elderly controls vs. young meditators vs. young controls	Visual oddball	State: NA Trait: P300 latencies longer in elderly than young; elderly meditators vs. elderly controls had shorter P300 latencies and longer RTs; dissociation of P300 latency and RT

Chapter 1 Table 2 continued. Summary of Meditation Studies Using Evoked Potential or Event-Related Potential Methods

Reference	Meditation Type	N	Experimental Design	EP/ERPs	Findings
Gordeev et al. (1992)	Yogic	29	Meditators vs. controls	Visual EPs, Somatosensory EP (SEP)	State: Amplitude of intermediate and late components of visual and somatosensory EPs diminished 2-4 fold; SEP early components decreased in amplitude in hemisphere ipsilateral to stimulation only Trait: None reported
Telles & Desiraju, (1993)	"Om" mantra meditation	14	Meditators vs. controls, before vs. during meditation technique	MLR	State: NA Trait: Nb latency decrease in meditator group but no effect seen in controls, small effect size
Zhang et al. (1993)	2 types of Qi-gong	48	2 groups of LTM vs. STM vs. controls	Flash VEP	State: VEP amplitude increase in one form of Qi Gong and decreased in the other Trait: NA
Telles et al. (1994)	"Om" Mantra meditation	18	Meditators vs. controls, baseline vs. "om" meditation vs. "one" meditation	MLR	State: Na amplitude increased in meditators and decreased in non-meditators during "om"; Na amplitude decreased in meditators during "one" Trait: NA
Travis & Miskov (1994)	TM	11	Before vs. after meditation vs. after rest	Auditory oddball	State: Decreased latency P300 after TM but not rest; trend towards higher amplitude P300 after TM Trait: NA
Murthy et al. (1997, 1998)	Kriya Yoga, 3 month training	45	Patients: depressed vs. dysthymic vs. controls	Auditory oddball	Sate: NA Trait: Improvement in depressive symptoms and increase of P300 amplitude in novice meditators; effect perhaps from arousal due to alleviation of depression

Chapter 1 Table 2 continued. Summary of Meditation Studies Using Evoked Potential or Event-Related Potential Methods

Reference	Meditation Type	N	Experimental Design	EP/ERPs	Findings
Panjwani et al. (2000)	Sahaja Yoga	34	Epilepsy patients: Yoga group vs. "sham Yoga" group vs. controls	ABR, MLR, VCS	State: NA Trait: ABR=no effects; MLR=increased Na-Pa amplitude at 6 months in meditation group, VCS increased
Travis et al. (2000)	TM	41	3 groups varying in TM experience, frequency of transcendent experiences	CNV—simple, CNV—distraction task	State: NA Trait: CNV amplitude proportional to TM practice and frequency of transcendental experiences; distraction effects (decreases in CNV amplitude) inversely proportional to frequency of transcendent experiences
Travis et al. (2002)	TM	51	LTM vs. STM vs. controls	CNV—simple CNV—choice task	State: NA Trait: Simple CNV amplitude proportional/choice CNV amplitude inversely proportional to frequency of transcendental experiences and TM practice

Note: ABR=auditory brain stem response, AEP=auditory evoked potential (long latency), CNV=contingent negative variation, MLR=middle latency response, LTM=long-term meditators, STM=short-term meditators, PR=Progressive Relaxation, SEP=somatosensory evoked potential, SRM=Self Regulation Method, TM=Transcendental Meditation, VCS=visual contrast sensitivity, VEP=visual evoked potential (flash stimulus), NA=not applicable

Table 2 summarizes the major EP and ERP meditation studies. The meditation effects are reviewed below for the sensory and cognitive domains. A summary of studies using contingent negative variation (CNV) is then presented. The rationale for these investigations derived from the early EEG studies outlined above. Meditators sometimes produced altered amplitudes and shorter potential latencies when stimuli were presented and EEG recorded, thereby suggesting increased attentional control and central nervous system quiescence (Banquet & Lesévre, 1980). This interpretation is consonant with results from the 1970's in normal subjects that selective attention and later cognitive processing were reflected by different ERP components. Advanced concentrative meditation practitioners seemed to demonstrate decreased amplitude and latency for several sensory EPs (e.g., (Anand, 1961; Gordeev, Baziian, & Liubimov, 1992), whereas mindfulness-based practices sometimes induced a decrease in habituation (e.g., (Banquet, 1973; Kasamatsu & Hirai, 1966). Thus, these methods were employed to characterize sensory and cognitive information processing in meditation as has been done with behavioral measures indicating enhanced perceptual acuity (D. Brown, Forte, & Dysart, 1984a, 1984b; Panjwani et al., 2000).

Auditory Stimulus Potentials

Brainstem potentials. Auditory brainstem responses occur within 10 ms after stimulus presentation and reflect initial sensory processing. Assuming that meditation practice affects attentional mechanisms, these potentials should not be influenced by either meditation state or trait. auditory brainstem responses were obtained from practitioners of "TM-Siddhi" meditation supposed to augment normal hearing by using

attention to special mantras constructed to sensitize the auditory system and lead to awareness of subtle inner sounds not normally perceived (Mahesh Yogi, 1963; McEvoy, Frumkin, & Harkins, 1980). Binaural click stimuli were presented at 5 to 70 dB in different conditions to elicit auditory brainstem responses before and after meditation. As stimulus intensity increased, Wave V latencies were differentially affected by meditation. At threshold intensities of 45-50 dB Wave V latency increased whereas at intensities of 65-70 dB latencies decreased relative to baseline, thereby leading to an increased intensity/latency relationship between 45 and 70 dB after meditation. Wave V-I latency differences (central transmission time) also increased after meditation for 50 dB but not other intensities. Background noise is 40-50 dB, so that meditation may attenuate the sensitivity to these intensities thereby enhancing sounds at threshold (5-40 dB) and speech (60-70 dB) intensity levels.

Middle latency potentials. Middle latency response potentials are generated post-brainstem and reflect initial cortical auditory processing occurring between 10 and 80 ms. Recordings of meditators using the traditional mantra "om" were made before and during meditation; a non-meditator control group was comparably assessed while resting quietly at two different times (Telles & Desiraju, 1993). The meditator subjects produced a small but reliable decrease in Nb component latency after meditating relative to the preceding rest period, whereas for the control group no changes were found. In a subsequent study, middle latency response measures from novice and expert mantra meditators before and after meditating on the syllable "om" were compared to meditating on the word "one" (Telles, Nagarathna, Nagendra, & Desiraju, 1994). Novice meditators demonstrated a

decrease in Na amplitude in the “om” condition; expert meditators demonstrated an increase in Na amplitude for the “om” but an amplitude decrease for the “one” condition. Brahmakumaris Raja Yoga meditators were assessed before and during meditation, with a decrease in Na peak latency found (Telles & Naveen, 2004). The Na potential is thought to be generated at the midbrain-thalamic level, so that concentrative mantra meditation may affect early thalamic sensory processes.

Sahaja Yoga emphasizes adopting the witness posture towards thoughts instead of flowing with them during meditation and is therefore very close to the mindfulness end of the meditational spectrum. The practice of this method was assessed in three groups of young adult epileptic patients (Panjwani et al., 2000). One group practiced Sahaja meditation, another group sat quietly in “sham” meditation, and a control patient group had no meditation instruction. Auditory brainstem response and middle latency response measures were obtained prior to the meditation intervention, three months, and six months later. No auditory brainstem response effects were obtained, but the Sahaja Yoga group demonstrated an increase in middle latency response Na-Pa amplitude at six months. Although Sahaja Yoga meditation in normal control subjects was not assessed, this outcome also suggests the influence of meditation on initial cortical auditory processing.

Qi-gong is a distinct meditation technique that emphasizes becoming aware of the “Qi” or “subtle energy” in the body and consciously manipulating it by means of intentionality, physical postures, and movements (McCaffrey & Fowler, 2003). Several different types of brain potentials were observed before, during, and after a Qi-gong

meditation session in a within-subject design (Liu et al., 1990). Auditory brainstem response waves I through V increased in amplitude 55-76%, whereas middle latency response Na and Pa amplitudes decreased 50-73% during Qi-gong meditation relative to the before and after conditions. The authors hypothesize that the brainstem may be synergistically released from descending inhibition to produce the auditory brainstem response amplitude increase when the initial cortical activity indexed by middle latency response potentials decreases during meditation.

Long latency potentials. TM meditators presented with auditory tones (1/s) demonstrated decreased P1, N1, P2, and N2 component latencies for meditators at baseline and meditation/rest states compared to non-meditator control group values (Wandhofer, Kobal, & Plattig, 1976). Another study used 50 tones (1 s duration) presented in three blocks to TM meditators before, during, and after meditation in a within-subject design; additional recordings were made during sleep. Although N1 latency was longer in the before-control relative to the meditation condition, this effect was unreliable and no other condition differences were found for any of the auditory long latency potential components (Barwood, Empson, Lister, & Tilley, 1978).

Ananda Marga meditative practice focuses initially on withdrawing from external orientation by means of breath-focused concentration, which is then followed by mantra meditation and therefore lies towards the concentrative meditation end of the spectrum. Experienced meditators were compared to novice meditators and non-meditating controls (Corby, Roth, Zarcone, & Kopell, 1978). Each subject was exposed to a series of tones presented at a rate of 1/s for 20 min, with the inclusion of an oddball tone (1/15) in each

of three conditions: baseline rest, breath-focused awareness, and mantra meditation. Non-meditating controls mentally repeated a randomly chosen two-syllable word, with all groups instructed to ignore the tones. For the experienced meditators compared to other subjects, EEG theta and alpha power was higher in both the baseline and meditative conditions. For all three groups, infrequent tones elicited smaller N1 amplitudes and a positive potential occurring at approximately 250 ms (dubbed “P2-3” but likely a P2). Auditory long latency potential components during the baseline rest were similar to the meditation conditions for both tones, but during meditation P2-3 amplitude decreased for infrequent tones and increased for frequent tones. Condition order was not counterbalanced, so it is likely that habituation effects produced the amplitude decrements. The reason for the P2-3 amplitude increase to the frequent tones is unclear.

Auditory long latency potentials were obtained from Zen, TM, Yoga, and two groups of non-meditator control subjects who were instructed either to "attend” or “ignore” loud click stimuli (115 dB) presented at 15 s intervals (Becker & Shapiro, 1981). As noted above, no differential alpha blocking was found among the five groups when meditators meditated and control subjects applied their instructed attentional focus at rest. No auditory long latency potential components demonstrated any differences other than the production of larger passive P300 amplitudes in the attend group as observed previously (Becker & Shapiro, 1980). N100 amplitude for the TM and Yoga meditation subjects was increased over the first 30 stimulus presentations then reduced to the same size as the other groups after 40-50 stimulus presentations. The authors suggested that given the mantras used by both groups, the attentional state of the TM and

Yoga meditators may have been attuned to "inner sounds" that could have contributed to a greater sensitivity for the auditory stimulus input, even above that of the control "attend" group specifically instructed to pay full attention to the auditory input.

Qi-gong meditators were assessed by presenting 10 ms tones and recording before, during, and after a 30 min Qi-gong meditation session (Liu, Cui, Li, & Huang, 1990). P200 amplitude decreased 44% from the baseline to the meditation state and returned to baseline after meditation. This outcome suggests that later auditory long latency potential measures may be sensitive to meditation state.

Auditory P300. TM practice was studied using a passive auditory paradigm listening study with variable inter-stimulus intervals (1-4 s) between identical tone stimuli (Cranson, Goddard, & Orme-Johnson, 1990). The subjects were non-meditator controls, novice, and highly experienced TM meditators with mean ages of 20, 28, and 41 years, respectively; IQ scores did not differ among the groups. Passive P300 potential latency was shorter for the two meditation groups, with the long-term meditators showing the shortest P300 latency regardless of their age (cf. (Polich, 1996). These results imply that auditory long latency potentials might reflect meditation trait differences.

An auditory oddball task was used with eyes-closed to assess experienced TM meditators at pre-test baseline, after 10 min of rest, or after 10 min of TM practice with conditions counterbalanced across subjects (Travis & Miskov, 1994). P300 latency decreased at Pz after TM practice relative to no change after the rest condition. Sudarshan Kriya Yoga is a meditation system that emphasizes breathing techniques. This technique was used as an intervention to assess dysthymic, dysthymic with melancholy, and

unaffected control subject groups (Murthy, Gangadhar, Janakiramaiah, & Subbakrishna, 1997, 1998). At three months, P300 amplitude increased to control levels in the patient groups after initial values at zero (7.5 μV) and one month (10.4 μV) that were well below normal values (14.4 μV) at both time points. Taken together, these reports suggest the possibility of some meditation effects on the P300 component.

Visual Stimulus Potentials

*Visual evoked potentials***.** Sensory potentials evoked by a light flashes were employed to compare four populations: (1) long-term Qi-gong meditation practitioners, (2) long-term Neiyang-gong practitioners—a variant of the older Qi-gong method, (3) beginning Neiyang-gong meditators, and (4) non-meditating control subjects (W. Zhang, Zheng, Zhang, Yu, & Shen, 1993). Visual flash potentials were obtained under eyes open conditions before, during, and after the meditative practice or analogously for a rest period in controls. The flash potentials were classified as early (N80-P115-N150) and late (N150-P200-N280) components, with peak-to-peak amplitudes measured. The long-term traditional Qi-gong practitioners demonstrated marginally significant decreased amplitude for the early and later flash potentials during meditation. However, the Neiyang-gong practitioners demonstrated increased amplitudes for both the early and late flash potentials. No effects of meditation were reported for the beginning Neiyang-gong or control groups. The authors concluded that the two types of Qi-gong meditative practice produce opposite effects on the relative excitability of the visual cortex, such that the more traditional Qi-gong leads to cortical inhibition and reduced flash potential amplitudes (Cui, 1987).

Visual P300. ERPs were obtained before and after a 30 min meditation or rest period from experienced Yogic meditators compared to matched non-meditator controls—i.e., the intervention was meditation for the meditator group and rest for the control group (Banquet & Lesévre, 1980). A go/no-go task using visually presented 450 letters with 10% randomly omitted. Subjects were instructed to respond to each stimulus and to refrain from responding whenever they detected an omitted stimulus, so that state and trait effects could be evaluated under response and non-response conditions. For the meditators, P300 amplitude increased post-meditation; for the controls P300 amplitude decreased post-rest. The meditators relative to controls also demonstrated shorter response time (RT) and greater accuracy before and after the meditation period, with RT shorter than P300 latency for the meditators but longer than P300 latency for the controls in both the pre- and post- conditions. For the meditators compared to controls, P200 amplitudes from both the go and no-go stimuli were larger in the pre- and post-meditation/rest conditions, and N120 amplitude increased in the post- no-go task but decreased in latency in pre- and post- conditions for the go task. The authors suggest that long-term meditative practice could increase selective attention capacity that improves vigilance level to affect ERP measures. Such state effects also are consistent with meditation affecting de-automization of stimulus processing.

Meditative practice and aging in TM meditators were evaluated relative to non-meditating controls (66 years) with visual ERPs elicited by female and male names in a button-press task (Goddard, 1989, 1992). P300 latency was shorter in meditators than controls (543 vs. 703 ms). The same subjects also performed an auditory oddball, but

neither P300 latency nor RT differed between the groups. The results were interpreted as indicating trait effects of long-term TM practice are observed only if mental processing demands are increased with more difficult visual tasks. A visual oddball task used to compare four groups of young (20 years) and older (69 years) meditators and controls found that P300 latency and RT increased as the discriminability of the targets was made more difficult for all groups (Goddard, 1992). P300 latencies were longer in older subjects in all conditions, while RTs were shorter only as task difficulty increased. Further, P300 latencies were shorter in the older meditators vs. non-meditator comparison. These results suggest the possibility of primarily P300 latency trait effects for meditating relative to non-meditating older subjects.

Somatosensory Potentials

Somatosensory potentials are often evoked using mild electric shocks applied to the median nerve, with a series of potentials indexing transmission of the signal from the periphery to the cortex (Chiappa, 1996). TM meditators with two years practice demonstrated increased amplitudes of early components relative to controls (Petrenko, Orlova, & Liubimov, 1993). Yogic concentrative meditators with a 10-12 year practice history evinced amplitude decreases in the later components (Lyubimov, 1999). Similar Yogic meditators produced somatosensory EP amplitude decreases when instructed to block out the sensory stimuli, whereas the controls produced no effects. Further, the early components decreased only on the recording sites ipsilateral to stimulation side, but late components decreased bilaterally (Gordeev, Baziian, & Liubimov, 1992). This outcome implies that some concentrative meditation practices states can block sensory input at a

subcortical level.

Contingent Negative Variation (CNV)

CNV is elicited by presenting two stimuli in succession such that the first serves as an indicator for an impending second stimulus to which a response is required (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). This negative-going waveform was one of the first reported cognitive ERPs and consists of an early deflection related to central nervous system orienting followed by a later deflection that is maximal before the imperative stimulus and thought to reflect stimulus expectancy (Gaillard, 1977; Irwin, Knott, McAdam, & Rebert, 1966; Rohrbaugh et al., 1997; Walter, Cooper, Aldridge, McCallum, & Winter, 1964).

An early study found meditation-induced state effects of increased CNV amplitudes following TM practice (Paty, Brenot, Tignol, & Bourgeois, 1978). The Self-Regulation Method is a meditation technique combining aspects of Zen practice and Autogenic Training (Ikemi, 1988; Ikemi, Tomita, Kuroda, Hayashida, & Ikemi, 1986). After a five-week training course, EEG and CNV assessments were carried out prior to and during practice as well as during a drowsy state. CNV was obtained with a choice task to the imperative second stimulus. During meditation accuracy increased and shorter RTs were observed, whereas during drowsiness accuracy decreased and longer RTs occurred. EEG demonstrated increased theta and decreased beta power for meditation, but during both meditation and drowsiness reduced CNV amplitudes for the choice-task were found. CNV processes therefore may be sensitive to meditation state.

Groups of age-matched TM meditators who differed in the length of practice and the frequency of self-reported transcendental (defined as experiences of "pure consciousness," devoid of thought, and marked by awareness of awareness itself) perceptions (<1/year, 10-20/year, every day) were evaluated using simple and "distracter" CNV tasks (Travis, Tecce, & Guttman, 2000). No group effects were observed for the earlier orienting CNV component, but greater negativity for the later expectancy wave was obtained as the frequency of reported transcendental experiences increased across groups and tasks (simple RT, distraction stimuli). The decrement in CNV amplitude induced by the distracting stimuli was inversely related to transcendental experience frequency. The findings implied that transcendental feelings may modulate cortical functioning by activating processing resources to facilitate greater attentional resource capacity and thereby increased CNV amplitude.

A follow-up study assessed groups of older individuals who varied in the their TM background and reported "transcendental experience" levels: (1) no meditation practice (39.7 years old), (2) TM practice and occasional transcendental events (42.5 years old, 7.8 years meditating), (3) long-term TM practice (46.5 years old, 24.5 years meditating) and continuous coexistence of transcendent experience in waking and sleeping states (Travis, Tecce, Arenander, & Wallace, 2002). For the simple RT task, CNV amplitudes were larger for subjects with more TM practice and greater frequency of transcendent experience. For the choice task, smaller CNV amplitudes were associated with more TM practice and transcendent experience frequency. These findings were interpreted as indicating that the brain of the meditators efficiently waited for the second stimulus

information rather than automatically committing attentional resources to the imperative event.

EEG recording during CNV task performance demonstrated increased theta-alpha (6-12 Hz) power across the groups. Frontal broad-band coherence values (6-12 Hz, 12-25 Hz, and 25-45 Hz) also were increased as meditation practice increased across groups. These effects suggested that development of transcendental awareness was a meditation trait. Follow-up psychometric assessment of these subjects indicated that greater meditation experience was also related to increased inner directedness, higher moral reasoning, lower anxiety, and more emotional stability (Travis, Arenander, & DuBois, 2004b). How self-selection bias of individuals choosing to meditate for long time periods may contribute to these outcomes is unknown.

The CNV findings imply that meditation reduces choice-task CNV amplitude for state (Ikemi, 1988) and trait (Travis, Tecce, Arenander, & Wallace, 2002). In the simple CNV tasks an increase in amplitude has been observed as both a state and trait effect of meditation (Paty, Brenot, Tignol, & Bourgeois, 1978; Travis, Tecce, Arenander, & Wallace, 2002; Travis, Tecce, & Guttman, 2000). One finding that may be related to these results is the inverse correlation between states of greater sympathetic activation and CNV amplitude, modifiable by autonomic biofeedback procedures (Nagai, Goldstein, Critchley, & Fenwick, 2004). Thus, CNV appears to be affected by meditative practice in a manner related to changes in attentional resource allocation and possibly autonomic activity.

Conclusions from ERP Meditation Studies

Sensory EP and cognitive ERP meditation assessments have produced a variety of effects. The major difficulties in many studies are a lack of methodological sophistication, no replication of critical conditions, and inconsistency of task and study populations. Some intriguing hints of meditation changing early cortical auditory processing appear reliable, with suggestions that P300 also can be affected by meditation practice. Possible stimulus modality differences in assessing meditation have not been systematically ascertained. Simple CNV tasks yield an increase in amplitude for both state and trait effects of meditation, such that CNV effects may reflect changes in attentional resource allocation.

Brain Imaging and Meditation

Table 3 summarizes the findings from other neuroimaging studies of meditation. These are reviewed next. The results complement and extend the neuroelectric findings presented above.

Positron Emission Tomography (PET)

A PET study measured regional cerebral metabolic rate of glucose (rCMRGlc) in Yoga meditation by comparing an eyes-open meditation and a control condition in which the subjects were instructed to think of daily affairs (Herzog et al., 1990). The meditators reported feeling relaxed, at peace, and detached during meditation but not during the control condition. Half the subjects showed an overall increase and half showed an overall decrease in general cerebral metabolic rate during meditation. This outcome may have resulted from the necessity of recording the two sessions on different days, so that

differential practice effects could underlie arousal differences between the groups. No statistically reliable meditation effects on rCMRGlc for any brain regions were obtained, although mean activation decreases in association with meditation were observed in the superior-parietal (6.30%) and occipital (9.95%) cortex. The rCMRGlc ratios of meditation-to-control activity yielded three results: (1) the intermediate-frontal/occipital ratio increased (0.99 to 1.12), (2) intermediate frontal/temporo-occipital activity increased (1.18 to 1.25), and (3) superior frontal/superior parietal activation increased (1.07 to 1.14). These patterns suggest that the decrease in the occipital area might reflect an inhibition of visual processing during Yogic meditation, whereas the relative increase in the frontal cortex could reflect the sustained attention required for meditation. Combined EEG and PET imaging techniques also have demonstrated an association between increased anterior cingulate cortex and dorsolateral prefrontal cortex glucose utilization with frontal midline theta production (Pizzagalli, Oakes, & Davidson, 2003).

A related technique termed rheoencephalography quantifies blood flow changes originating from associated variation in electrical impedance. This measure and has been shown to reliably index relative cerebral activity although its resolution is low compared to other methods (Jacquy et al., 1974; Jevning, Fernando, & Wilson, 1989). TM meditators while meditating compared with non-meditator controls who sat quietly resting demonstrated increased frontal (20%) and occipital (17%) flow rates with no parietal changes observed (Jevning, Anand, Biedebach, & Fernando, 1996). As overall arousal level is positively correlated with increased cerebral blood flow (Balkin et al., 2002), these findings are consistent with the subjective reports of increased alertness

during TM and bolster the distinction between TM and Stage I/II sleep, since in these states cerebral blood flow is decreased rather than increased (cf. (Lazar et al., 2000; Stigsby, Rodenberg, & Moth, 1981; P. Williams & West, 1975).

Chapter 1 Table 3. Summary of Meditation Studies Using Neuroimaging Methods

Reference	Meditation Type	N	Experimental Design	Method	Findings (State Effects)
Herzog et al. (1990)	Yoga meditation, eyes open	8	Meditation vs. resting thought, separate days	PET	Increase—frontal/parietal and frontal/occipital activation ratios, low resolution analysis Decrease—slight for posterior/anterior ratios
Jevning et al. (1996)	TM	34	Meditators vs. controls, rest → meditation	Rheoenceph-alography	Increase—frontal, occipital Decrease—none, low resolution analysis
Lou et al. (1999)	Yoga Nidra (guided)	9	Rest → meditation	PET	Increase—anterior parietal (postcentral gyrus), fusiform gyrus, occipital cortex Decrease—dorsolateral orbital, cingulate, temporal, caudate, thalamus, pons, cerebellum
Lazar et al. (2000)	Kundalini Yoga mantra	5	Meditation vs. control periods silently generating number lists	fMRI	Increase—DLPFC, ACC, parietal, hippocampus, temporal, striatum, hypothalamus, pre/post central gyri Decrease—20% Globally
Khushu et al. (2000)	Raja Yoga	11	Rest → meditation	fMRI	Increase—PFC Decrease—none, low resolution analysis
Baerentsen et al. (2001)	Mindfulness	5	Rest → meditation	fMRI	Increase—DLPFC, ACC Decrease—occipital

Note: ACC=anterior cingulate cortex, DLPFC=dorsolateral prefrontal cortex, fMRI=functional magnetic imaging, PET=positron emission tomography, PFC=prefrontal cortex, PSPL=posterior superior parietal lobe, SPECT=single photon emission computed tomography, PSPL=posterior superior parietal lobe

Chapter 1 Table 3 continued. Summary of Meditation Studies Using Neuroimaging Methods

Reference	Meditation Type	N	Experimental Design	Method	Findings (State Effects)
Newberg et al. (2001)	Tibetan Buddhist imagery-meditation	8	Meditators vs. controls, rest → meditation (self-reported peak)	SPECT	Increase—cingulate, inferior-orbital, DLPFC, bilateral thalamus, midbrain, sensorimotor Decrease—PSPL; increases in left DLPFC correlated with decreases in left PSPL
Azari et al. (2001)	Psalm 23 recitation	12	Religious vs. non-religious subjects, rest, reading, and reciting psalm 23 vs. versus nursery rhyme vs. reading phone book	PET	Increase—right and left DLPFC, right medial parietal dorsomedial prefrontal (pre-supplemental motor area), cerebellum Decrease—none reported
Kjaer et al. (2002)	Yoga Nidra (guided)	5	Separate days for meditation and baseline	PET—^{11}C-raclopride binding, EEG	Increase—EEG theta Decrease—raclopride binding in ventral striatum, indicating increase dopamine binding
Ritskes et al. (2003)	Zen	11	Interleaved periods of meditation and rest	fMRI	Increase—DLPFC (R>L), basal ganglia Decrease—right anterior superior occipital gyrus, ACC
Newberg et al. (2003)	Christian prayer	3	Franciscan nuns, rest → prayer	SPECT	Increase—PFC, inferior parietal lobes, inferior frontal lobes Decrease—PSPL
Lazar et al. (2003)	Mindfulness vs. Kundalini Yoga	33	Mindfulness vs. Kundalini Yoga meditators vs. controls, meditation vs. random number generation	fMRI	Increase—both showed cingulate activation, right temporal lobe (Vipassana only) Decrease—none reported; different distribution of activated networks in the two groups

A PET (^{15}O-H_2O) study of Yoga meditators was conducted while subjects listened to a tape-recording, with a general instruction followed by distinct and different phases of guided meditative experience (Lou et al., 1999). The control condition consisted of replaying only the instruction phase after meditation conditions, and all sessions were recorded on the same day. A common experience of emotional and volitional detachment was reported throughout the meditation session but not during the control sessions. The meditating subjects practiced intensely for two hours prior to the PET scans and listened to the previously heard tape that presented focusing exercises on body sensation, abstract joy, visual imagery, and symbolic representation of self. Across all meditation phases relative to control conditions, overall increases in bilateral hippocampus, parietal, and occipital sensory and association regions were observed along with general decreases in orbitofrontal, dorsolateral prefrontal, anterior cingulate cortices, temporal and inferior parietal lobes, caudate, thalamus, pons, and cerebellum.

However, each of the guided meditation phases was associated with different regional activations during meditation relative to the control condition: Body sensation correlated with increased parietal and superior frontal activation including the supplemental motor area; abstract sensation of joy was accompanied by left parietal and superior temporal activation including Wernicke's area; visual imagery produced strong occipital lobe activation excluding area V1; symbolic representation of self was associated with bilateral activation of parietal lobes. Hence, specific activation was obtained for different meditation conditions, although given the "guided" nature differentiation of these from a hypnotic state is difficult. Indeed, simultaneous EEG

measures demonstrated an 11% increase in theta power in the meditative states over the control condition, which was observed from all 16 electrodes thereby indicating a generalized increase in theta.

Body sensation meditation and activation of the supplementary motor areas may be due to covert unconscious motor planning, despite subject self-reports of a distinct lack of volitional activity in this study. The meditation on joy and corresponding left-sided activation may have originated from the "abstract and verbal" nature of the instructions, or alternately from the association between left-side-dominant frontal activity and positive emotional valence (R. J. Davidson & Irwin, 1999). The visual imagery meditation produced activations similar to voluntary visual imagery, although greater prefrontal and cingulate activity were often observed in the latter. The subjects may have had less volitional control and emotional content than might be present in normal visual scene imagining. Similar patterns are observed for REM sleep except that the anterior cingulate is inactivated (Lou et al., 1999). The lack of V1 activation during the visualization meditation adds to a considerable body of evidence suggesting that it is not part of the necessary neural substrate of visual awareness (Koch, 2004). The symbolic representation of the self condition and associated bilateral parietal activity may reflect bodily representation, with temporal cortex activation also implicated (Karnath, Ferber, & Himmelbach, 2001).

The increased hippocampal activity for overall meditation sessions compared to the control state may underlie the increased theta activity, as the increases were not related to prefrontal activation (Kahana, Seelig, & Madsen, 2001). The areas more active in the

control state include those that subserve executive attention such as the dorsolateral prefrontal cortex, which has been shown to specifically activate in preparation for voluntary motor activity. Anterior cingulate cortex activation in the control state is thought to be involved in emotional circuits and executive functions. Moreover, the relative control state striatal activation may index low preparedness for action during meditation. Similar regions also have been shown to be decreased in activity during slow wave sleep—an outcome attributed to the common decreased executive activity in both deep sleep and this form of guided meditation. The cerebellum can participate in attention, motoric feedback loops, as well as prediction of future events (Allen, Buxton, Wong, & Courchesne, 1997), and this structure was less active in the meditative state. In sum, the meditational states produced activity in the hippocampal and posterior sensory/associative systems related to imagery, whereas the control condition was characterized by increased activity for executive/attentional systems and the cerebellum.

A related study of the same meditative state found that dopaminergic changes were associated with the observed decreases in striatal activity, supporting the hypothesis that endogenous dopamine release may increase during the loss of executive control in meditation (Kjaer et al., 2002). Radioactive ^{11}C-raclopride selectively and competitively binds to D2 receptors, such that the amount of binding inversely correlates with endogenous dopamine levels. The findings demonstrated a 7.9% decrease in ^{11}C-raclopride binding in the ventral striatum during meditation, results that correspond to an approximate 65% increase in dopamine release based on rat microdialysis studies of ^{11}C-raclopride binding dynamics in relation to dopamine levels. Increased dopamine tone

underlying the meditative experience may thereby reflect its self-reinforcing nature once proficiency is attained, at least for this form of meditation.

A single photon emission computed tomography study was conducted on Tibetan Buddhist meditators in which subjects report "becoming one with" the visualized image (Newberg et al., 2001). The meditators were scanned at baseline and after approximately one hour when they had indicated entering into the deepest part of their meditation session. The baseline activation patterns revealed a difference in the thalamic laterality index in which meditators showed a significantly greater rightward dominance of thalamic regional cerebral blood flow relative to control subjects. Meditation compared to baseline was related to increased activity in the cingulate gyrus, inferior and orbital frontal cortex, dorsolateral prefrontal cortex, midbrain, and thalamus. The midbrain activation may be correlated with alterations in autonomic activity during meditation (Infante et al., 2001; Kubota et al., 2001; Newberg & Iversen, 2003; Orme-Johnson, 1973; Travis, 2001; Travis & Wallace, 1999; Wenger & Bagchi, 1961). Decreased activity in the left posterior superior parietal lobe was negatively correlated with the activity increase observed in left dorsolateral prefrontal cortex.

Functional Magnetic Resonance Imaging (fMRI)

A form of Kundalini Yoga entailing a mantra combined with heightened breath awareness was assessed with fMRI (Lazar et al., 2000). The control activity was the mental construction of animal names. The five meditation subjects each had practiced Kundalini Yoga at least four years and listened to a tape of loud fMRI clicking previous

to the scanning sessions to promote meditative focus during this possibly distracting stimulus field. The meditation compared to control conditions produced activity increases in the putamen, midbrain, pregenual anterior cingulate cortex, and the hippocampal/parahippocampal formation, as well as areas within the frontal and parietal cortices. Assessment of early versus late meditation states found robust activity increases in these areas, a greater number of activation foci, larger signal changes, and higher proportion of individuals with significant changes during the late meditation states. These results suggest that with increased meditation time, subjects produce altered brain states that may index changed states of consciousness as they continue their meditation. Indeed, the major increased activity areas were those subserving attention (frontal and parietal cortex, particularly the dorsolateral prefrontal cortex) and those subserving arousal and autonomic control (limbic regions, midbrain, and pregenual anterior cingulate cortex). The authors specifically point out that their findings were distinct from previous studies due to the very different meditation styles (cf. Lou et al., 1999), since a guided meditation procedure is particularly susceptible to a lack of executive attentional engagement and therefore the lack of prefrontal cortex enhancement.

Subjects with extensive training in Kundalini (mantra-based) or Vipassana (mindfulness-based) meditation were imaged with fMRI during meditation and several (simple rest, generation of a random list of numbers, and paced breathing) control tasks (Lazar et al., 2003). The results indicated that each style of meditation was associated with a different pattern of brain activity. In the two meditator groups, similar but non-overlapping frontal and parietal cortices were engaged as well as sub-cortical structures,

and these patterns differed from those observed during control tasks. The main area of common activation was the dorsal cingulate cortex. Vipassana subjects experienced little or no decrease in ventilatory rate, whereas Kundalini subjects typically had decreases of greater than four breaths/min during meditation compared to baseline. Based on preliminary analyses, different forms of meditation appear to engage different neural structures, as has been previously reported in multiple meditation studies (Dunn, Hartigan, & Mikulas, 1999; Lehmann et al., 2001; Lou et al., 1999; Lutz, Greischar, Ricard, Converse, & Davidson, 2003).

Zen practitioners were assessed with fMRI using an on-off design of 45 s blocks in which meditators counted their breath as in normal practice during three meditation periods and engaged in "random thoughts" during the intervening three rest periods, each of which was 45 s long. Comparing meditation to rest revealed increased activity in the dorsolateral prefrontal cortex that was stronger in the right and bilateral basal ganglia. Decreased activity was found in the right anterior superior occipital gyrus and anterior cingulate (Ritskes, Ritskes-Hoitinga, Stodkilde-Jorgensen, Baerentsen, & Hartman, 2003). Activity decrease in the anterior cingulate was not as strong as the increase in dorsolateral prefrontal cortex and was attributed to a decreased experience of will in the meditative state. Given the evidence for anterior cingulate involvement in other studies, this finding may have been related to the very short periods of time allotted for the successive Zen states. A second fMRI study was conducted on five mindfulness meditation practitioners, with two repetitions of the onset of meditation assessed as successive 45 s off-on stages of meditation onset (Baerentsen, 2001). Activations in the

paired hippocampi, left frontal, right temporal, and anterior cingulate cortices, with deactivations in the visual cortex and left frontal lobe were observed. These two fMRI studies of Zen techniques found opposite activation patterns for the anterior cingulate. The small sample sizes, lack of phenomenological measures, and their preliminary nature require verification.

The significant increased activations in cingulate cortex, prefrontal and orbitofrontal cortex have been found in the majority of non-guided meditation studies (Herzog et al., 1990; Khushu, Telles, Kumaran, Naveen, & Tripathi, 2000; Lazar et al., 2000; Lazar et al., 2003). Besides the importance of anterior cingulate cortex activation as a marker of the increased attentional focus in meditative states, this structure also appears related to feelings of love (Bartels & Zeki, 2000, 2004). Some meditators consistently report such feelings during meditation (Mahesh Yogi, 1963), although these experiences are not the explicit goal in the most commonly practiced meditation techniques such as TM, Vipassana, and Zen (Goleman, 1996; B. A. Wallace, 1999).

The prefrontal areas are activated in attention-focusing tasks not involving the distinct altered sense of relating to experience seen in meditation but are likely related to the effortful intentional activity involved in most meditative practice (Frith, 1991; Pardo, Fox, & Raichle, 1991). Studies comparing internally generated versus externally generated word rehearsal demonstrated a shift from medial prefrontal activation to more lateral areas (Crosson et al., 2001). The increased activity of the dorsolateral prefrontal cortex may contribute to the self-regulation of brain functioning, as it has been shown to contribute to self-regulating emotional reactions (Beauregard, Levesque, & Bourgouin,

2001; Levesque et al., 2003) and decreased emotional reactivity is reported to ensue from meditative practice (Goleman, 2003; B. A. Wallace, 2000). Engagement of the left superior parietal lobe during visual-spatial orientation tasks so that activity decreases in conjunction with the increase in left dorsolateral prefrontal cortex suggest a neural basis for the altered sense of spatial awareness present in the meditative state (Cohen et al., 1996; D'Esposito et al., 1998). Several investigations have reported decreased posterior superior parietal lobe activity associated with decreased experience of self/non-self boundaries (d'Aquili & Newberg, 1993, 1998, 2000), and one found decreased superior parietal lobe activation (Herzog et al., 1990).

A limited number of studies have been carried out with Christian prayer practices. Religious subjects were compared to a non-religious group during recitation versus reading of Psalm 23, a popular German nursery rhyme, and a phone book (Azari et al., 2001). The religious subjects reported achieving a religious state while reciting Psalm 23 and significant activations were found in left and right dorsolateral prefrontal cortex, right medial parietal (precuneus), and dorsomedial prefrontal cortex compared to other reading and non-religious control subjects. The increases in right dorsolateral prefrontal cortex and dorsomedial prefrontal cortex were especially strong and significantly increased relative to all comparisons. In contrast, the non-religious subjects reported experiencing a happy state in reciting the nursery rhyme, which was associated with left amygdala activation that was correlated with affective state (LeDoux, 2003; Morris et al., 1996; Phan, Wager, Taylor, & Liberzon, 2004). The authors speculate that a frontoparietal circuit is involved in cognitive processing with felt emotionality, but the

lack of a phenomenological religious experience report limits comparisons with previous studies as meditative training de-emphasizes recursive thought.

Franciscan nuns praying were measured with single photon emission computed tomography in fashion similar to Tibetan Buddhist Meditators (Newberg, Pourdehnad, Alavi, & d'Aquili, 2003). They engaged in “centering prayer,” which “requires focused attention on a phrase from the Bible” and involves ”opening themselves to being in the presence of God” and “loss of the usual sense of space,” making it a relatively good approximation of some forms of mantra-based meditational practices. Compared to baseline, scans during prayer demonstrated increased blood flow in the prefrontal cortex (7.1%), inferior parietal lobes (6.8%), and inferior frontal lobes (9.0%), and a strong inverse correlation between the blood flow changes in the prefrontal cortex and in the ipsilateral superior parietal lobe was found. The findings further suggest that meditative/spiritual experiences are partly mediated through a deafferentiation of the superior parietal lobe, which helps to generate the normal sense of spatial awareness (d'Aquili & Newberg, 2000).

Conclusions and Directions

The present review of meditation state and trait indicates considerable discrepancy among results, a fact most likely related to the lack of standardized designs for assessing meditation effects across studies, the variegated practices assayed, and a lack of technical expertise applied in some of the early studies. EEG meditation studies have produced some consistency, with power increases in theta and alpha bands and overall frequency

slowing generally found. Additional findings of increased power coherence and gamma band effects with meditation are starting to emerge. ERP meditation studies are sparse but suggestive of increased attentional resources and stimulus processing speed and/or efficiency. Neuroimaging results are beginning to demonstrate some consistency of localization for meditation practice, with frontal and prefrontal areas shown to be relatively activated. These outcomes appear to index the increased attentional demand of meditative tasks and alterations in self experience. However, none of the approaches has yet isolated or characterized the neurophysiology that makes explicit how meditation induces altered experience of self. Studies of the reported intense absorptive experience that merges self with the phenomenal world are needed to establish this state effect. Prospective longitudinal assessments are required to establish trait effects that may reflect subtle neural alterations underlying the shift in the locus of self-experience and the development of stable unchanging awareness.

Psychological and Clinical Effects

A number of studies investigating the psychological concomitants to meditation have been conducted with some consistency of results obtained. An important caveat when using subjective reporting of psychological functioning is that impact of expectancy and performance motivation within meditator participants is difficult to control (West, 1987; Shapiro & Walsh, 1984). Nevertheless, a number of the clinical reports—both psychological and medical—are suggestive of significant effects and together with the

other psychological studies provide intriguing correlates of the meditation and brain activity findings summarized above.

The primary psychological domain mediating and affected by meditative practice is attention (Davidson & Goleman, 1977), but relatively few empirical evaluations of meditation and attention have been conducted. Longitudinal studies of breath-focused meditation in children and adults have reported improved performance on the embedded figures test requiring the subject to ignore distracting stimuli (Kubose, 1976; Linden, 1973). A cross-sectional study of children practicing TM and a cohort of age and sex-match controls found that meditation practice led to improved measures of attention (Rani & Rao, 1996). Mindfulness and concentrative practices were compared using an auditory counting task susceptible to lapses in sustained attention (Sweet & Valentine, 1995; Wilkins, Shallice, & McCarthy, 1987). Superior attentional performance was obtained for meditators compared to controls, as well as long-term compared to short-term meditator status. Further, mindfulness meditators demonstrated better performance than concentrative meditators in a second task assessing sustained attention on unexpected stimuli. In contrast to these trait effects on attentive capacity, short-term meditation effects on a focusing task suggested that TM produced no improvement in concentrative functioning (Sabel, 1980), a finding consistent with the explicit lack of emphasis on concentrative effort using the TM technique.

The CNV studies reviewed above support the view that attentive capacities are increased in long-term TM meditators relative to controls (Travis et al., 2000, 2002). Given that meditation is a form of attentional training, the neurophysiologic findings

imply increased activity in the frontal attentional system, with additional studies needed to confirm this hypothesis. A related clinical study assessed the impact of a Yogic concentrative meditative practice on attention deficit hyperactivity disorder in adolescents, with findings indicating a substantial improvement in symptoms following a six-week training intervention (Harrison, Manoch, & Rubia, 2004).

The psychological trait 'absorption' is related to attentional deployment and appears to have relevance to meditative practice (Tellegen & Atkinson, 1974). Absorption refers to the tendency to have episodes of total attention that occupy representational resource mechanisms, thereby leading to transient states of altered self and reality perception. The data suggest that absorption and anxiety reduction are independently related to proficiency in meditative practice, but it is not clear whether this is due to a predisposition for meditative practice or a result of such practice (Davidson, Goleman, & Schwartz, 1976). Further research assessing the neurophysiologic functioning of meditators with regard to absorption might be of benefit in characterizing the individual differences for the range of brain and mind responses to meditative training (Ott, 2003).

Perceptual sensitivity is a psychological domain that appears to be impacted by meditation (Goleman, 1996). The ERP studies reviewed above are consonant with the general view that meditation may lead to improvements in perceptual acuity and/or processing, but rigorous tests of perception effects are scarce. A study on perceptually ambiguous visual stimuli with a binocular rivalry task demonstrated that one-pointed concentrative meditation may stabilize one of the perceptual possibilities in awareness (Carter et al., 2005). More germane to reports of enhance perceptual clarity, visual

sensitivity threshold to short light flashes was lower in mindfulness meditators than controls, and a three-month intensive mindfulness meditation retreat seemed to produce further decreases in threshold (Brown et al., 1984a, 1984b). Studies of yogic concentrative meditation (Sahaj Yoga) have found that children, young adults, and adults all evince improvements in critical flicker fusion frequency after training compared to control groups who did not undergo such training (Raghuraj & Telles, 2002; Telles, Nagrathna, & Nagendra, 1995; Manjunath & Telles, 1999). Visual contrast sensitivity was also shown to increase secondary to Sahaj Yoga training in a group of epileptic adults (Panjwani et al., 2000). The long-standing descriptions of the enhancement of the perceptual field due to meditation combined with the suggestive effects reviewed here and the consistency with event-related potential findings warrant further studies of perceptual acuity, preferably in combination with neurophysiologic monitoring.

A considerable body of research supports the idea that meditative training can mitigate the effects of anxiety and stress on psychological and physiological functioning. The functional plasticity of the central nervous system affords significant neurophysiologic state changes that may evolve into trait effects secondary to the long hours of practice, stylized attentional deployment, reframing of cognitive context, and emotional regulation involved in meditative training (R. J. Davidson, 2000). This possibility is consonant with the relationships among increased stress, increased corticosteroid levels, and inhibition of hippocampal neurogenesis (McEwen, 1999). Meditation decreases experienced stress load (Carlson, Speca, Patel, & Goodey, 2003; Gaylord, Orme-Johnson, & Travis, 1989; Holmes, 1984; Kabat-Zinn et al., 1992; Lehrer,

Schoicket, Carrington, & Woolfolk, 1980), which appears related to decreased cortisol and catecholamine levels (Carlson, Speca, Patel, & Goodey, 2004; Infante et al., 1998; Infante et al., 2001; Kamei et al., 2000; MacLean et al., 1997; MacLean et al., 1994; Michaels, Parra, McCann, & Vander, 1979; Sudsuang, Chentanez, & Veluvan, 1991). Some studies with meditators have assessed physiological responses to stressful stimuli, which is particularly relevant given the purported benefits of decreased automatization and reactivity combined with greater calm and compassion due to meditation (Kabat-Zinn, 1990; Goleman, 2003; Mahesh Yogi, 1963). Meditators exhibited a quicker return to baseline for heart rate and skin conductance measures after exposure to stressful film clips (Schwartz & Goleman, 1976). Meditators also were shown to lack frontal gamma induction found for non-meditators in response to stressful film clips (Aftanas & Golocheikine, 2005). These studies are preliminary but provide motivation to further study neurophysiologic response to emotionally challenging stimuli.

Mindfulness-based practices have produced positive clinical outcomes for anxiety, immunoprotective functioning assays, pain, and stress-related skin disorders (Beauchamp-Turner & Levinson, 1992; Carlson, Speca, Patel, & Goodey, 2003, 2004; R. J. Davidson et al., 2003; Kabat-Zinn, 1982, 2003; Kabat-Zinn, Lipworth, & Burney, 1985; Kabat-Zinn et al., 1998; J. J. Miller, Fletcher, & Kabat-Zinn, 1995; S. L. Shapiro & Walsh, 2003). These results are consistent with the hypothesis that meditation induces a significant reorganization of frontal hemispheric activity associated with emotional reactivity and outlook perhaps related to the increases in theta and alpha EEG activation (R. J. Davidson et al., 2003; Dunn, Hartigan, & Mikulas, 1999; Lazar et al., 2003).

Concentrative practices also have been examined in medical contexts (Castillo-Richmond et al., 2000; Murthy, Gangadhar, Janakiramaiah, & Subbakrishna, 1998; Schneider, 1995; Zamarra, 1996), with low-effort mantra-based TM the most frequently evaluated as a complementary therapy that contributes to decreasing the impact of stress (Gelderloos, Walton, Orme-Johnson, & Alexander, 1991; Jevning, Wallace, & Beidebach, 1992; Walton, Pugh, Gelderloos, & Macrae, 1995). In this context, it would be helpful to obtain concurrent neurophysiologic measures with the assessment of medical and/or psychological outcome in order to characterize the neural mediating factors associated with clinical improvement. Examples of this approach include observed left-over-right asymmetry shifts of frontal activity that correlated with increases in immune measures secondary to mindfulness meditation training (Davidson et al., 2003), as well as increased in auditory P300 amplitude correlated with improvements in depression in response to yogic meditation (Murthy et al., 1997, 1998). Further research into meditation and the biological mechanisms of stress/emotional reactivity would provide needed substantiation for theories implicating such practice in the functional reorganization of stress-related limbic structures (Esch, Guarna, Bianchi, Zhu, & Stefano, 2004).

Meditative practices employing mental role-playing and the generation of specific sustained feelings or intentions of love/compassion have begun to be investigated (Goleman, 2003; Lehmann et al., 2001; Lutz, Greischar, Ricard, Converse, & Davidson, 2003). However, meditation effects on emotional functioning have not been extensively explored with neuroimaging methods, even though clinical studies suggest that the psychological variable mindfulness is enhanced through meditative practice and seems to

powerfully mitigate susceptibility to depression. In particular, Mindfulness-Based Cognitive Therapy, which commonly incorporates mindfulness meditation, has been successful in treating depression (Ma & Teasdale, 2004; O. Mason & Hargreaves, 2001; Rohan, 2003; Segal, Williams, & Teasdale, 2002; Teasdale, Segal, & Williams, 1995; Teasdale et al., 2000). The specific effects appear related to the prevention of depression relapse in patients already experiencing three or more previous depressive episodes (Teasdale et al., 2000).

The psychological variable most associated with the increased resistance to depression after Mindfulness-Based Cognitive Therapy is "metacognitive awareness," the shift towards experiencing negative thoughts as observable mental contents rather than the self (Teasdale et al., 2002). As with stress, depression is linked to increased cortisol and decreased hippocampal neurogenesis (E. S. Brown, Rush, & McEwen, 1999; Gould, Tanapat, Rydel, & Hastings, 2000; B. L. Jacobs, 2002; Malberg & Duman, 2003; Thomas & Peterson, 2003; Vollmayr, Simonis, Weber, Gass, & Henn, 2003), implicating meditative training in eliciting a cascade of neuroprotective events that are possibly related to the enhancement of the frontal attentional control system and/or the decreased arousal associated with alpha increases. The increase in metacognitive awareness that seems associated with the efficacy of mindfulness-based approaches to therapy is difficult to reconcile with current neuroimaging data but appears related to the fundamental goals of meditative practice in producing lasting impact on the self-non-self relationship (Austin, 2000; Levenson, Jennings, Aldwin & Shiraishi, 2005; Walsh, 1982). The recent development of a number of experimental paradigms aiming to assess the

subtleties of self-referential processing in health and illness provide a means to quantify further psychometrically-derived claims for changes in self experience with brain-based measures (Kircher & David, 2003; Kircher et al., 2000; Lou et al., 2004; Platek, Keenan, Gallup, & Mohamed, 2004).

Understanding the state and trait neurophysiologic and psychological changes induced through meditative practices requires better psychometric assessment of the elicited states and traits. Several investigators have produced such measures for both state and trait changes (Brown & Ryan, 2003; Buchheld, Grossman, & Walach, 2001; Levenson et al., 2005; Ott, 2001; Piron, 2001). Such trait-based research suggests that the psychological variable mindfulness, which has influenced theories of psychological intervention, is increased after meditative training and associated with the experience of well-being (Brown & Ryan, 2003). A recent proposal to pare down altered states of consciousness into a four-dimensional "state space" consisting of activation, awareness span, self-awareness, and sensory dynamic constructs is an appealing proposal for meditation research as well (Vaitl et al., 2005). This approach provides encompassing signatures of experienced state that may map more easily than higher dimensional state spaces onto neurophysiologic differences, although this limited four-dimensional space may not adequately address the full range of alterations induced by meditation (Travis, Arenander & DuBois, 2004; Walsh, 1982; Wilber, Engler, & Brown, 1986).

Given the wide range of possible meditation methods and resulting states, it seems likely that different practices will produce different psychological effects and also that different psychological types will respond with different psychobiological alterations.

Indeed, recent reports have shown that novices in Zen meditation demonstrated low trait anxiety correlated with frontal alpha coherence effects (Murata et al., 2004), whereas novelty seeking scores correlated with frontal alpha power increases and harm avoidance scores correlated with frontal theta increases (Takahashi et al., 2005). These findings are preliminary in nature but serve as a potentially important model for how psychological set may be related to meditation state neurophysiology. Quantification of the trait changes elicited by given different mental sets may foster insight into specific avenues of meditation's psychobiologic impact, with rigorous comparison of techniques needed to identify specific psychological outcomes.

Additional Future Directions

As outlined above, several recent studies have suggested that different meditation practices lead to different neurophysiologic outcomes, so that the neurophenomenological comparison of meditative practices with other methods of altered state induction are becoming warranted to isolate the functional brain activity associated with psychological states. Assessments of psychological changes, clinical outcomes, and state-trait neuro-activity markers across meditative practices will be necessary for developing the clinical utility of these methods. Targeted assays of theta, alpha, and gamma power as well as coherence effects in both state and trait studies of meditation will help establish a necessary data base for future applications.

A major challenge for basic meditation research remains the clear quantitative differentiation and topographic mapping of the difference between meditation and early

sleep stages. The most widely found state effects of meditation—periods of alpha and theta enhancement—overlap significantly with early drowsing and sleep states (Corby, Roth, Zarcone, & Kopell, 1978; Pagano, Rose, Stivers, & Warrenburg, 1976; Rechtschaffen & Kales, 1968; Younger, Adriance, & Berger, 1975). The increases in theta power observed in some long-term meditators may be related to learning to hold awareness at a level of physiological processing similar but not identical to sleep Stage I. Awareness maintenance practice may enhance awareness even as deep sleep develops thereby affecting associated neurophysiologic markers.

This hypothesis provides a phenomenological link between the physiological similarities of the meditative and sleep-related states. In both cases there is an increased access to a witnessing awareness of state. It may be that the difference between the slow activity in meditative practices and that of normal sleep reflects the distribution of theta *versus* alpha power changes, the increases in theta and alpha coherence during meditation *versus* decreases during sleep, and possibly the high frequency activity that accompanies increases in low frequency power with meditation practice that are decreased in sleep. The theta increase in meditative states is the frontal midline theta generated by the anterior cingulate, dorsal, and medial prefrontal cortices (Aftanas & Golocheikine, 2001; Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Hebert & Lehmann, 1977; Ishii et al., 1999). The theta typically seen at the transition from Stage I to Stage II sleep is less stable across time and also originates from more widespread sources. A comprehensive empirical distinction of these two increased theta states could provide a much needed differentiation between the phenomenology of meditative experience and that of sleep.

Conclusion

Meditation states and traits are being explored with neuroelectric and other neuroimaging methods. The findings are becoming more cohesive and directed, even though a comprehensive empirical and theoretical foundation is still emerging. Central nervous system function is clearly affected by meditation, but the specific neural changes and differences among practices are far from clear. The likelihood for clinical utility of meditation practice in conjunction with psychological and neuropharmacological therapies is a strong impetus for future studies. The present review has attempted to set the stage for this development by providing an organized state-of-the-art summary of how meditation affects the brain.

Chapter 1, in full, is a reprint of the material as it appears in Psychological Bulletin, Cahn, BR and Polich, J. Meditation States and Traits: EEG, ERP, and Neuroimaging Studies. Volume 132, Issue 2, March 2006. The dissertation author was the primary investigator and author of this paper.

CHAPTER 2

The effects of meditation on the processing of auditory stimulation as assessed by event-related potentials and induced theta power

Abstract

The auditory oddball paradigm involving the presentation of tones with occasional rare tones and distracting white noise stimuli was used with long term Vipassana meditators in a state of meditation versus prolonged thought. In response to the distracter white noise stimulus a less frontally distributed N1 event-related potential component was observed during meditation compared to thinking conditions. Additionally, for the distracter stimulus meditation induced P3a component reduction and a trend towards P2 component amplitude reduction. Frontal theta power (3-4 Hz) was increased in the distracter epochs relative to the standard and rare tone epochs. Meditation reduced this frontal theta power overall as well as the observed oddball and distracter stimulus-driven theta power increase. This pattern of findings reflects neurophysiologic measures of decreased attentional capture by distracting, aversive stimuli in meditation relative to thought conditions. Implications are discussed.

Introduction

Despite many years of experimental investigation, the effects of meditation on brain activity are not well-characterized. This may be due to a number of reasons

including the wide variation among practices and the lack of a sustained research effort amongst a core group of impartial investigators. One particular meditative form, the Transcendental Meditation (TM) technique, has been well studied, primarily by members of the TM community (Travis, 1991; Travis, Arenander, & DuBois, 2004a; Travis, Tecce, Arenander, & Wallace, 2002; Travis & Wallace, 1997). The present study sought to establish whether the automated processing of auditory stimuli would be altered in Vipassana meditation relative to an equal period of silent closed-eyed sitting while engaged in a recollective memory thought task.

There is no consensus as to whether some of the most standard sensory and cognitive evoked and event-related potentials are altered in a systematic way through the many long hours that typical dedicated meditators devote to their practice, although, as reviewed in the previous chapter, some findings of increased attention-related activities including frontal midline theta (Aftanas & Golocheikine, 2001; Hebert & Lehmann, 1977), P300 amplitude (Banquet & Lesévre, 1980; Murthy, Gangadhar, Janakiramaiah, & Subbakrishna, 1997) and contingent negative variation amplitude (Travis, Tecce, Arenander, & Wallace, 2002; Travis, Tecce, & Guttman, 2000) have been reported.

Specifically, Banquet & Lesévre (1980) found that P300 amplitudes to visual stimuli were increased after a period of meditation in experienced yoga meditators in contrast to P300 amplitude decreases after a period of rest in non-meditators. These researchers also found shorter reaction times and increased N1 and P2 component amplitudes in the experienced meditator cohort. Becker and Shapiro (1981) found no systematic effects of yoga, TM, or Zen meditation on P3 or other ERP component

responses to auditory stimuli, although the TM and yoga groups did show increased N1 component amplitudes towards the beginning of the stimulus train. A series of reports presented as poster sessions by TM researchers showed tendencies towards decreased P3 latencies associated with length of meditation practice (Cranson, Goddard, & Orme-Johnson, 1990; Goddard, 1989, 1992). In a study of depressed and dysthymic individuals, Murthy et al. found increases in auditory oddball P3 amplitudes after a period of meditation training undertaken to treat their depression (Murthy, Gangadhar, Janakiramaiah, & Subbakrishna, 1997). A recent study by Sarang and Telles (Sarang & Telles, 2006) found that auditory oddball P3 amplitudes were increased after a session of yogic meditation with "stimulating" properties. Lastly, another recent study (Slagter et al., 2007) found that after a 3-month intensive Vipassana meditation retreat, meditators showed a decreased attentional blink effect associated with decreased visual P3 amplitudes to the T1 stimulus. In sum, the evidence to date suggests that the P3 component may be subject to modulation by meditative practice, although it remains to be seen whether these findings are robust and also whether different forms of meditation tend to have different effects.

Vipassana meditation is a traditional Buddhist meditative form that involves focusing on present-moment awareness, especially on physical sensation. It is the form of meditation that served as a foundation for the development of the modern mindfulness meditation techniques that are being widely taught in the West today, led by researcher-practitioners such as Jon Kabat-Zinn (Kabat-Zinn, 1982, 2003). It has been hypothesized that in the process of developing greater awareness of and non-reactivity to sensory

stimuli during formal practice, the Vipassana/mindfulness meditation practitioner becomes able to use this enhanced self-awareness to more successfully manage stressful life situations, selectively responding in appropriate ways instead of automatic non-adaptive reactions (Segal, Williams, & Teasdale, 2002).

Recent investigations of Vipassana meditation shed some light on the possible key neurophysiologic correlates to this practice. A recent study investigating the fMRI effects of Vipassana showed that experienced meditators in meditation show higher levels of activity in rostral anterior cingulate cortex and medial prefrontal cortex than novice meditators (Hölzel et al., 2007). Another study showed that after a 3-month intensive retreat in Vipassana meditation, practitioners but not control subjects showed a decrease in the strength of attentional blink which associated with a decrease in P300 amplitude to the T1 stimulus (Slagter et al., 2007). Taken in combination with the finding that experienced meditators show higher levels of activity in attention-related prefrontal areas, a picture emerges of increased selective attentional control secondary to meditative practice. Lazar et al. (Lazar et al., 2005) found that Vipassana meditators showed increased cortical thickness in a number of cortical regions related to somatosensory, auditory, visual and interoceptive processing. The greatest effects were seen in the right anterior insula, an area known to be related to bodily attention and increased visceral awareness (Craig, 2002, 2003; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Because this study was cross-sectional in nature these findings did not conclusively show that meditative practices were the cause for the observed cortical thickness. However, in the young subjects assayed the cortical thickness of the meditation

vs. control groups was similar, thus indicating that the engagement with meditation may have slowed the age-related thinning of the cortical areas identified including the insular and prefrontal cortical areas.

One of the many areas of research lacking to date is the systematic study of the difference between long periods of active thinking vs. long periods of meditative absorption. None of the studies reviewed above were designed in order to allow for such a within-subject analysis of the state effects of meditation. The current study sought to control for possible effects of habituation on EEG and ERP parameters by employing a counterbalanced design wherein half the participants engaged in a prolonged stylized "thought" condition followed by a meditation session of the same length and half the participants reversed this order. In both cases, after 25 minutes of eyes-closed sitting in the recording chamber they were exposed to a passive auditory oddball paradigm.

We hypothesized that after a prolonged engagement in meditative practice the automatic processing of stimuli would be altered compared to an equal period of time spent engaged in the attempt to recollect past memories. In particular, given the previous findings showing that meditation can modulate neurophysiologic measures of attentional control and increases in the selective filtering sensory and cognitive information, we expected to see markers of decreased attentional capture in the meditation state, as indicated by lower amplitude late cognitive potentials. Stimulus-related theta effects have not previously been assayed in studies of meditation. Given the known association between attentional capture and increased frontal theta power (Melloni et al., 2007) we also expected to see reduced theta power induction to deviant stimuli during the

meditation state.

Methods

Subjects

This study of meditation state effects was conducted with a sample of 16 long-term Vipassana meditators who had been practicing for at least 2 years daily meditation of one hour or more at the time of testing. The average number of year's daily practice in this meditator cohort was 13.0 $\pm$ 10.7 yrs, the average number of hours of meditation per day was 1.3 $\pm$ 0.7, and the average age was 45.5 $\pm$ 9.8. Subjects were recruited through the local Vipassana meditation community of San Diego through word of mouth and e-mail listserves.

EEG Data acquisition

EEG data was collected using an InStep system from the following 19 standard scalp locations according to the International 10-20 System using active Ag-AgCl electrodes mounted in a an EGI elastic cap: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, T7, T8, Cz, P3, P4, P7, P8, Pz, O1, and O2. Electrodes were applied to both earlobes and scalp electrodes were recorded with reference to the linked earlobes and a ground electrode was applied to the forehead. Additional electrodes were applied to the outer canthi of both eyes for horizontal EOG monitoring and the infraorbital and supraorbital regions of the left eye in line with the pupil for vertical EOG monitoring. All impedances were checked to assure they were below 10 kΩ. EEG signals were sampled at 256 Hz, amplified and analog band-pass filtered between 0.01 and 70 Hz (6 dB octave/slope).

Stimuli and Procedure

After applying the 21-channel electrode cap and assuring that noise-free data was being collected the participants were told to either meditate or engage in thinking about past events of their life with no particular emotional relevance. Participants were informed that after 25 minutes of eyes-closed meditation or thinking they would hear a series of tones and that they were to simply continue their meditation or thinking exercise. The auditory oddball paradigm employed the pseudorandom presentation of 250 auditory stimuli. Standards of 500 Hz were presented with a probability of 0.8, Oddballs of 1000 Hz with a probability of 0.1, and Distracters (white noise) with a probability of 0.1. All stimuli were of 80 dB SPL intensity and 60 msec in duration. The interstimulus interval was exactly 1 second. At the conclusion of the first recording period the participants were given the opportunity to stand up and stretch before taking the same posture and seating position for the second recording of equal length. At this time they also filled out a short form indicating whether they had felt any drowsiness during the meditation/thought session and also to rate the depth of meditative experience on a 1-10 scale. Of the 16 participants, 8 performed the meditation task first and 8 performed the thinking task first.

ERP Analysis

Offline the data were imported into BrainVision Analyzer V1.05 for ERP analysis. Subsequently, data was band-pass filtered using zero-phase butterworth filters

(1–20 Hz, 48 dB/octave), and trials were epoched from -50 to +950 ms relative to standard, oddball, and distracter stimulus presentation. Single trials were investigated for signs of artifact and those trials containing voltages of greater magnitude than 100uV were rejected. Mean number of trials per trial condition were 164.6 for the standards, 21.3 for the oddballs, and 19.7 for the distracters and for each condition at least 15 trials were included. EOG artifacts were corrected according to the procedure described by Gratton and Coles (Gratton, Coles, & Donchin, 1983). Baseline removal was accomplished by subtracting the average voltage over the -50 to 0 msec pre-stimulus interval in each trial. ERPs were averaged separately for the standard, oddball, and distracter trials.

Inspection of the global field power for each trial condition was conducted so as to assess the time periods of greatest maximal response to the stimuli (Lehmann & Skrandies, 1980, 1984). This analysis revealed an N1 component with a central distribution peaking at about 110 msec in the oddball and standard trials and at about 125 msec in the distracter trials. All three trial types evoked a P2 with a central distribution peaking at about 225 msec in the standard and target trials and about 250 msec in the distracter trials. Lastly, in the distracter trials a second period of activation after the peak of P2 activity was observed peaking at about 330 msec, which we labeled a P3a in accord with the literature on the passive auditory oddball (Katayama & Polich, 1998); see figures 1a-1c for grand averages). For all components the average activity over the observed component maxima was extracted for channels F3, C3, P3, Fz, Cz, Pz, F4, C4, and P4. Specifically, for the N1 component the average amplitude over the 85-135 msec

poststimulus interval was extracted for the standard and target trials, and the average amplitude over the 100-150 msec poststimulus interval was extracted for the distracters. For the P2 component the average amplitude over the relevant poststimulus intervals were extracted: 175-275 msec for the standards, 200-250 msec for the targets, and 220-280 msec for the distracters. The P3a component was extracted from the average amplitude over the 300-360 msec poststimulus interval to the distracters.

All ERPs were quantitated over the period of their maximal activity in the grand averages for channels F3, C3, P3, Fz, Cz, Pz, F4, C4, and P4 as described above. Amplitude values were then subjected to ANOVA analysis with factors state (meditation vs. thought), lateral location (left, midline, and right), and anterior-posterior (frontal, central, and parietal) location. Significant effects were assessed using Greenhouse-Geisser corrected for repeated measures factors containing three or more levels. Tukey post-hoc analyses were carried out where significant interactions were found so as to assess for significant differences. The criterion level was set to $p < 0.05$.

Stimulus-induced spectral perturbations on theta activity were conducted by applying a Fourier-transform decomposition over the 1-second epochs corresponding to each of the stimulus types in the meditation and thought conditions so as to derive spectral powers for each stimulus type. As the theta power in the 3-4 Hz range was seen to vary comparing meditation to thought conditions the values. ANOVA analysis of the theta power in the epochs following the standard, oddball, and distracter trials with factors stimulus type, state, lateral location and A-P location were conducted with Greenhouse-Geisser corrections for multiple comparisons and Tukey post-hoc analyses

where appropriate.

Results

Psychometrics

The "depth of meditative state" was recorded using a self-report 0-10 scale that participants completed at the end of each of the two experimental conditions. The difference between the reported depth of meditative experience comparing the thought period to the meditation period was 3.2 ± 1.7 (range 0 – 6.6). 7 of the 16 participants self-reported drowsiness during the meditation condition and 10 of the 16 reported drowsiness during the thought condition. There was no correlation between the number of years of daily practice and either the self-reported depth of meditative state or the incidence of reported drowsiness during the meditative or rest states.

Event Related Potentials

N1

The 3 stimuli of the oddball paradigm evoked an N1 component with a frontocentral distribution. Analysis of the N1 amplitude to the standard stimuli (Figures 2a – 2b) indicated no effect of meditation ($p = 0.59$). There was an effect of A-P location ($F(2,30) = 4.64$, $p < 0.05$), with central locations showing greater magnitude than parietal ($p < 0.05$) while a trend effect of lateral location was observed as right and midline areas tended to show greater magnitudes than left ($p = 0.067$). For the target stimuli (Figure 2a-b) again an effect of A-P location was observed ($F(2,30) = 8.47$, $p < 0.01$) reflecting greater amplitudes at frontal and central areas than parietal (both $p < 0.01$). A trend

towards a *state* x *A-P location* interact was observed that missed the $p < 0.05$ criterion level after correction for multiple comparisons ($F(2,30) = 3.37$, G-G adjusted $p = 0.078$). The trend reflected a tendency towards greater N1 amplitudes at frontal sites in the meditation condition.

As the N1 to the standard and oddball stimuli was quite similar in location and latency yet showed some slight differences in location and meditation effects a combined ANOVA analysis on the N1 amplitudes to both stimuli was conducted. This analysis revealed that target N1 amplitudes were greater than standards ($F(1,15) = 12.76$, $p < 0.01$). There was *stimulus type* x *A-P location* effect ($F(2,30) = 4.74$, $p < 0.05$) as the amplitudes to the oddball stimuli were of greater magnitude at frontal ($p < 0.001$) and central ($p < 0.01$) sites but not parietal ($p = 0.68$). The *state* x *A-P location* interaction only approached significance because of correction for multiple comparisons ($F(2,30) = 3.87$, Greenhouse-Geisser adjusted $p = 0.054$). As seen in the analysis of the target N1, the trend was toward N1 amplitudes in meditation being of slightly larger amplitude than thought at frontal sites but of lower amplitude at parietal sites.

The N1 to the distracter peaked at a slightly later latency and was of significantly greater magnitude than the N1 to the standards or oddballs (Figures 4a-c). A main effect for A-P location was again found ($F(2,30) = 8.99$, $p < 0.01$), indicating greater magnitudes at central vs. parietal locations ($p < 0.001$). Interestingly, a *state* x *A-P location* effect was revealed as well ($F(2,30) = 6.91$, $p < 0.05$), indicative of a changed N1 distribution in meditation relative to thought condition (see Figure 4c). In meditation N1 amplitude was greater at central sites than both frontal and parietal sites (both $p <$

0.001), while in the thought state N1 amplitudes were not different comparing frontal and central sites ($p = 0.72$). Instead, in thought, both frontal and central sites demonstrated greater N1 amplitude than parietal areas (both $p < 0.001$). Additionally, there was a trend towards lower N1 amplitudes at frontal sites in meditation ($p = 0.095$) relative to thought.

P2

There was a prominent P2 component to all three stimuli peaking around 250 msec and showing a central scalp distribution (Figures 5a-7b). Analysis of P2 amplitude to the standards revealed no effect of state ($p = 0.66$) and main effects for both A-P location ($F(2,30) = 12.24$, $p < 0.001$) and lateral location ($F(2,30) = 15.89$, $p < 0.001$), consistent with the strong maximal activity seen for frontocentral midline location. Midline sites exhibited greater P2 magnitude than both left ($p < 0.05$) and right ($p < 0.001$) locations, while both frontal ($p < 0.01$) and central ($p < 0.001$) sites yielded greater amplitudes than parietal sites. A significant *lateral* x *A-P location* interaction ($F(4,60) = 4.15$, $p < 0.01$) indicated that at both left and midline areas central sites exhibited greater magnitudes than frontal sites, which in turn exhibited greater magnitudes than parietal sites (all $p < 0.01$). In contrast, on the right side frontal and central sites exhibited equivalent magnitudes, both of which were greater than parietal magnitudes.

Analysis of the P2 component to the oddball stimuli (Figures 6a-b) again revealed main effects for lateral location ($F(2,30) = 10.78$, $p < 0.01$) and A-P location ($F(2,30) = 8.64$, $p < 0.01$) with the same pattern of frontocentral maximum indicated. There was no main effect for state ($p = 0.75$). As with the P2 component to the standard stimuli, a significant lateral location by A-P location interaction was revealed ($F(4,60) = 3.42$, $p <$

0.05), and the same pattern of findings were obtained with regards to location (see preceding explication of *lateral* x *A-P location* interaction for standards) indicating that the scalp distribution to the standards and oddballs was generally equivalent.

The P2 component to the distracter stimuli (Figures 7a-b) was of much greater magnitude than that of the standard or oddball stimuli. In addition, as the grand average scalp maps suggest, a trend towards main effect of dose was found, but it failed to reach statistical significance ($F(1,15) = 3.69$, $p = 0.074$). Main effects for lateral location ($F(2,30) = 20.89$, $p < 0.00001$) and A-P location ($F(2,30) = 10.58$, $p < 0.01$) were strongly significant, as was the *lateral* x *A-P location* interaction ($F(4,60) = 17.89$, $p < 0.00001$). As with the P2 distribution for the standards and oddballs, midline sites exhibited greater magnitudes than left and right locations (both $p < 0.01$). In contrast to the oddball and standard P2 distribution, left locations exhibited greater magnitude than right ($p < 0.05$), an effect that was driven by significance at central and parietal areas (both $p < 0.01$). In similarity to the P2 distribution for the standards and oddballs, at frontal locations midline, left, and right locations were equivalent in magnitude. Central sites exhibited greater magnitude than both frontal and parietal ($p < 0.001$) in contrast with the equivalent amplitudes at frontal and central locations for the standards and oddballs.

P3a

The standard and oddball stimuli did not appear to evoke an identifiable P3-like component but the distracter stimuli did. As shown in figures 8a-c, a P3a component in the 300 – 360 msec time range a small but identifiable positivity with a characteristic

centroparietal distribution was evoked to the distracter stimuli. ANOVA analysis of this P3a component indicated a main effect of state ($F(1,15) = 5.61$, $p < 0.05$) and a *state* x *lateral location* interaction that approached significance after corrections for multiple comparisons ($F(2,30) = 3.47$, G-G adjusted $p = 0.057$). The main effect of state indicated that in meditation, there was a smaller amplitude P3a component evoked relative to the thought condition (see figure 8d). The borderline significant interaction between state and lateral location was due to a trend level elevation of midline amplitudes over right amplitudes only in the thought condition.

Induced theta activity

Analysis of the spectral decomposition of the standard, oddball, and distracter trials indicated that processing of the stimuli had an effect on frontocentral theta power. The distracter stimuli seemed in particular to increase the theta power at frontocentral locations. Figures 9a and 9b show grand average difference scalp maps for the distracter minus standard conditions in the 3-4 Hz theta frequency range. ANOVA analysis of the theta power in the epochs following the standard, oddball, and distracter trials with factors stimulus type, state, lateral location and A-P location revealed significant main effects for all four factors. The highly significant main effect for stimulus type ($F(2,30) = 58.63$, $p < 0.00001$) indicated that the distracter stimuli evoked greater theta power than either the standard or oddball stimuli (both $p < 0.001$). The main effect of A-P location ($F(2,30) = 9.73$, $p < 0.01$) indicated that central areas exhibited greater theta power than parietal areas ($p < 0.001$). Frontal sites evidenced a trend for greater power than parietal ($p = 0.053$), while the difference between frontal and central was not significantly

different ($p = 0.14$). The main effect of lateral location ($F(2,30) = 48.17$, $p < 0.00001$) indicated that central sites exhibited far greater power than left or right locations (both $p < 0.001$). The main effect of state ($F(1,15) = 12.91$, $p < 0.01$) indicated that theta power was reduced in meditation relative to thought conditions.

A significant interaction between stimulus type and state ($F(2,30) = 8.71$, $p < 0.01$) indicated that there was no meditation-related difference in theta power in the standard epochs ($p = 0.44$), but a significantly decreased theta power in both the oddball ($p < 0.01$) and distracter ($p < 0.001$) epochs. A significant triple interaction between stimulus type, state, and lateral location ($F(4,60) = 3.43$, $p < 0.05$) yielded insight into the locus of significant effects for meditation in the three stimulus conditions. Comparing between stimulus types for the meditation state revealed that while the distracter condition increased theta power relative to both the standard and oddball stimuli (all $p < 0.001$), there was no significant difference between oddball and standard stimuli theta power ($p > 0.9$). In contrast, in the thought state there was again increased power at all locations for the distracter relative to both the oddball and standard stimuli and, in addition, a significant increase in theta power for the oddball stimuli relative to the standard stimuli (all $p < 0.001$).

A significant triple interaction between stimulus type, A-P location, and lateral location ($F(8,120) = 11.82$, $p < 0.0001$) indicated that in the standard and oddball trials there was a significantly greater theta power at the midline sites than the left and right sites only for central and parietal areas (all $p < 0.001$) and that no differences were seen between left and right theta power (all $p > 0.9$). In contrast, in the post-distracter period

theta power was greater for midline areas over both left and right areas at central, parietal, as well as frontal leads ($p < 0.001$ in all cases) indicating an engagement of the more frontal component of the frontal midline theta power to this class of stimulus.

Correlations

No significant correlations were found when using the reported measure of the difference in meditative depth between thought and meditation sessions as a covariate for the findings with regards to P3a or theta effects. There was, however, a significant interaction between whether the subjects self reported drowsiness during their meditative session. 7 subjects reported some drowsiness and 9 subjects did not. An interaction between drowsiness during meditation and state was observed in an ANOVA analysis of the P3a amplitude data using drowsiness as a covariate ($F(1,14) = 4.71$, $p < 0.05$). As shown in figure 8c, the interaction was due to the fact that a significant reduction in P3a amplitude was only observed for those subjects not reporting drowsiness during their meditation session ($p < 0.05$), but not for the group who did report drowsiness ($p = 0.99$).

When assessing the theta reduction, including the covariate length of daily meditation practice yielded a significant interaction. Ten of the subjects had meditated on a daily basis for over 10 years (19.3 ± 8.5) where as the remaining six had been meditating on a daily basis for only a few years (2.5 ± 1.4). When including this factor in the analysis of the theta power to the distracter stimuli an interaction was observed with the *state* x *A-P location* effect on theta power ($(2,28) = 6.54$, $p < 0.05$, see figure 9d). While there was no difference in theta power between the two groups at any of the

channels in either the meditation or thought conditions, the two groups did evidence a different topographical distribution of the significant theta difference between states. In the meditators with over 10 years daily practice significant decreases in theta power to the distracter in meditation were observed at frontal ($p < 0.01$) and central ($p < 0.01$) sites. In the shorter-term meditators the difference was significant at central ($p < 0.001$) and parietal ($p < 0.01$) sites. Further, in the longer-term meditators in the thought condition theta powers at frontal and central sites were equal in amplitude and both greater than parietal sites (both $p < 0.001$) while in meditation the only significant difference was seen in central over parietal sites ($p < 0.01$). In contrast, the shorter term meditators in the thought condition demonstrated greater theta power at central than both frontal ($p < 0.001$) and parietal ($p < 0.01$) sites and in the meditation condition the same pattern was observed but with only borderline significance (central over frontal, $p < 0.05$; central over parietal, $p = 0.06$). Thus a pattern of more specifically frontal decreases in theta power to the distracter stimuli was observed in the longer term meditators.

In order to assess whether the theta effects - differing between states and stimulus classes as shown above - was strongly related to P2/P3a amplitudes, correlational analysis between theta power in response to the 3 stimulus classes at Fz, Cz, and Pz and the P2 and P3a amplitudes to the stimuli in both thought and meditation states were conducted. There were no strong associations observed. Looking at the data from the thought condition, all correlational analyses between theta power and both P2 and P3a amplitude at Fz, Cz, and Pz yielded r values less that 0.2 and p values greater than 0.5. In contrast, in the meditation data there were some correlations and trends between theta

power and P2/P3a amplitude. Specifically, during the distracter trials Cz theta power was positively correlated at trend levels with both P2 amplitude ($r = 0.46$, $p = 0.076$) and P3a amplitude ($r = 0.45$, $p = 0.077$) while at Pz theta power was positively correlated with P2 amplitude ($r = 0.50$, $p = 0.047$) and with P3a amplitude at trend levels ($r = 0.44$, $p = 0.090$). There were no significant trends or correlations between P2 amplitude and theta power during the target or standard trials.

Discussion

This pattern of meditation-induced alterations in the event-related potentials and theta power during the auditory oddball paradigm is suggestive of altered sensory processing during Vipassana meditation relative to the thinking control state. The Vipassana practice that the participants employed involves the adoption of a mindful and receptive state, focused on awareness of present moment sensations in the body while allowing any thoughts to arise and pass away without cognitive engagement. In contrast to this mindfulness-based approach, one might hypothesize that a more concentrative form of meditative practice would yield even more significant changes on the evoked potentials given the strong focus in those forms of practice on engaging in the narrowing of attentional focus, possibly removing the attentional systems even further from the immediate sensory surround (Cahn & Polich, 2006).

The choice of a control task in the study of meditation is a difficult one and previous investigations have not attempted to assay comparative brain measures during a control vs. meditation period of equal length (Cahn & Polich, 2006); the current study

employed the instruction to participants to keep their mind engaged with recollective processes during the control thought period . Even with the explicit instruction to keep their mind engaged in the process of thinking a significant number of the subjects reported difficulty in avoiding the automatic engagement in their meditative practice and some reported reaching the same depth of meditative state in the thought and meditation session due to the combined challenge of meditating as usual in the experimental room with the uncomfortable electrode cap and earphones and the attempt to not meditate during the thinking session.

Despite these challenges, there was an average difference in reported meditative depth of 3.2 (out of 10) and significant neurophysiologic effects differentiating meditation from the thought condition were observed. At the neurophysiologic level, there was a trend towards enhanced early sensory processing of the oddball stimuli as indexed by a trend towards enhanced N1 amplitudes at frontal sites during meditation. In contrast, for the distracter stimulus which evoked the strongest brain response, there was a trend towards decreased N1 amplitudes at frontal sites during meditation as well as significant reductions in the amplitude of the P2 and P3a components. There was also a robust decrease in the amplitude of frontal theta induction to both the deviant oddball stimulus and the distracter stimulus. Given the known involvement of frontal cortex and attentional systems in the generation of the P3a (Polich, 2003), it seems likely that these observed effects were due to a disengagement of the attentional networks to external sensory stimulation.

Looking at the response to the auditory stimuli from the earliest manifestations

onward we see that the N1 response to the auditory stimuli of this paradigm was greatest in amplitude to the distracter stimuli, but was also somewhat increased in amplitude to the oddball stimuli. Furthermore, the N1 component did not differ between meditation and thought for the standard stimuli. The N1 to the oddball stimuli showed a trend level increase in frontal component amplitude in meditation, whereas the N1 to the distracter stimuli revealed the opposite trend towards a decreased N1 component amplitude in frontal locations during meditation. Furthermore, in meditation the N1 distribution revealed central sites with greater magnitude than both frontal and parietal sites whereas in thought the N1 distribution showed greater magnitude of both frontal and central sites over parietal sites. In sum, we see here a pattern that indicates that in the meditation condition there may have been some slight sensitizing of the early auditory processing of oddball stimuli while at the same time a decreased engagement of frontal areas in the early processing of the distracter stimuli.

The P2 component showed no variation with meditation for either the standards or the oddballs but a trend towards a decrease in amplitude to the distracter stimuli ($p = 0.074$). The P3a component was only present in response to the distracter stimulus and was reduced in meditation relative to thinking conditions.

The theta power described in this study showed greater amplitude to the distracter stimuli than the standard or oddball stimuli. Further, there was a more frontal midline theta distribution to the distracter stimuli than the standard and targets. Additionally, there was a main effect of meditation indicative of decreased theta power in the meditative condition. Post-hoc analysis revealed that there was no difference in theta

power to the standards but there was a significantly reduced theta power to both the oddball and distracter stimuli in meditation, indicating that the effect of meditation was to decrease the engagement of the neural circuitry responsible for increasing this theta power in response to deviant unexpected stimuli.

Assessment of the relationship between the observed meditation-induced neurophysiologic changes and psychometric measures showed no correlation between self-reported experienced meditative depth and any of the brain measures. It may be that a more sophisticated measure of experienced altered state, assessing some of the core dimensions of meditative experience, would have showed greater correlation with the alterations. One self-reported experiential measure that did prove to be a significant co-variate of the meditation-induced decrease in P3a component amplitude was the experience of drowsiness during the meditation session. Those individuals experiencing drowsiness during meditation did not contribute to the observed decrease in P3a amplitude, and instead the significance of the effect was driven by those individuals who reported experiencing no drowsiness during their meditative state. Had the decrease in P3a amplitude been driven by changes during the meditative state associated with a shift towards a reduction in vigilance and attentiveness as observed with the onset of sleep, the opposite pattern would have been obtained. Given that the meditators who did not experience drowsiness contributed most to the observed decrease in P3a to the distracter it thus appears that it is the active engagement and attentional upregulation associated with the meditative state that was responsible for these effects.

The pattern of correlations with the observed theta effects may shed some light on

their significance. The participants were separated into two groups based on those who had been meditating every day for 10 years or more (10 of the 16 participants) and those who had not (all of whom had been meditating daily for 4 years or less). When membership in the daily meditation for 10 years or more group was used as a co-variate in the ANOVA analysis of the theta power to the distracter stimuli a significant interaction between long-term daily meditator status, state, and location revealed that the longer-term meditators showed more of their meditation-induced decreases in frontal locations as opposed to parietal locations. For example, in response to the distracter stimuli the meditators with greater than 10 years of daily meditation practice showed greater theta power in the rest state than the meditation state at frontal, central, and parietal electrodes whereas those with under 4 years daily meditation practice only showed significant effects at central and parietal electrodes. This suggests that greater number of hours of meditative practice leads to further disengagement of the frontal contribution of the theta effect due to distracting stimuli. Lastly, the theta power values were not correlated to the P2 or P3a amplitudes during the thought condition, but a pattern of significant to near-significant correlations was found for the correlations during the meditation condition.

In looking at the distracter stimulus, where the main effects of meditation were found, the pattern of ERP findings is first an alteration in the scalp map of the N1 to a less frontal distribution, second a trend reduction in P2 amplitude and finally a significant reduction of the P3a component. This series of altered potentials is consistent with a decreased involvement of frontal cortex in the response to these stimuli. In this context it

is also interesting to note that there was an almost significant trend towards increased N1 amplitude to the oddball stimuli especially in frontal areas ($p = 0.054$). The fact that this trend stands in opposition to the finding with regards to the N1 distribution to the distracter provides some insight into the altered state of processing induced by the meditation; as opposed to a general blocking of sensory processing it seems that meditation damps down processing of the aversive stimulus by disengaging some of the frontal response seen in the thought state.

Previous findings on theta power in meditation have assessed spontaneous EEG finding increases in theta power during meditative practice as both trait and state effects (Aftanas & Golocheikine, 2001; Elson, Hauri, & Cunis, 1977; Hebert & Lehmann, 1977). The neural substrate responsible for concentration-related frontal theta effects include the anterior cingulated and other medial prefrontal cortical areas (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999). Mindfulness-based practices such as Vipassana meditation have not yet been shown to induce such theta effects in studies of spontaneous EEG, but a recent fMRI study has shown that expert Vipassana meditators tend to engage the medial prefrontal cortex (MPFC) and rostral anterior cingulate (rACC) during meditation to a greater extent than novice meditators, consistent with a possible increased theta power state effect (Hölzel et al., 2007).

The findings reported here are indicative of a decreased theta power induction by unexpected and distracting stimuli during meditation. These findings imply that the Vipassana meditative state may induce a pattern of brain activity rendering the frontal attentional circuits less responsive to both deviant unexpected and aversive stimuli.

Integrating this finding with the recent fMRI findings of increased activity in MPFC and rACC in expert Vipassana meditators leads to a view that this form of meditation may upregulate the frontal attentional network in a manner wherein sensory input in the immediate surround recruits fewer attentional resources.

These findings are also consistent with the recent finding that after an extensive 3-month Vipassana meditation retreat experienced meditators showed a decreased P3 amplitude to the T1 stimulus in an attentional blink paradigm, which was associated with behavioral measures indicating that the meditation intervention decreased the attentional disengagement induced by T1 processing (Slagter et al., 2007). In both cases, Vipassana meditation is seen to mediate a decrease in the automatic recruitment of attentional resources in a context where such recruitment is not expedient for the task at hand, in one case the continued focus on the meditative state and in the other the preparation to perceive the second target of the attentional blink paradigm. The finding that Vipassana meditation may lead to a decrease of cortical thinning in prefrontal and insular areas (Lazar et al., 2005) may be related to these attention-related findings, indicating that while measures of involuntary attentional capture are decreased by Vipassana, long-term measures of enhanced attentional engagement with interoceptive processes are increased.

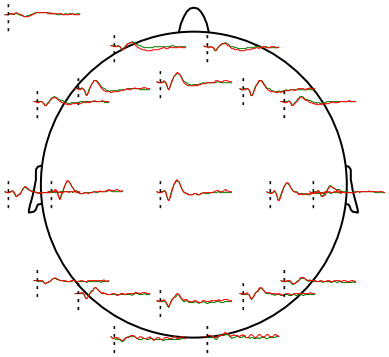
The finding that correlations between the P2 and P3a amplitudes to the distracters and theta power were moderately significant in the meditation state but not the thought state must be interpreted within the context of the overall decrease in all of these measures during meditation. The significance is unclear but may be related to a greater quiescence in the meditative brain state allowing for these subtle correlations to be more

readily expressed in the association that has previously been observed (Demiralp, Ademoglu, Comerchero, & Polich, 2001).

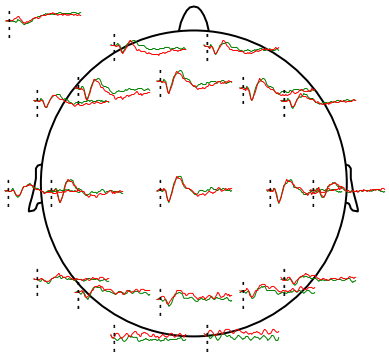
The data presented herein supports the notion that Vipassana meditation does have significant effects on the attentional systems of the brain. In a within-subject study assessing state effects of Vipassana meditation specific to mental engagement in meditative concentration a decrease in P3a amplitude to distracting stimuli in concert with a selective reduction in theta power induction to both deviant and aversive stimuli has been demonstrated. The P3a effect was shown to be driven by those subjects who did not experience drowsiness during the meditative session, reinforcing the notion that it is the active mental engagement with meditation that leads to this decrement. It would be of interest to apply a similar paradigm and analysis with meditators practicing more concentrative forms of meditation such as mantra or visualization-based methods. The relative effects on ERP component amplitudes and distracter-related theta induction would give insight into the difference between these two major forms of meditative practice and lead to hypotheses as to what kinds of brain changes are induced by the concentrative vs. open-awareness practices.

Chapter 2, in part, is in preparation for submission for publication with John Polich as co-author. The dissertation author is the primary investigator and author of this paper.

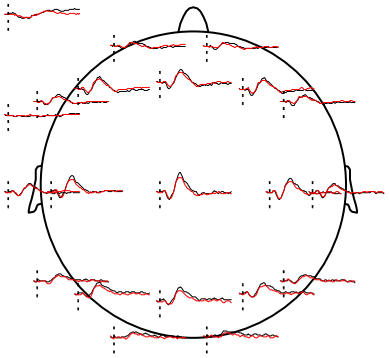
1a.



1b.

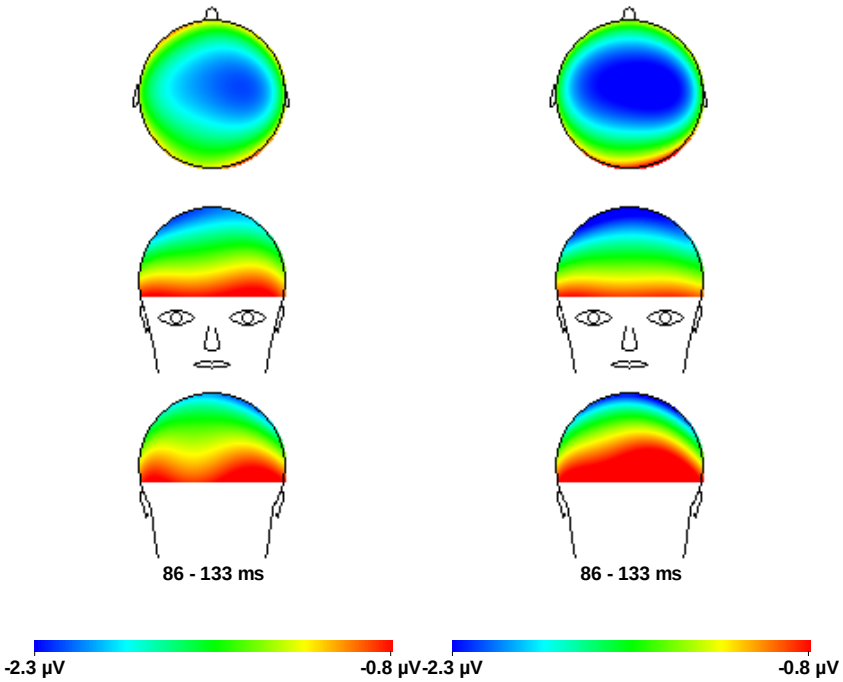


1c.



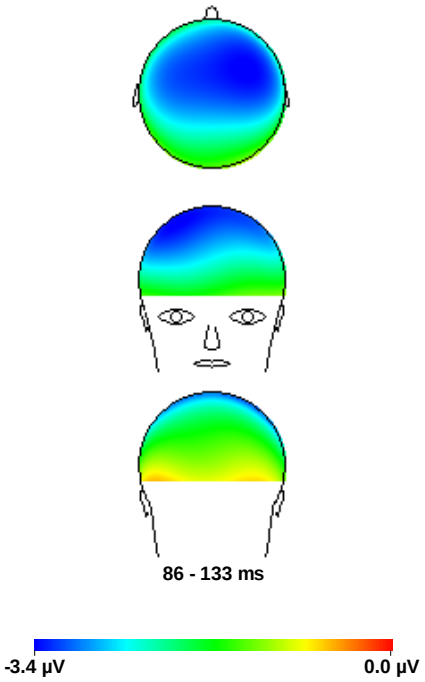
Chapter 2 Figure 1 legend. Grand average waveforms for the Standard, Target and Distracter trials. Dark green traces indicate thought condition, red traces indicate meditation condition, and the VEOG channel is indicated in the upper left quadrant. Figure 1a, waveform to Standards; 1b, waveforms to Targets; 1c, waveforms to Distracters.

2a. 2b.

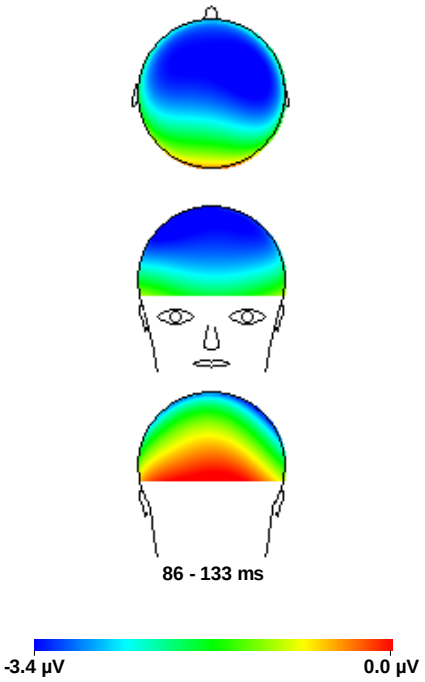


Chapter 2 Figure 2 legend. Scalp map of N1 component amplitudes to Standard Stimuli; 2a, in Thought condition, 2b, in Meditation condition.

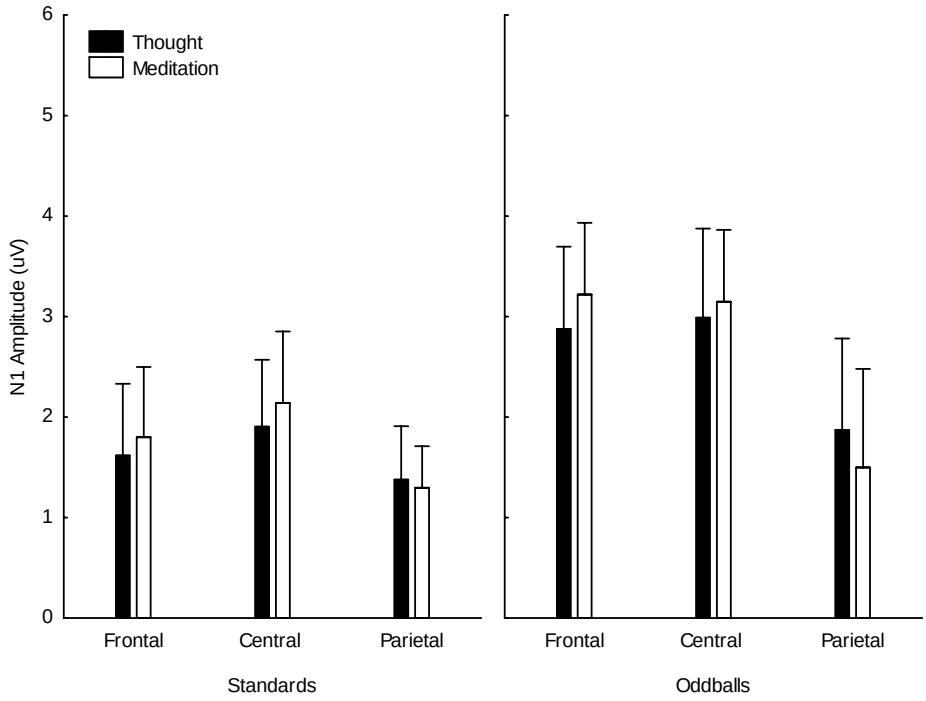
3a.



3b.

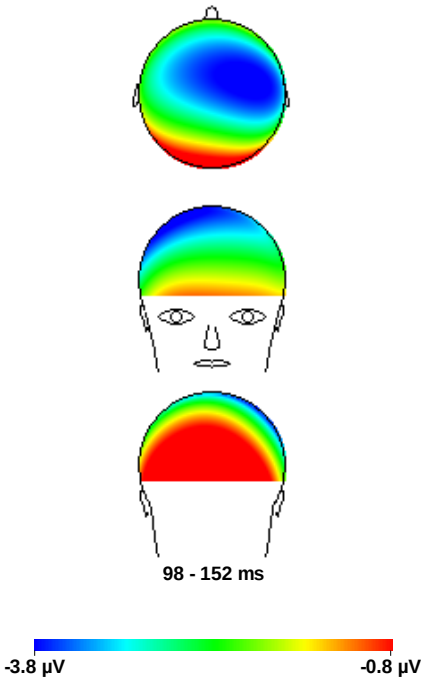


3c.

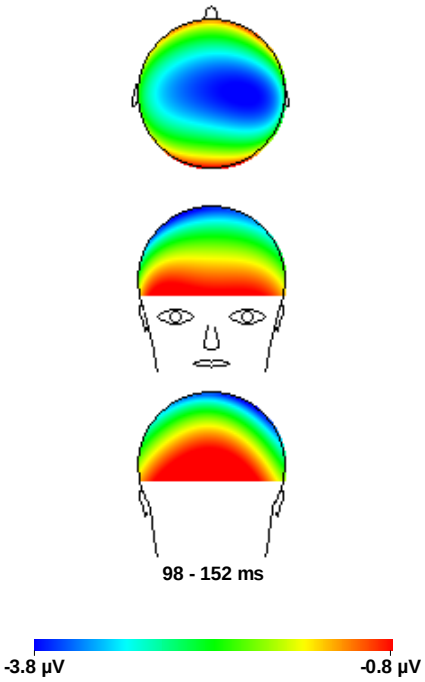


Chapter 2 Figure 3 legend. N1 amplitudes to Oddball Stimuli. 3a, Scalp map of N1 in Thought condition; 3b, Scalp map of N1 in Meditation condition; 3c, ANOVA of N1 amplitudes to Standards and Oddballs in Thought versus Meditation conditions.

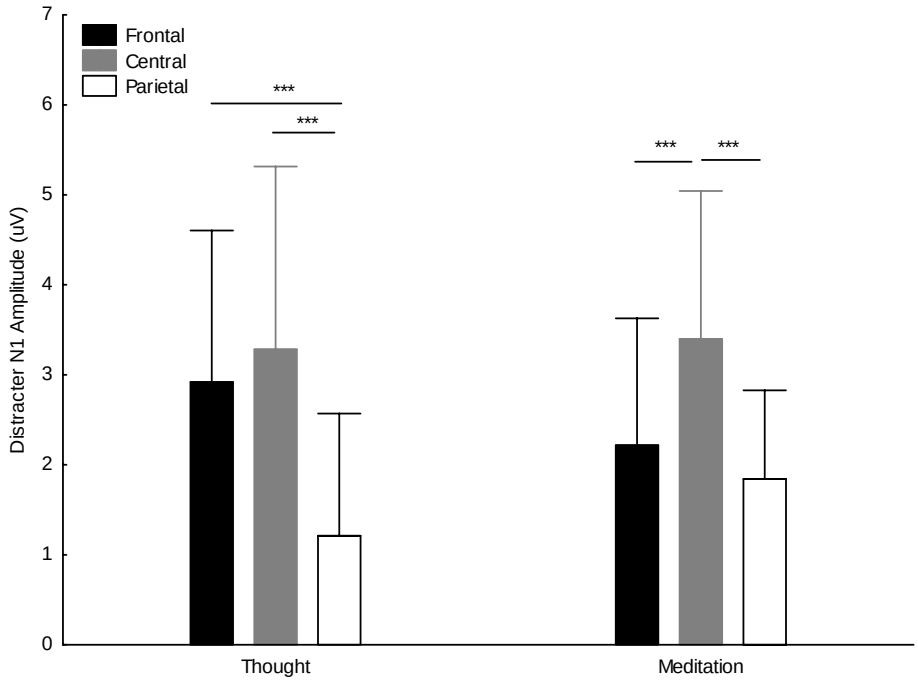
4a.



4b.

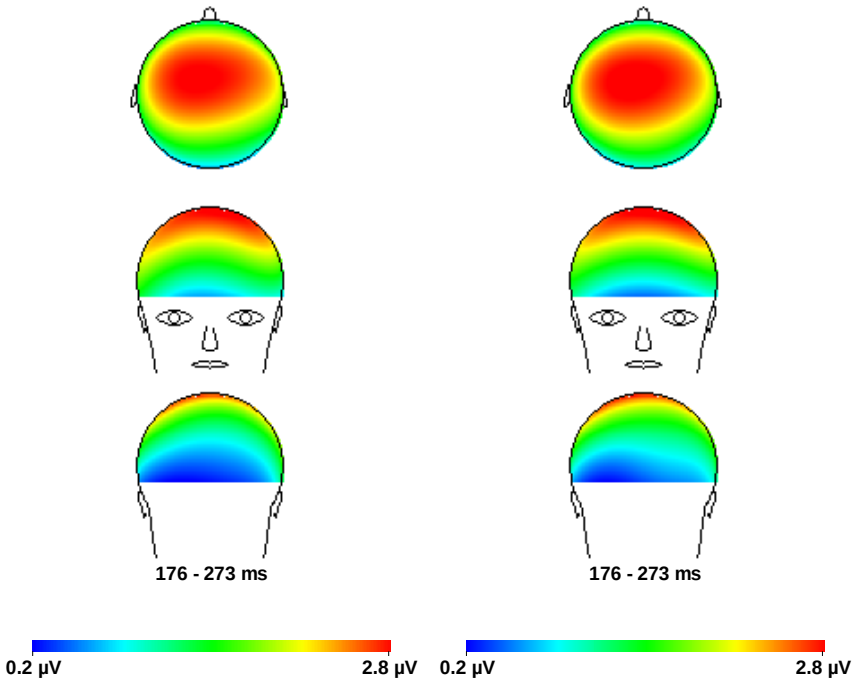


4c.



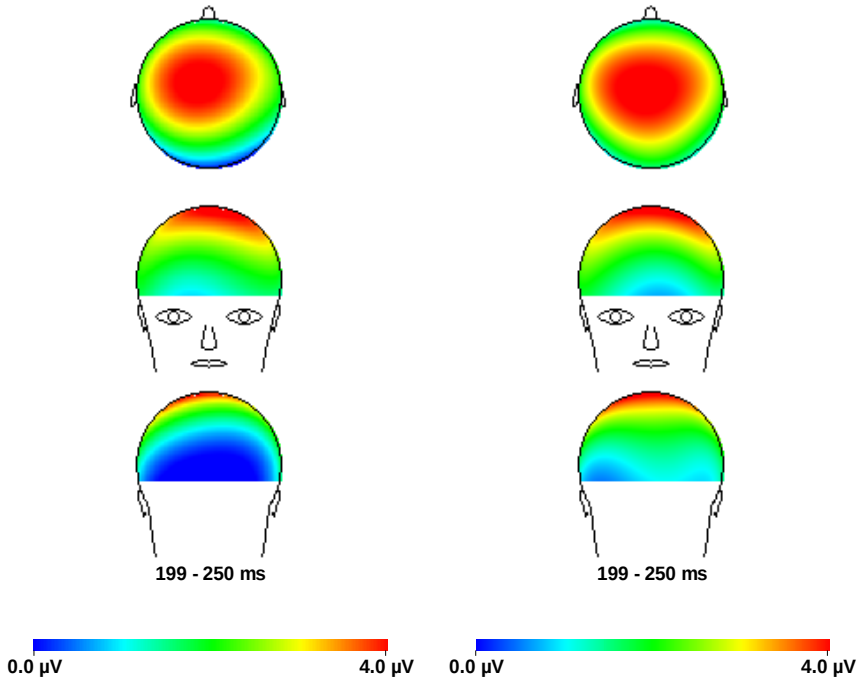
Chapter 2 Figure 4 legend. N1 amplitudes to Distracter Stimuli; 4a, Scalp map of N1 in Thought condition; 4b, Scalp map of N1 in Meditation condition; 4c, N1 amplitudes in Thought versus Meditation Conditions.

5a. 5b.



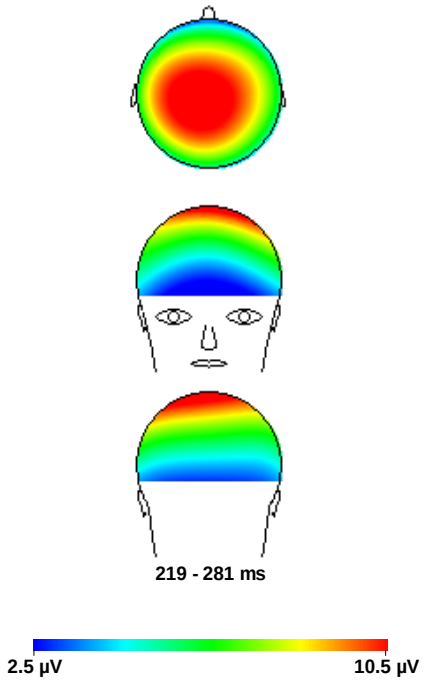
Chapter 2 Figure 5 legend. Scalp map of P2 amplitude to Standard Stimuli; 5a, in Thought condition; 5b, in Meditation condition.

6a. 6b.

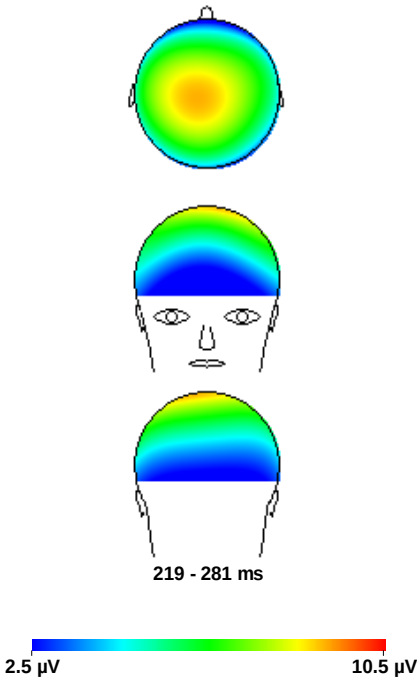


Chapter 2 Figure 6 legend. Scalp map of P2 amplitude to Oddball Stimuli; 6a, in Thought condition; 6b, in Meditation condition.

7a.

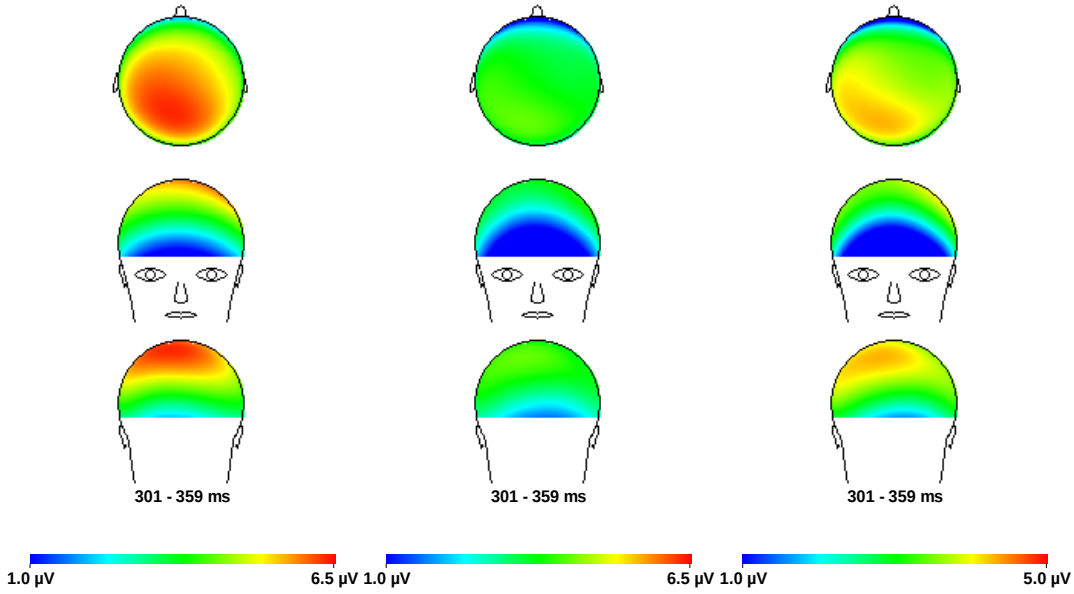


7b.

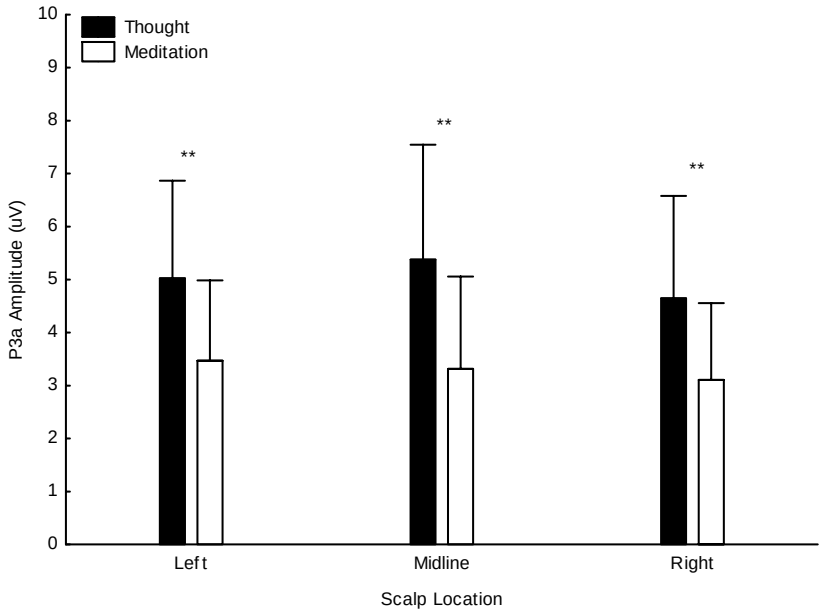


Chapter 2 Figure 7 legend. Scalp map of P2 amplitude to Distracter Stimuli; 7a, in Thought condition; 7b, in Meditation condition.

8a. 8b. 8c.

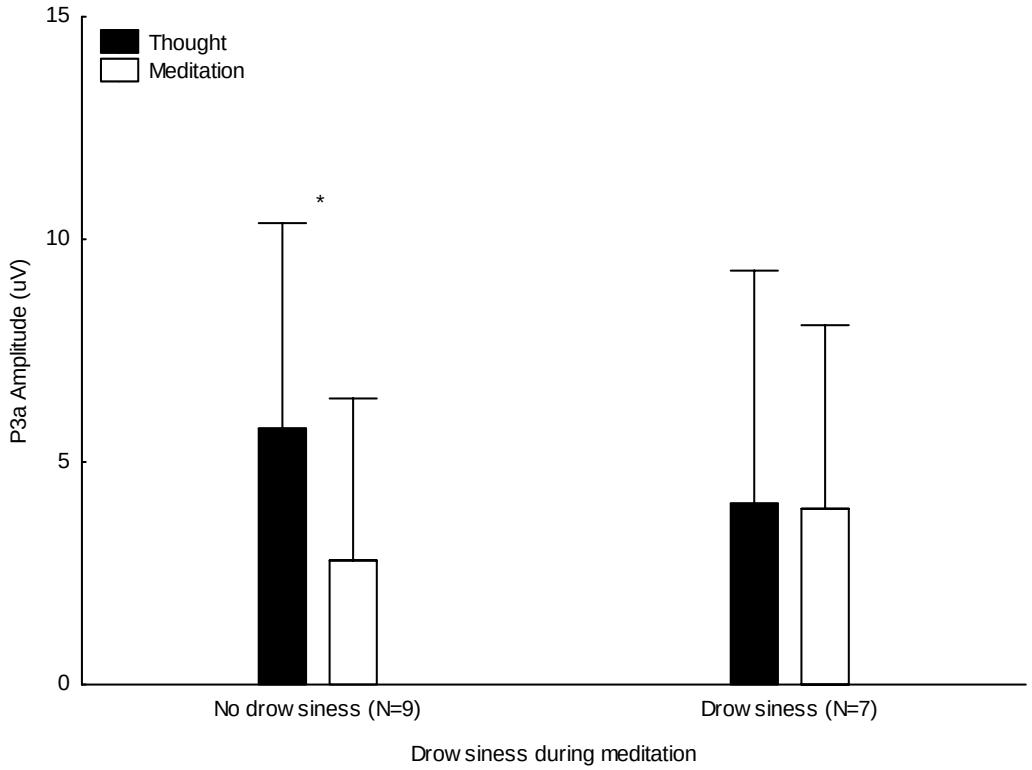


8d.



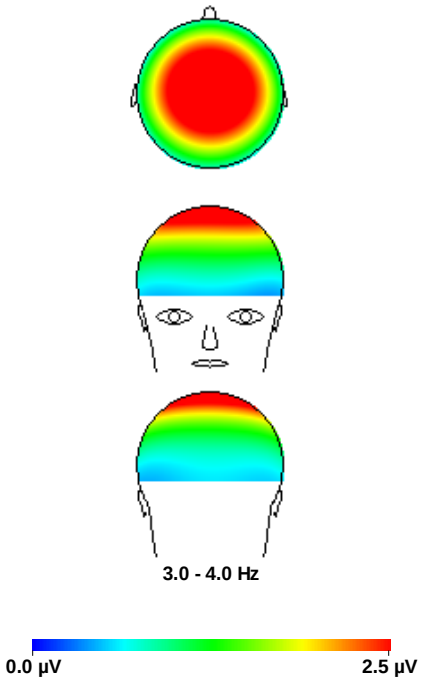
Chapter 2 Figure 8 legend. P3a component amplitudes to Distracter Stimuli; 8a, in Thought condition; 8b, in Meditation condition; 8c, same as 8b except scaling; 8d, P3a amplitude in Thought versus Meditation Conditions; 8e, Interaction between reported drowsiness during meditation and P3a reduction.

8e.

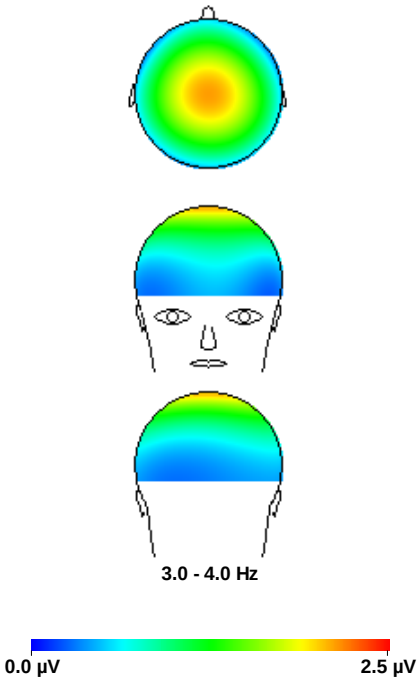


Chapter 2 Figure 8 continued. 8e, Interaction between reported drowsiness during meditation and P3a reduction.

9a.

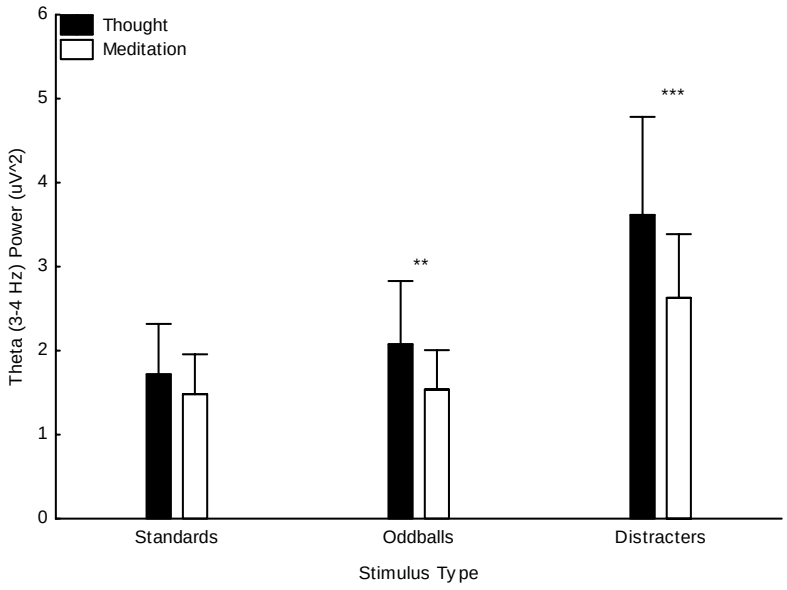


9b.

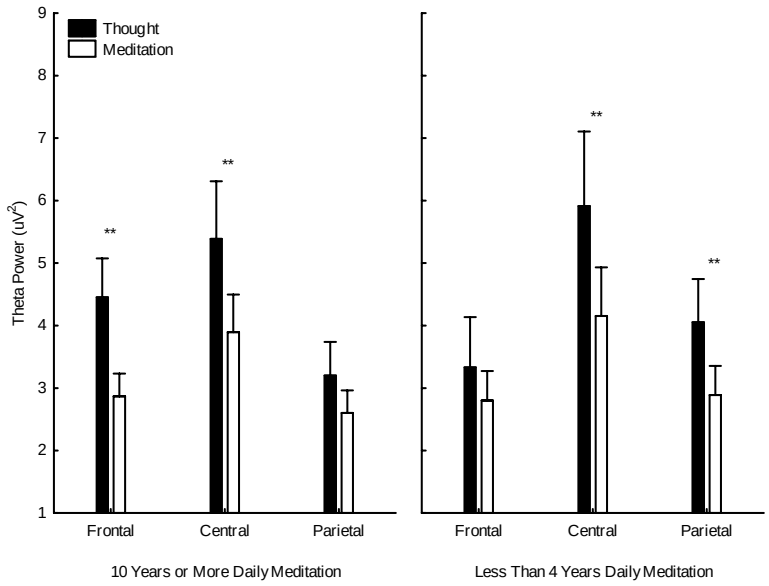


Chapter 2 Figure 9 legend. Distracter-Induced Frontocentral Theta Power. 9a, Normalized (Post-Distracter – Post-Standard) theta power in Thought condition; 9b, Normalized theta power in meditation condition; 9c, Frontal Theta Power In Thought versus Meditation Conditions; 9d, Relationship between frontal theta power and length of daily meditation practice.

9c.

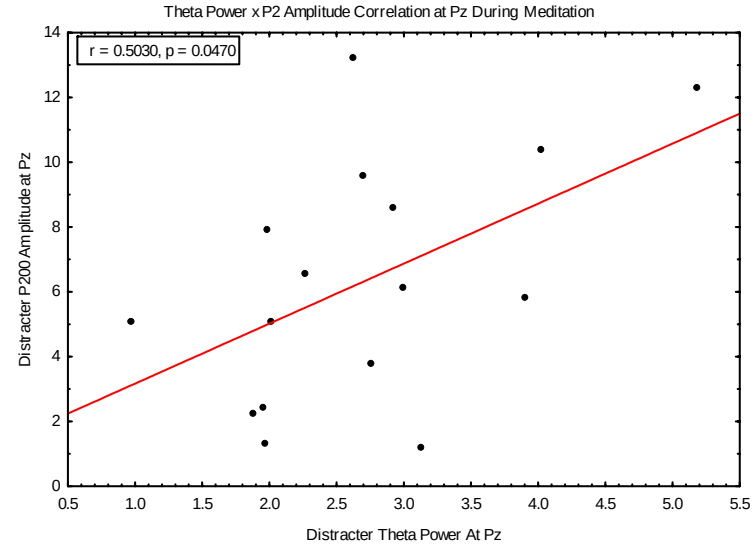


9d.



Chapter 2 Figure 9 continued. 9c, Frontal Theta Power In Thought versus Meditation Conditions; 9d, Relationship between frontal theta power and length of daily meditation practice.

10a.



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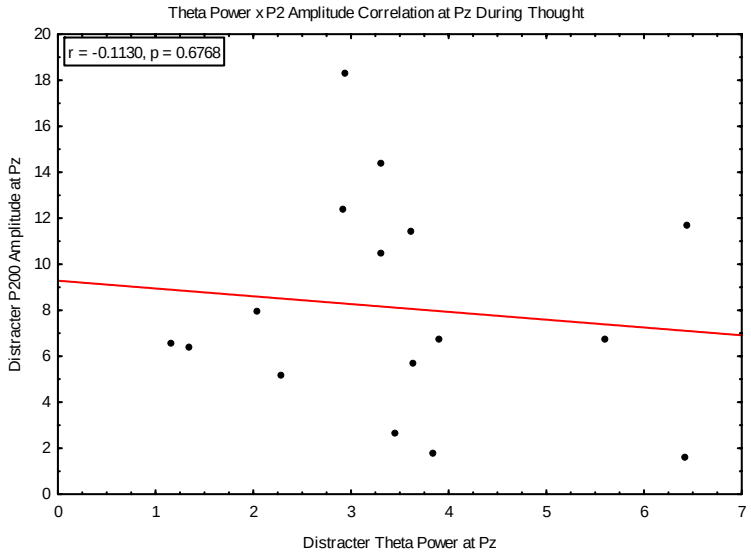
10b.



Chapter 2 Figure 10 legend. Correlation between 3-4 Hz theta power and P2 amplitude to the distracter stimuli; 10a, correlation in Meditation condition; 10b, correlation in thought condition.

CHAPTER 3

5HT1a/2a agonist psilocybin causes increased early visual processing but decreased later cognitive processing: An event-related potential study of the visual oddball paradigm

Abstract

Psilocybin, a 5HT1a/2a agonist, causes an altered state of consciousness marked by visual hallucinations, alterations in the experience of time and space, altered experience of self and a range of symptoms with possible relevance to schizophrenia. The visual oddball paradigm provides a good test of the cognitive system, assessing parameters of visual perception as well as cognitive functions including working memory, context updating, and focal attention. We demonstrate that psilocybin causes increased early visual cortex activity as assessed by P1 component amplitude, especially to distracter stimuli. Despite the initial increase in visual processing later event-related potentials including the N1, P3a, and P3b are significantly reduced in amplitude. Frontal theta power, normally potently induced by distracter stimuli, is also shown to be strongly reduced by psilocybin. An association between the reduction of P3 amplitude and the induced alterations in visual experience suggests a role for alterations to the neural substrate of the visual P3 contributing to the altered visual processing induced by hallucinogens.

Introduction

Previous work with hallucinogens has suggested the possible relevance of hallucinogen-induced brain alterations to the study of psychosis and/or schizophrenia (Gouzoulis-Mayfrank et al., 1998; Vollenweider, 1998; Vollenweider & Geyer, 2001b). Some of the similarities previously explicated have focused on the subjective experience, where similarities such as altered sense of self and experience of boundaries to self as well as illusions, delusions, and formal thought disorder have been noted. In addition, distinct differences including the tendency for more insight or metaconsciousness regarding the altered state are often present in the awareness of people experiencing brain states influenced by the altered neurotransmission evoked by hallucinogens. This is the first study to assess the alterations in the brain processing of a target detection paradigm induced by hallucinogens in humans. We employ a visual oddball paradigm with the inclusion of both rare targets and distracters so as to elicit the standard P1 and N1 event-related sensory potentials as well as both P3a (to the distracter) and P3b (to the target) components.

The endogenous activity of the serotonin system has been shown to be dominated by the spontaneous firing of serotonergic neurons within the dorsal raphe. These neurons have been shown to be tonically active during wakefulness and decreased in activity during sleep stages, becoming virtually silent in REM sleep. Interestingly, it has also been shown in animal models that the serotonergic neurons of the dorsal raphe also decrease in firing rate at times of attentional orienting (B. L. Jacobs & Fornal, 1991; B. L. Jacobs, Wilkinson, & Fornal, 1990). Given that psilocybin is a 5HT-2a agonist

interacting with postsynaptic serotonin receptors responding to these dorsal raphe neurons it is reasonable to assume that it might interfere with attentional orienting.

Previously it has been found that attentional mechanisms are impaired by psilocybin and related serotonergic hallucinogens. Gouzoulis-Mayfrank et al. have reported psilocybin induced inhibition of visual attention-related functions that mimic the findings observed in schizophrenia including inhibition of return and covert attentional orienting (Gouzoulis-Mayfrank et al., 2006; Gouzoulis-Mayfrank et al., 2002). Carter, et al. (Carter et al., 2004) reported that psilocybin inhibited high-level but not low-level motion perception, inferring that the lack of psilocybin effect on local motion thresholds may indicate that the visual disturbances and hallucinations associated with this drug are not likely to reflect changes either at the retinal level or in the transfer of information from the retina through the lateral geniculate nucleus (LGN) to primary visual cortex.

Recent studies have noted decreased amplitudes of the early visual evoked potentials P1 and N1 (Campanella, 2006; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005) in schizophrenia, although there is still not a consensus regarding these effects. Moreover, the P3 potential has been shown to be deficient in schizophrenics for auditory stimuli, but not reliably so for visual stimuli (Ford, 1999; Ford, White, Lim, & Pfefferbaum, 1994; Muller, Kalus, & Strik, 2001). Both auditory and visual P3 amplitudes have additionally been shown to correlate inversely with both negative and positive symptoms in schizophrenia, (Ford, Mathalon, Kalba, Marsh, & Pfefferbaum, 2001; Ford et al., 1999; Mathalon, Ford, & Pfefferbaum, 2000; Papageorgiou et al., 2004). Given the lack of consistent visual P3 amplitude decrements in schizophrenia, but

demonstrations of inverse relationship between symptoms of schizophrenia and visual P3 amplitude it is hard to make predictions regarding the likely effect of hallucinogens on this variable.

Methods

18 healthy right-handed subjects (age 27.6 +/- 3.4 y.o., 8 males) were recruited through advertisement at a local University. The screening procedure involved a thorough physical examination by a licensed medical doctor including EKG, hematogram and detailed clinical-chemical blood analysis. The DIA-X diagnostic expert system (Wittchen and Pfister, 1997) was used to assess present or antecedent psychiatric disorders. Major psychiatric conditions in first degree relatives, as revealed in the explorative clinical interview, were used as exclusion criteria as was personal history of drug abuse. The screening procedure was supplemented by standard psychometric instruments (Freiburg Personality Inventory FPI (Fahrenberg et al., 1984) and Hopkins Symptom Checklist SCL-90 (Derogatis, Rickels, & Rock, 1976)). Since the personality trait factors “rigidity” and “emotional lability” as revealed in these questionnaires were identified to be predictors of negative experiences during ASC (Dittrich, 1994), scores exceeding two standard deviations from the mean value of normative data in the respective subscales of the FPI (i.e., “openness” and “neuroticism”) were used as exclusion criteria. After being informed by written and oral description of the aims, procedures and associated possible risks of the study, all volunteers gave their written consent as requirement for participation.

On three experimental days separated from each other by two weeks or more the subjects came to the lab at 9 am and confirmed they had not eaten breakfast or taken caffeine that morning. The subjects were then given pills with either placebo, 125 ug/kg psilocybin, or 250 ug/kg psilocybin and a protein drink. Neither the subjects nor the experimenters knew the content of the pills. After 40 minutes of unstructured time in a spacious room at the clinic, the subjects were brought to an EEG room and a headcap with 64 active electrodes (Biosemi) was applied (see EEG data acquisition below for more details). Spontaneous EEG data was recorded starting at 80 minutes post-ingestion of drug (this data will be presented elsewhere). Starting at 110 min post-drug ingestion a visual oddball stimulus paradigm was begun. The distance from the subject's eyes to a 17" Sony Multiscan computer monitor was set to 1 meter.

During the paradigm a white 4mm x 4mm fixation cross was kept constant in the middle of a black screen between presentations of three types of stimuli: standard, target, and distracter. The standard stimulus was a blue circle of 4.1 cm diameter, the target stimulus was a blue circle with 3.4 cm diameter (17% decrease in diameter compared to the standard), and the distracter was a black-and-white checkerboard of 4.2 cm on each side. A total of 255 stimuli were shown in one continuous block which included 40 targets (15.7%) and 40 distracters (15.7%) pseudo-randomly distributed. Each stimulus remained on screen for about 75 msec and the interstimulus interval was set to 1800 msec. Subjects were asked to respond as quickly as possible to the target stimuli with a button-press of their right (dominant) forefinger and otherwise to refrain from responding. Prior to ingestion of the pills on the first experimental day, subjects were

given a practice session composed of 40 stimuli to ensure detectability of the target stimulus as well as familiarity with the paradigm and the recording situation,

Altered State of Consciousness Quantification

The Altered States of Consciousness rating scale 5D-ASC (A. Dittrich, 1998; A. Dittrich, von Arx, S., Staub, S., 1985) consists of 94 items that are visual-analogue scales of 10 cm length. These items measure alterations in mood, perception, experience of self in relation to environment, and thought disorder. Scores of each item range between zero ('No, not more than usually') and ten ('Yes, much more than usually'). The ASC items are grouped into five main factors comprising several items. (1) Oceanic Boundlessness (OB) measures derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria and alterations in the sense of time. The component subscales are positive derealization, positive depersonalization, altered perception of time and space, positive mood, and mania-like experience. (2) Anxious Ego Dissolution (AED) measures ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. The component subscales are anxious derealization, thought disorder, paranoid ideation, fear of loss of self control, and fear of loss of body control. (3) Visual Restructuralization (VR) includes the item clusters elementary hallucinations, complex hallucinations, synesthesia, changed meaning of percepts, facilitated recollection, and facilitated imagination. (4) Auditory Alterations (AA) refers to acoustic hallucinations and distortions in auditory experiences and (5) the dimension Reduction of Vigilance (RV) relates to states of drowsiness, reduced alertness,

and related impairment of cognitive function. Prior to the beginning of the experiment the participants were introduced to the language of the 5D-ASC and given some of the exemplar statements for the dimensions oceanic boundlessness, visual restructuralization, and the AED subscale thought disorder. Participants filled out the full questionnaire at about 6 hours post-dosing, at such a time when they reported feeling no more subjective effects of the drug. During the continuous EEG recording just prior to the beginning of the ERP paradigm, they were also asked to rate their experience on some of these dimensions using a mouse to move a cursor from left (no change in the dimension from normal) to right (maximal change from normal). The position of the cursor was recorded as a coarse measure of their experienced alteration of consciousness along the primary 5D-ASC dimensions OB and VR as well as the AED subscale thought disorder as it was hypothesized that changes in physiological processing might be related to the currently perceived alteration along these three dimensions.

EEG Data acquisition

EEG data was collected EEG was recorded from 64 standard scalp locations according to the International 10-10 System using active Ag-AgCl electrodes (BioSemi, Active 2) mounted in an elastic cap: Fp1, Fp2, Fpz, AF7, AF3, AF4, AF8, F7, F5, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P9, P7, P5, P3, P1, Pz, P2, P4, P6, P8, P10, PO7, PO3, POz, PO4, PO8, O1, Oz, O2, Iz. Additionally single active Ag-AgCl electrodes were applied to the left mastoid, the outer canthi of both eyes (for

horizontal EOG monitoring) and the infraorbital and supraorbital regions of the left eye in line with the pupil (for vertical EOG monitoring). EEG signals were sampled at 256 Hz, amplified and analog band-pass filtered between 0.01 and 67 Hz by the Biosemi Active II amplifier system. The Biosemi electrode-amplifier system uses a common-mode reference for on-line data acquisition and impedance measures are not necessary due to the active electrode circuitry.

ERP Analysis

Offline the data were imported into BrainVision Analyzer V1.05 for ERP analysis and referenced to average reference. Subsequently, data were band-pass filtered using zero-phase butterworth filters (1–20 Hz, 48 dB/octave), and trials were epoched from -200 to +800 ms relative to standard, target, and distracter stimulus presentation. Incorrect-response target trials were removed. Single trials were investigated for signs of artifact and those trials containing voltages of greater magnitude than 100uV were rejected. For each drug condition at least 20 correct trials were included. Due to a dose-related decrease in accuracy there was a small decrease in number of target trials under the low dose (29.3 $\pm$ 4.3) and high dose (28.9 $\pm$ 5.1) conditions compared to the placebo (33.4 $\pm$ 4.2) condition. There was no effect of psilocybin on the number of correct trials included for the distracter (33.0 $\pm$ 5.9) or standard (158.7 $\pm$ 23.4) conditions. EOG artifacts were corrected according to the procedure described by Gratton and Coles (Gratton, Coles, & Donchin, 1983). Baseline removal was accomplished by subtracting

the average voltage over the -200 to 0 ms pre-stimulus interval in each trial. ERPs were averaged separately for the standard, target, and distracter trials.

Inspection of the data revealed a P100 component peaking at about 120 msec after stimulus onset in lateral occipital scalp areas and an N175 component peaking at about 175 msec (maximal at PO7, PO8). The N1 peak distribution was focused over mid-parieto-occipital areas for the standard and target stimuli (maximal at PO7, P7, P5, P3) and over lateral occipital areas for the distracter stimuli (maximal at PO7, PO8). A P2 component peaking at midline occipital areas (maximal at O1, Oz, O2) was clearly visible for all three stimuli at a latency of approximately 235 msec for the standard and target stimuli and 260 msec for the distracter stimuli. A P3 component with a parieto-central maximum was also present, peaking at about 400 ms in the standard and distracter trials and at about 450 ms in the target trials. Finally, a late sustained occipital negativity was observed for all three trial types in the 600 – 800 msec post stimulus time range, maximal at occipital locations (PO7, O1, Oz, O2, PO8); we refer to this component as the N600 herein. The P1 and N1 components were quantitated by means of picking the maximal positive and negative peaks in the 80-140 msec and 140-220 msec time frames at electrodes PO7 and PO8. The P2 component was quantitated by means of picking the maximally positive peak at electrodes O1, Oz, and O2 between 200 and 300 msec. The P300 component was assessed for latency effects by picking the maximal peak in channels Fz, Cz, and Pz in the 300 – 700 msec time range. For the purpose of component amplitude assessment, 12 scalp regions of interest were defined so as to cover the full extent of the maximal P300 component amplitude. These regions were composed of the

following pooled channels: frontal left (F1, F3), frontal right (F2, F4), frontocentral left (FC1, FC3), frontocentral right (FC2, FC4), central left (C1, C3, C5), central right (C2, C4, C6), centroparietal left (CP1, CP3, CP5), centroparietal right (CP2, CP4, CP6), parietal left (P1, P3, P5), parietal right (P2, P4, P6), occipito-parietal left (PO3) and occipito-parietal right (PO4). The average amplitude over the 150 msec time range centered on the peak of the grand average global field power P3 waveform (Lehmann & Skrandies, 1980, 1984) was extracted for each of these 12 regions of interest for each trial type and dose condition individually. This led to an assessment of P3 amplitude over the following 150 msec poststimulus time intervals: placebo standards, 320 – 470; low dose standards, 345 – 495; high dose standards, 340 – 490; placebo targets, 400 – 550; low dose targets, 390 – 540; high dose targets, 400 – 550; placebo distracters, 305 – 455; low dose distracters, 340 – 490; high dose distracters, 380 - 530. For the late N600 occipital negativity the average amplitude for the occipital channels showing maximal late negativity (PO7, O1, Oz, PO8, O2) was extracted for the time interval 600 – 750 msec post stimulus for the standard and distracter trials. Although a similar N600-like response was seen in the target trials, it overlapped with the late part of the target-detection related P3 component and was thus not assessed.

Stimulus-related changes in theta power were assessed by means of a fast Fourier-transform spectral decomposition. Prior to averaging, the data from each trial type was subjected to a fast Fourier transform algorithm over the 0 – 1000 msec post-stimulus interval. The epochs were then averaged and the average power at 4-6 Hz (theta) was calculated. The scalp distribution of alpha effects indicated that \significant increases in

theta power were observed over frontocentral areas. Post stimulus theta power was extracted for channels F3, C3, P3, Fz, Cz, and Pz and theta power values were then entered into ANOVA analysis with factors dose, stimulus type, anterior-posterior (A-P) location, and lateral location (left, midline, and right).

Results

Altered State of Consciousness

The 94-item 5D-ASC Altered State of Consciousness questionnaire was used to quantify the change in consciousness. This questionnaire produces scores for three primary dimensions of altered state of consciousness with subscales (Oceanic Boundlessness (OB), Visionary Restructuralization (VR), and Anxious Ego Dissolution (AED)) and as well as two additional main scales of significance without subscale components (Auditory Alterations (AA) and Reduction of Vigilance (RV), see Methods). ANOVA analysis conducted on each of the main scale scores expressed as a percentage of maximum with factors dose and main scale (Figure 2a) revealed a main effect of dose ($F(2, 34) = 29.42$, $p < 0.00001$), main scale ($F(4,68) = 11.61$, $p < 0.00001$), and a dose by main scale interaction ($F(8, 136) = 4.52$, $p < 0.0001$). Post-hoc analysis of the main effect of dose indicated that each of the three dose conditions was significantly different from each other: high-dose vs. placebo ($p < 0.001$); high-dose vs. low-dose, $p < 0.01$; low-dose vs. placebo, $p < 0.001$). Post-hoc analysis of the *dose* x *main scale* interaction indicated that high dose psilocybin induced significantly higher ratings than placebo for all five main scales: Oceanic Boundlessness (OB); $p < 0.0001$, Anxious Ego Dissolution

(AED); $p < 0.01$, Visionary Restructuralization (VR); $p < 0.0001$, Auditory Alterations (AA); $p < 0.0001$, and Reduction of Vigilance (RV) $p < 0.0001$. Low-dose psilocybin induced 5D-ASC ratings significantly higher than placebo for the main scales Oceanic Boundlessness ($p < 0.001$), Visionary Restructuralization ($p < 0.0001$), and Reduction of Vigilance ($p < 0.01$). High dose relative to low dose scores on the 5D-ASC were significantly increased for the OB ($p < 0.01$) and VR ($p < 0.05$) scales only.

The main contributing subscale for the effect on Oceanic Boundlessness was the "altered perception of time and space" subscale with low-dose and high-dose psilocybin inducing (mean $\pm$ S.E.M.) 38.0 $\pm$ 6.7 % and 47.0 $\pm$ 8.5 % of the scale maximum, respectively. The main contributing subscale for the effect on Anxiety of Ego Dissolution was the "thought disorder" subscale with low-dose and high-dose psilocybin inducing 12.7 $\pm$ 5.5% and 25.2 $\pm$ 5.2% of the scale maximum, respectively. The two subscales contributing most to the increase in the Visionary Restructuralization scores were complex hallucinations (LD, 47.5 $\pm$ 8.0%; HD, 63.0 $\pm$ 8.0% scale maximum) and elementary hallucinations (LD, 37.7 $\pm$ 7.7%; HD, 54.4 $\pm$ 6.7% scale maximum). Of the 18 participants, all experienced moderate to marked alterations in their subjective state on the low dose psilocybin day and 15 experienced marked alterations in their subjective state on the high dose psilocybin day. Unusually, three participants felt that they may not have had any drug or had only a very low dose effect on the high dose psilocybin day and of these, one experienced a subjective alteration in consciousness on the placebo day, accounting for virtually all of the small increases above zero seen in the 5D-ASC placebo data.

As we were particularly interested in the visual changes induced by psilocybin and their relation to changes in the electrophysiology, we assessed the dose-related effects on the subscales of the Visionary Restructuralization (VR) main scale with factors dose and subscale (Figure 2b). ANOVA analysis indicated a main effect of dose ($F(2,34) = 25.08$, $p < 0.00001$) and subscale ($F(5,85) = 13.58$, $p < 0.00001$) as well as a *dose* x *subscale* interaction ($F(10,170) = 3.94$, $p < 0.0001$). Post-hoc analysis of the significant dose effect revealed that both low and high dose conditions evoked greater scores than placebo (LD, $p < 0.001$; HD, $p < 0.001$) but that the two doses were not significantly different from each other (LD vs. HD, $p = 0.11$). Post-hoc testing of the significant *dose* x *subscale* interaction showed that both high and low dose psilocybin induced greater scores than placebo on the VR subscales elementary hallucinations (LD and HD both $p < 0.0001$), complex hallucinations (LD and HD both $p < 0.0001$), synesthesia (LD and HD both $p < 0.0001$), facilitated recollection (LD, $p < 0.01$; HD, $p < 0.001$) and facilitated imagination (LD, $p < 0.05$; HD, $p < 0.001$). On the subscale changed meaning of percepts, HD psilocybin induced greater scores than placebo ($p < 0.01$) but LD psilocybin did not ($p = 0.74$), however the scores at the two different doses were not significantly different from each other ($p = 0.16$).

The results of the computerized short ASC assessment done during the EEG recording just prior to the ERP paradigm (while the subjects were still feeling the acute effects of psilocybin) indicated a similar pattern of results in that the visual restructuralization-like scale showed the largest response to psilocybin with the oceanic boundlessness-like scale close behind, with each well above the anxious ego dissociation-

related scales. ANOVA analysis with factors dose and scale indicated a main effect of dose ($F(2,34) = 26.55$, $p < 0.00001$), scale ($F(3,51) = 24.59$, $p < 0.00001$), and a significant *dose* x *scale* interaction ($F(6,102) = 10.31$, $p < 0.00001$). Post-hoc analysis of the *dose* x *scale* effect indicated that the OB-like score was significantly different comparing placebo to low dose ($p < 0,001$) and high dose (0.001) and that low and high dose were not significantly different ($p = 0.30$). The VR-like score was also significantly increased above placebo by both low ($p < 0.001$) and high dose ($p < 0.001$) and was additionally higher in the high dose than low dose condition ($p < 0.05$). The AED-like scale was not affected by psilocybin ($p = 1.0$ for all comparisons) but the thought disorder scale was increased from placebo by both low ($p < 0.05$) and high dose ($p < 0.01$), though again was not significantly different comparing low vs. high dose ($p = 1.0$). The short form and long form ratings for the low dose psilocybin correlated well with each other: OB-like (short form) to OB (long form), $r = 0.68$, $p < 0.01$; VR-like to VR, $r = 0.67$, $p < 0.01$, thought disorder to AED subscale thought disorder, $r = 0.57$, $p < 0.05$. However, the short form ratings for the high dose psilocybin condition showed much less correlation with the scale scores as assessed by the 5D-ASC with only the OB scores being significantly correlated: OB-like to OB, $r = 0.50$, $p < 0.05$; VR-like to VR, $r = 0.15$, $p = 0.57$; thought disorder to AED subscale thought disorder, $r = -0.04$, $p = 0.87$). The AED-like subscale was not correlated with the AED scores on either the low or high dose days, largely accounted by the fact that subjects endorsed little experience of this kind on the computerized short form report (average percent maximum scores for LD and HD

were 0.44 $\pm$ 0.21 and 1.25 $\pm$ 0.73 for the short AED-like scores vs. 5.35 $\pm$ 2.13 and 14.63 $\pm$ 3.96 on the AED scale).

Behavioral response

ANOVA analysis conducted on the percentage correct data for the target trials and standard trials showed a dose effect of psilocybin in increasing false positives to the standards ($F(2,34) = 5.97$, $p < 0.01$) as well as the misses to the targets ($F(2,34) = 8.14$, $p < 0.01$). Post-hoc analysis comparing placebo to the psilocybin conditions indicated that low dose psilocybin did not increase the false positive rate ($p = 0.67$) but that high dose increased false positives relative to placebo ($p < 0.01$) and low dose ($p < 0.05$). Post-hoc analysis of the target accuracy data indicated that increases in target misses was seen for both low dose ($p < 0.01$) and high dose ($p < 0.01$) conditions. In further contrast to the false positive data, there was no significant difference between low and high dose psilocybin for the target miss rate ($p = 0.87$). The reaction time to the targets was increased by psilocybin ($F(2,34) = 8.31$, $p < 0.01$) and both low dose ($p < 0.05$) and high dose ($p < 0.001$) showed significant difference from placebo. The difference in reaction time was not significant comparing low to high dose psilocybin ($p = 0.27$).

Electrophysiological data

All stimuli under all 3 drug conditions elicited prominent P1, N1, P2, and P3 components as well as a late N600 occipital negativity. The P1 component peaked with an average latency of about 120 msec at the lateral occipital scalp areas, maximal at

electrodes PO7 and PO8, whereas the N170 component peaked with an average latency of about 185 ms, also at electrodes PO7 and PO8. Figures 4a-c show the average event-related potential to the standard, target, and distracter stimuli for all 64 electrodes of the montage as well as a magnified view of the occipital electrodes with global field power indicated in the upper right corner. Figures 5a-c, 6a-c, and 7a-c show the scalp distribution of the P1 component in response to the standard, target, and distracter, respectively, under all three drug conditions, plotted at the P1 peak of the global field power. Figures 8a-c, 9a-c, and 10a-c show the scalp distribution of the N1 component in response to the standard, target, and distracter, respectively, under all three drug conditions, plotted at the N1 peak of the global field power. Figures 11a-c, 12a-c, and 13a-c show the scalp distribution of the occipital P2 component to the three stimuli again mapped at the peak of the P2 global field power. Figures 14a-c, 15a-c, and 16a-c show the scalp distribution of the P3 component to the standard, target and distracter stimuli at the global field power peak for each dose. Lastly, figures 17a-c and 18a-c depict the late occipital component we term the N600, plotted from 600-750 msec post stimulus over the period at which it was maximal in the grand average data.

P1

Latency analysis of the P1 component assessed at channels PO7 and PO8 for the standard stimuli with factors dose and hemisphere indicated a main effect for psilocybin only ($F(2,34) = 7.53$, $p < 0.01$). Post-hoc analysis found that both low dose ($p < 0.05$) and high dose ($p < 0.01$) psilocybin conditions yielded longer latencies to the standards

relative to placebo with no difference between the two ($p = 0.36$). Analysis of the P1 latency to the target stimuli yielded no effect of either dose ($p = 0.38$) or hemisphere. Analysis of the P1 latency to the distracter stimuli indicated a highly significant main effect of dose ($F(2,34) = 12.90$, $p < 0.0001$). Both low and high dose distracter P1 latencies were longer than placebo ($p < 0.001$ for both comparisons), but there was no difference in P1 latency between low and high dose conditions ($p = 0.86$).

Assessment of P1 amplitude for the standards at PO7/PO8 yielded no effect of dose ($p = 0.59$), but a significant effect of hemisphere ($F(1,17) = 5.32$, $p < 0.05$) as the right hemisphere showed greater amplitude response than left. A similar finding was obtained with regard to the P1 amplitudes to the targets, as again there was no effect of dose ($p = 0.52$) but the right hemisphere showed greater amplitude than left ($F(1,17) = 6.65$, $p < 0.05$). There was also a trend towards a *dose* x *hemisphere* interaction ($F(2,34) = 2.60$, $p = 0.089$) as the difference between left and right amplitudes tended to be greater in placebo than psilocybin conditions (see figures 6a – 6c). P1 amplitude to the distracters indicated a main effect of both hemisphere ($F(1,17) = 8.18$, $p < 0.01$) and dose ($F(2,34) = 4.63$, $p < 0.05$). The distracter P1 was right lateralized and psilocybin increased the amplitude of the P1 component. Post-hoc analysis of the dose effect indicated that low dose psilocybin induced significantly greater P1 amplitude than placebo ($p < 0.05$) and high dose exhibited a trend ($p = 0.073$), but the two dose conditions were not significantly different from each other ($p = 0.81$).

As it was noticed from the scalp maps of the P1 time range (figures 5a – 7c) that there seemed to be a different neural generator invoked for the P1 component a more

comprehensive assessment of P1 amplitude was accomplished by extracting the average amplitude at the occipital channels P7, PO7, O1, P8, PO8, and O2 over the 105 – 135 msec post stimulus time frame. ANOVA analysis of this data with factors dose, hemisphere, and laterality of scalp position indicated that there was an enhancing effect of psilocybin on the P1 amplitude at medial scalp areas in response to all the stimuli.

ANOVA analysis of the P1 amplitude to the standards yielded a main effect of dose ($F(2,34) = 6.83$, $p < 0.01$), hemisphere ($F(1,17) = 6.98$, $p < 0.05$), laterality of scalp position ($F(2,34) = 8.42$, $p < 0.001$), and a significant *dose* x *laterality* interaction ($F(4,68) = 8.35$, $p < 0.0001$). Post-hoc analysis of the critical *dose* x *laterality* interaction revealed that at the medial O1/O2 locations both low and high dose psilocybin induced larger magnitude P1 component relative to placebo (both comparisons $p < 0.001$). Additionally there was a trend towards greater medial P1 amplitudes in the high dose relative to low dose comparison ($p = 0.077$).

Analysis of the P1 amplitude to the targets yielded a main effect of hemisphere ($F(1,17) = 4.89$, $p < 0.05$), and laterality of scalp position ($F(2,34) = 14.27$, $p < 0.0001$), a *hemisphere* x *laterality* interaction ($F(2,34) = 3.83$, $p < 0.05$), and again a significant *dose* x *laterality* interaction ($F(4,68) = 3.24$, $p < 0.05$), although no main effect of dose ($p = 0.16$). Post-hoc analysis of the *hemisphere* x *laterality* interaction indicated that the P1 component evinced greater amplitudes at P8 relative to P7 ($p < 0.01$) and at PO8 relative to PO7 ($p < 0.001$) but that the amplitudes at O2 and O1 were indistinguishable ($p = 0.33$). Post-hoc analysis of the critical *dose* x *laterality* interaction revealed that at the

medial O1/O2 locations both low and high dose psilocybin induced larger magnitude P1 component amplitudes relative to placebo (both comparisons $p < 0.001$).

Unlike the P1 to the standard and target stimuli, the P1 to the distracter showed greater amplitude at PO7 and PO8 by the analysis on the individually picked peaks. However, an analogous assessment over the 105 – 135 msec post stimulus time range was carried out to further characterize the dynamics of the P1 psilocybin effect across the scalp surface. This analysis indicated a highly significant effect of dose ($F(2,34) = 6.83$, $p < 0.0001$) as well as hemisphere ($F(1,17) = 11.13$, $p < 0.01$), and laterality of scalp position ($F(2,34) = 4.60$, $p < 0.05$). Additionally a significant *hemisphere* x *laterality* interaction ($F(2,34) = 4.37$, $p < 0.05$) as well as a highly significant *dose* x *laterality* interaction ($F(4,68) = 23.90$, $p < 0.00001$) were again found. As with the dose effect observed at the peak-picked values for PO7/PO8, post-hoc analysis of the dose effect again indicated greater amplitudes for low dose ($p < 0.01$) and high dose ($p < 0.001$) relative to placebo with no difference between the two ($p = 0.75$). The hemisphere by laterality interaction indicated that while the amplitude at each of the scalp positions along the medial-lateral axis was greater on the right, the strongest right-over-left increase was exhibited at the mid-lateral occipital electrodes PO7/PO8 (P7 vs. P8, $p < 0.05$; PO7 vs. PO8, $p < 0.001$; O1 vs. O2, $p < 0.05$). Finally, the *dose* x *laterality* interaction indicated larger P1 amplitudes for the low dose and high dose conditions relative to placebo at PO7/PO8 and O1/O2 (all comparisons $p < 0.001$) but not at lateral positions P7/P8. Further, the high dose evoked larger P1 amplitudes than the low dose at the medial O1/O2 electrodes ($p < 0.05$) but not PO7/PO8 ($p = 1.0$) or P7/P8 ($p = 0.99$).

N1

As shown in figures 8a – 10c each of the three stimuli in the visual oddball paradigm evoked an N1 component. The N1 to the standard and target stimuli was similar in posterior parietal location while the N1 to the distracter stimulus was focused over lateral occipital areas and of much greater amplitude. Analysis of the N1 latency and amplitude with factors dose (placebo, low dose, high dose) and hemisphere (left – PO7, right – PO8) was done for each of the stimulus types. Analysis of the N1 latency to the standard stimuli indicated a main effect for psilocybin ($F(2,34) = 4.52$, $p < 0.05$) but not hemisphere ($p = 0.20$). Post-hoc analysis indicated that high dose N1 latency was later than placebo ($p < 0.05$) and that low dose latency was significantly delayed at only a trend level ($p = 0.094$) while the difference between dose conditions was not significant ($p = 0.74$). Target N1 latency was not affected by dose ($p = 0.64$) or hemisphere ($p = 0.59$). In contrast to the standard and target stimuli, the latency of the more occipitally-focused distracter N1 was strongly affected by psilocybin ($F(2,34) = 38.88$, $p < 0.00001$). Post-hoc analysis indicated significant slowing for both the low ($p < 0.001$) and high ($p < 0.001$) dose conditions relative to placebo, with a mild trend towards significant difference between dose conditions ($p = 0.11$).

In contrast to the P1 amplitude where a right-sided dominance was observed for all the stimuli, the N1 amplitude to the standard stimuli was greater on the left ($F(1,17) = 4.94$, $p < 0.05$). Additionally there was a trend towards reduction of amplitude due to psilocybin that failed to reach significance ($F(2,34) = 3.00$, $p = 0.063$). Target N1

amplitude was also greater on the left ($F(1,17) = 4.50$, $p < 0.05$). Psilocybin was found to significantly reduce target N1 amplitude ($F(2,34) = 4.27$, $p < 0.05$). Post-hoc analysis indicated that high dose psilocybin induced smaller amplitudes than placebo ($p < 0.05$) but that low dose relative to placebo ($p = 0.15$) and high dose relative to low dose ($p = 0.60$) comparisons showed no significance. Unlike the P1, and the N1 to standards and targets, the distracter N1 was not lateralized (main effect of hemisphere $p = 0.42$). As with its latency, the distracter N1 amplitude was very sensitive to psilocybin as indicated by a highly significant main effect of dose ($F(2,34) = 12.86$, $p < 0.0001$). Post-hoc analysis of the dose effect on N1 amplitude indicated that the placebo N1 was of greater amplitude than that evoked in low ($p < 0.05$) and high ($p < 0.001$) dose conditions. Additionally, high dose relative to low dose psilocybin yielded significantly reduced distracter N1 amplitudes ($p < 0.05$).

P2

As shown in figures 11a – 13c each of the three stimuli in the visual oddball paradigm evoked a P2 component of similar central occipital distribution across the scalp. The P2 to the standard and target stimuli occurred with an average latency of about 230 msec whereas the P2 to the distracter stimulus had an average latency of about 260 msec. The latency and amplitude measures for the P2 component as assessed at electrodes O1, Oz, and O2 were subjected to ANOVA analysis with factors dose and location for each of the stimulus types.

The P2 latency to the standards was not affected by psilocybin ($p = 0.18$) or location of measurement ($p = 0.98$). Similarly, no effects of psilocybin ($p = 0.30$) or location ($p = 0.21$) were found for the P2 latency to the target stimuli. In contrast, the P2 latency to the distracter stimulus was slowed by psilocybin ($F(2,34) = 4.04$, $p < 0.05$) and post-hoc analysis indicated that high dose psilocybin evinced significantly longer P2 latency than placebo ($p < 0.05$), while low dose vs. placebo ($p = 0.16$) and low vs. high dose ($p = 0.64$) comparisons showed no significance.

The P2 was the largest component to the standard stimuli in contrast to the targets where the P3 dominated and distracters where the N1 was the component with largest strength as assessed by global field power. Analysis of P2 amplitude to the standards indicated that there was no significant effect of dose or location although a trend was evident for both factors (dose, $p = 0.10$; location, $p = 0.095$). The trends indicated an insignificant tendency towards increased P2 amplitude with low dose and decreased P2 amplitude with high dose as well as a tendency for the central electrode Oz to exhibit higher magnitudes than left and right electrodes. Target P2 amplitude did show a significant location effect ($F(2,34) = 4.54$, $p < 0.05$) with post-hoc analysis indicating that Oz exhibited higher P2 amplitude than O1 ($p < 0.05$) and a trend towards higher amplitudes than O2 ($p = 0.061$). There was additionally a trend *dose* x *location* interaction ($p = 0.093$) indicating some tendency for increased target P2 amplitude with both low and high dose psilocybin in the right hemisphere. Distracter P2 amplitude showed no variation with either dose ($p = 0.63$) or location ($p = 0.48$).

P3

As shown in figures 14a – 16c each of the three stimuli in the visual oddball paradigm evoked a P3 component. While the P3 amplitude was greatly reduced to all three stimuli, the scalp distribution was generally similar across doses for the target and distracter stimuli. In contrast as shown in figures 14a-c, the P3 scalp map to the standards tended to have a more occipital distribution, lacking the centro-parietal contribution seen in the placebo condition. The latency of the P3 was assessed at channels Fz, Cz, and Pz and ANOVA analyses of these values were conducted for each of the stimulus types with factors dose and anterior-posterior location on the scalp.

P3 latency values for the standard stimuli averaged 427 $\pm$ 22 msec at Pz in the placebo condition and showed a main effect of anterior-posterior location ($F(2,34) = 5.68$, $p < 0.01$) but no effect of dose ($p = 0.75$). Post-hoc analysis indicated that latencies were longer at Fz than Cz ($p < 0.05$) and Pz ($p < 0.01$) but that there was no difference between Cz and Pz values ($p = 0.91$).There was a trend towards a *dose* x *location* interaction that achieved the $p < 0.05$ criterion level before correction for multiple comparisons but just missed significance after Greenhouse-Geisser correction ($F(4,68) = 2.53$, $p = 0.073$). The trend was towards psilocybin causing longer latency P3 at frontal locations but having no effect on latencies at the maximal central and parietal locations.

P3 latency to the target simuli averaged 450 $\pm$ 15 msec at Pz in the placebo condition and again showed no main effect of dose ($p = 0.26$) but a significant effect of location ($F(2,34) = 5.62$, $p < 0.05$). Post-hoc analysis of the effect on location again indicated that slowest latencies were observed at Fz. The only significant comparison

between channels on target P3 latency showed that Fz demonstrated longer latencies than Pz ($p < 0.05$; Fz vs. Cz, $p = 0.28$; Cz vs. Pz, $p = 0.19$).

Distracter P3 latency averaged 378 $\pm$ 13 msec at Pz in the placebo condition and unlike target and standard P3 showed a strong sensitivity to psilocybin. ANOVA analysis of distracter P3 latency revealed a main effect of dose ($F(2,34) = 6.92$, $p < 0.01$), a main effect of location ($F(2,34) = 3.27$, $p = 0.071$), and a *dose* x *location* interaction ($F(4,68) = 2.50$, $p = 0.074$) that just missed significance after Greenhouse-Geisser correction. Post-hoc analysis of the dose effect indicated that psilocybin slowed distracter P3 latency at both low ($p < 0.05$) and high ($p< 0.01$) dose conditions, while the comparison of low vs. high dose was not significant ($p = 0.76$). The *dose* x *location* interaction just missing significance level suggested that the psilocybin-induced slowing of the P3 component was especially strong at frontal and central locations.

P3 amplitude was assessed over the P3 peak observed in the GFP of the grand average for each stimulus and dose condition at the 12 regions of interest, left and right along the anterior-posterior axis as described in methods. For each of the 3 stimulus types, ANOVA analysis was conducted with factors dose, anterior-posterior location, and hemisphere. Analysis of P3 amplitude to the standard stimuli revealed a main effect of dose ($F(2,34) = 11.06$, $p < 0.0001$), A-P location ($F(5,85) = 14.41$, $p < 0.00001$), and a *dose* x *location* interaction ($F(10,170) = 3.62$, $p < 0.001$). Post-hoc testing of the main effect of dose indicated reduced standard stimulus P3 amplitude for both low ($p < 0.01$) and high ($p < 0.001$) dose conditions, with no significant difference between dose conditions ($p = 0.64$). Post-hoc analysis of the *dose* x *location* interaction indicated that

placebo P3 amplitude was greater than low dose P3 amplitude specifically at frontocentral locations ($p < 0.01$) with only a trend towards significance at central locations ($p = 0.064$). Placebo amplitudes were greater than high dose amplitudes at frontocentral ($p < 0.001$), central ($p < 0.001$), and centroparietal ($p < 0.01$) locations and comparisons between the dose conditions yielded no significant differences at any scalp area.

Analysis of the P3 amplitude to the target stimuli revealed an even more significant main effect of dose ($F(2,34) = 27.93$, $p < 0.00001$) and A-P location ($F(5,85) = 27.01$, $p < 0.00001$) as well as a strongly significant main effect of hemisphere ($F(1,17) = 22.84$, $p < 0.001$) indicating right-sided dominance. Significant interactions were found between dose and A-P location ($F(10,170) = 8.17$, $p < 0.00001$) as well as A-P location and hemisphere ($F(2,34) = 27.93$, $p < 0.00001$). Analysis of the *A-P* x *hemisphere* interaction indicated that right-sided amplitudes were greater than left at the four forward-most regions of interest – frontal ($p < 0.01$), frontocentral ($p < 0.001$), central ($p < 0.001$), and centroparietal ($p < 0.05$), but not the parietal ($p = 0.98$) or parieto-occipital ($p = 0.10$) regions. The dose effect indicated that placebo amplitudes were greater than both low ($p < 0.001$) and high ($p < 0.001$) dose conditions, with only a trend towards greater amplitudes in low vs. high dose conditions ($p = 0.10$). Post-hoc testing of the *dose* x *A-P* interaction indicated that placebo amplitudes were greater than those at low dose for central ($p < 0.001$), centroparietal ($p < 0.0001$), and parietal ($p < 0.01$) regions and significantly greater than high dose for central, centroparietal, parietal

and parieto-occipital (all comparisons $p < 0.0001$) regions. No region of interest differed significantly for target P3 amplitude between dose conditions (all $p > 0.2$).

Assessment of P3 amplitude to the distracter stimuli revealed the most highly significant effect of dose seen for the three stimulus types ($F(2,34) = 43.57$, $p < 0.00001$) as well as an A-P location effect ($F(5,85) = 16.22$, $p < 0.00001$); neither hemisphere nor the possible interactions between factors reached significance levels. Post-hoc analysis of the dose effect indicated that placebo evoked greater distracter P3 amplitudes than both low ($p < 0.001$) and high ($p < 0.001$) dose conditions, and that low-dose amplitude was significantly greater than high-dose amplitude ($p < 0.01$).

In order to assess in more detail the relative impact of psilocybin on the P3 to the three classes of stimuli we ran an ANOVA analysis on the P3 amplitudes to the standards, targets, and distracters for each dose condition with factors stimulus type, A-P location and hemisphere. The analysis of the placebo P3 data indicated main effects for stimulus type ($F(2,34) = 18.81$, $p < 0.001$), A-P location ($F(5,85) = 21.33$, $p < 0.0001$), and hemisphere ($F(1,17) = 7.67$, $p < 0.05$) in addition to *stimulus type* x *A-P* ($F(10,170) = 5.76$, $p < 0.01$), *stimulus type* x *hemisphere* ($F(2,34) = 10.16$, $p < 0.001$), and *stimulus type* x *A-P* x *hemisphere* ($F(10,170) = 3.76$, $p < 0.01$) interactions. Post-hoc analysis of the main effect of stimulus type indicated greater P3 amplitudes to targets ($p < 0.001$) and distracters ($p < 0.001$) than standards. The stimulus type by scalp location interactions were indicative of the different scalp topographies for the three stimulus types, for example the significant right-sided dominance of P3 amplitude to the targets ($p < 0.001$) and distracters ($p < 0.05$) but not standards ($p = 1.0$) as noted above. The findings with

regards to A-P location were in line with the known greater frontal involvement in P3a-type responses to distracters vs. greater parietal involvement in P3b-type responses to targets and are not analyzed in detail here. Analysis of the low dose P3 amplitudes to all three stimulus types yielded the same significant main effects and interactions but with lower significance values. Specifically, significance was seen for main effects of stimulus type ($F(2,34) = 8.51$, $p < 0.01$), A-P location ($F(5,85) = 27.80$, $p < 0.00001$), and hemisphere ($F(1,17) = 6.55$, $p < 0.05$) in addition to *stimulus type* x *A-P location* ($F(10,170) = 2.92$, $p < 0.05$), *stimulus type* x *hemisphere* ($F(2,34) = 10.16$, $p < 0.05$), and *stimulus type* x *A-P* x *hemisphere* ($F(10,170) = 3.76$, $p < 0.05$) interactions. Post-hoc analysis of the stimulus type main effect again indicated greater P3 amplitude to targets ($p < 0.01$) and distracters ($p < 0.01$) than standards and no difference between P3 amplitude to targets and distracters ($p = 0.86$). Analysis of the high dose P3 amplitudes yielded only a significant effect for A-P location ($F(5,85) = 27.80$, $p < 0.00001$), with the *stimulus type* x *hemisphere* interaction missing significance due to Greenhouse-Geisser corrections ($F(2,34) = 3.53$, $p = 0.059$). No main effect of stimulus type was found ($p = 0.14$), nor any of the other location effects indicative of the altered scalp distribution of P3a vs. P3b responses. Exploratory post-hoc testing of the *stimulus type* x *hemisphere* interaction that just missed significance indicated that there was no right-sided dominance for any of the stimulus types and the only significant effect between stimulus conditions was that the right-sided target amplitudes were greater than the right-sided standard amplitudes ($p < 0.05$, but note lack of justified post-hoc given that the

interaction missed the $p = 0.05$ significance criterion after Greenhouse-Geisser corrections).

N600

As shown in figures 17a – 18c the standard and distracter stimuli evoked a late negativity with an occipital focus which we term here the N600 which was of negligible magnitude to the target stimuli. This component was evident as a late peak in the grand average GFP curves, especially visible in the placebo condition. ANOVA analysis of this late negativity was done separately for the standard and distracter stimuli with factors dose and location (PO7, O1, Oz, O2, PO8). Analysis of N600 amplitudes to the standard stimuli yielded a main effect only for dose ($F(2,34) = 8.06$, $p < 0.01$). Post-hoc analysis indicated that the N600 was decreased relative to placebo in the low ($p < 0.05$) and high ($p < 0.01$) dose conditions and that there was no significant difference between dose conditions ($p = 0.73$). Analysis of N600 amplitudes to the distracter stimuli again indicated a significant effect of dose ($F(2,34) = 8.68$, $p < 0.01$) with no other effects. Post-hoc testing indicated that, relative to placebo, low dose N600 amplitudes were only reduced at a trend level ($p = 0.12$) while high dose amplitudes were greatly reduced ($p < 0.001$) and there was a trend towards reduced N600 in high dose vs. low dose ($p = 0.099$). The N600 potential appeared with similar latency and location to the standard and distracter stimuli but grand average scalp maps indicated it was of greatest magnitude in response to distracter stimuli. An ANOVA analysis of the N600 data for both stimuli was conducted to assess whether this was statistically significant with factors stimulus, dose,

and electrode. This analysis across stimulus conditions yielded the expected main effect of dose and also a highly significant main effect of stimulus type ($F(1,17) = 21.47$, $p < 0.001$) indicating that the N600 was indeed of greater magnitude in response to the distracter stimuli.

Relative effects of psilocybin on the early sensory components to the standards and targets

The similarity of inducing stimuli (small blue circles on black background), as well as the similarity of latencies, scalp distributions, and psilocybin-induced changes for the P1, N1, and P2 components to the standards and targets indicated that they were indexing similar steps in the early sensori-cognitive process for the standards and targets. Direct statistical comparisons were necessary in order to assess whether the standards vs. targets invoked different strengths for these early sensory processes. To test the possible differential effect of psilocybin on these early processes for the standards *vs.* the targets ANOVA analyses of the P1, N1, and P2 measures were conducted with factors stimulus (standards vs. targets), dose, and electrode location.

Analysis of P1 amplitude to the standard and target stimuli revealed only the above mentioned right-sided dominance and tendency for psilocybin to specifically increase the amplitudes at the medial occipital electrodes as seen for the analysis on each stimulus type individually. No main effects for stimulus type or additional interaction between stimulus type and location or dose effects were observed. Analysis of the N1 to the target and standard stimuli yielded a main effect of stimulus type ($F(1,17) = 6.22$, $p <$

0.05) indicating that target stimuli evoked greater N1 amplitudes. Further, a main effect of dose ($F(2,34) = 6.22$, $p < 0.05$) and hemisphere ($F(1,17) = 6.22$, $p < 0.05$) were observed reflecting the larger amplitudes on the left and the decrease in amplitude due to psilocybin. Post-hoc analysis of the dose effect indicated a significantly greater amplitude in placebo than high dose ($p < 0.01$) with only a trend present for the low dose comparison ($p = 0.11$) and no difference between dose conditions ($p = 0.51$).

Post-hoc analysis of the P2 amplitude again indicated a main effect of stimulus type ($F(1,17) = 13.33$, $p < 0.01$) with the standards evoking greater P2 amplitudes. There was also a main effect of location ($F(2,34) = 3.96$, $p < 0.05$) and a significant *dose* x *location* interaction ($F(4,68) = 2.78$, $p < 0.05$). The main effect of location was indicative of greater P2 amplitudes at Oz than O1 ($p < 0.05$), with a trend for greater amplitudes than O2 as well ($p = 0.11$). Post-hoc analysis of the *dose* x *location* interaction yielded the finding that at Oz and O2 low dose psilocybin P2 amplitudes were greater than both placebo ($p < 0.05$, $p < 0.001$, respectively) and high dose ($p < 0.001$ for both) amplitudes. Additionally, placebo amplitude was greater than high dose amplitude at O1 ($p < 0.05$).

Effects of psilocybin on frontal theta power

As shown in figures 19a – 21c the target and distracter stimuli evoked a frontal theta (4-6 Hz) power increase in placebo conditions. ANOVA analysis of the theta power was conducted across all three stimulus conditions to assess the influence of the cognitive events evoked by the three stimulus classes on this frontal theta and the impact of psilocybin on these dynamics. Electrodes included for analysis were F3, C3, P3, Fz,

Cz, Pz, F4, C4, and P4. Factors were stimulus condition, dose, lateral location, and A-P location.

Analysis of theta power amplitudes to the standard stimuli yielded main effects of dose ($F(2,34) = 39.36$, $p < 0.00001$), lateral location ($F(2,34) = 39.79$, $p < 0.00001$), A-P location ($F(2,34) = 24.70$, $p < 0.0001$), and stimulus type ($F(2,34) = 17.23$, $p < 0.001$). The main effect of dose reflected the strong inhibitory effect of psilocybin on the frontal theta power as both low and high dose conditions inhibited theta power relative to placebo (both $p < 0.001$), with high dose also evidencing lower theta powers than low dose across stimulus conditions ($p < 0.05$). The main effect of stimulus type reflected the strong increase in theta power invoked by the distracter stimuli relative to both standard and target stimuli (both $p < 0.001$).

A significant interaction was observed between dose and stimulus type ($F(4,68) = 5.25$, $p < 0.01$) indicating that the decrease in theta power was functionally relevant. In addition to the finding that for all three stimulus types placebo theta values were of greater magnitude than both low dose and high dose theta values (all p's < 0.001), it was observed that in the placebo and low dose conditions the distracter stimuli evoked greater theta amplitudes than both the standard and target stimuli (for placebo, p's < 0.001, for low dose, p's < 0.01). However, in the high dose condition there was no significant difference between the theta amplitude to the targets and the distracters. A significant interaction was observed between dose, stimulus type, and A-P location ($F(8,136) = 3.12$, $p < 0.05$) indicated that while in the placebo state the theta power to the distracters was greater than that to the targets at frontal ($p < 0.001$), central ($p < 0.001$), and parietal ($p <$

0.01) areas, in the low dose and high dose conditions the distracter only evoked greater theta amplitudes than the targets at frontal and central sites, but not parietal. Further, while frontal, central and parietal electrode sites all showed reduced theta power in both low and high dose states relative to placebo (all $p < 0.01$), the only significant differences between low and high dose theta values were observed at frontal ($p < 0.001$) and central ($p < 0.01$) sites in response to the distracter stimuli, implying that psilocybin specifically interacted with the frontocentral increases due to distracter stimulus processing.

Correlations between neurophysiologic variables and altered state

Pearson's product-moment correlations were calculated for the theta power values in the different dose conditions at Fz and Cz, the average P3 amplitudes pooled across parietal and centroparietal electrodes, the normalized change scores for both parameters, accuracy and reaction time change scores, and the scores on the 5-D ASC questionnaire. Interestingly, the strongest correlations were found between theta powers and induced altered state on the Oceanic Boundlessness scale in the high dose condition. This correlation was true both for frontal theta power in the placebo condition (r values from 0.5 to 0.8, p values < 0.05 to < 0.001) (see figure 22a) as well as in the high dose condition (r values from 0.5 to 0.67, p values < 0.05 to < 0.01), implying that the subjective response to high dose hallucinogen challenge might be predicted by frontal theta power. The placebo theta power at frontal and central electrodes negatively correlated with the high dose-induced P3 amplitude reduction to all three stimuli (see figure 22b, r-values from 0.5 – 0.6 p-values < 0.05) but the same correlation was not

obtained for the low dose condition.

It was revealed that the reduction of P3 amplitudes to the standard stimuli in the low dose condition correlated with increased scores on the short form visual hallucination scale ($r = 0.53$, $p < 0.05$), the depersonalization subscale of the Oceanic Boundlessness scores ($r = 0.47$, $p < 0.05$), and the complex hallucination subscale of the Visionary Restructuralization score ($r = 0.47$, $p < 0.05$). In the high dose condition the reduction of P3 amplitude to the target was correlated with the reported visual hallucination score on the short form computer report, although not with the score as assessed by the 5D-ASC at the conclusion of the experiment, possibly reflecting the utility of having the subjective report given closer to the time of neurophysiologic reporting.

Discussion

We found significant effects of psilocybin on psychometric assessment of experienced altered state, behavioral measures, and neurophysiologic patterns associated with the visual oddball task. All dimensions of the 5D-ASC standardized assessment of experienced altered state showed increases following psilocybin administration. Reaction time was increased and accuracy, as measured both by false positives to the standard stimuli and misses to the targets, was decreased. The early sensory P1 ERP component showed greater amplitudes at medial locations, and the later more cognitively-involved N1 and P3 components showed decreased amplitudes. A late N600 component possibly reflecting late visual processing was decreased in amplitude, as was the engagement of frontal theta activity to distracter stimuli.

Both the increase reaction time and the decrease in accuracy to the target was significant for both low and high dose psilocybin although the two doses were indistinguishable from each other in terms of effects on RT and target accuracy. In contrast, the increase in false positive rate was only significant in the high dose condition where it was significantly greater than either the placebo or low-dose condition. This implies that while low dose psilocybin interfered significantly with the relatively challenging target detection task only in the presence of high dose psilocybin were the subjects challenged to the point where they started making errors of commission as well.

Psilocybin-induced alterations in the neurophysiologic response to the stimuli were visible at the onset of the visual response to the stimuli – the P1 component. Here we found increased latency to the standard and distracter stimuli but not the target stimulus. This implies that the effect of psilocybin on latency may interact with task relevance. Further, the effect of psilocybin on the scalp distribution and amplitude of the P1 component was dramatic. For all three stimuli the amplitude of the P1 component was increased at medial locations. Further, the amplitude of the P1 component to the distracter stimulus was increased at both lateral locations and medial locations. The fact that only the distracter stimulus showed increased amplitude at lateral locations seems to imply a significance of the relevance of stimuli to the P1 effect elicited by psilocybin.

Previous work has shown that the P1 component does show variation in amplitude with attention (Gomez Gonzalez, Clark, Fan, Luck, & Hillyard, 1994), but the increase in P1 amplitude we observe here would seem to be independent of attention as the strong decrease in the later P3 amplitude and frontal theta power, as well as the decrease in

accuracy and increase in reaction time would tend to argue for a decrease of attentional engagement with the task.

The significant P1 effect observed here bears some significance in understanding the neural locus of the effects of psilocybin in visual processing. The visual P1 component has been previously shown to be generated largely by V1. As shown in figure 7f, the LORETA mapping of the grand average difference in the P1 component induced by psilocybin was largely localized to primary visual cortex in addition to right lateral occipital cortex. This evidence argues against the notion that V1 processing is unaffected by psilocybin, although given the recent evidence that a widespread system of sensory, parietal, and prefrontal areas is activated in less than 30 ms post visual stimulation and these brain areas are involved in feedback contribution to the generation of the P1 component (Foxe & Simpson, 2002) it is quite possible that our observed P1 effects are due to altered feedback processing from higher stages in the visual hierarchy.

The N1 component was observed over the posterior parietal areas in response to the standard and target stimuli, but over the lateral occipital areas in response to the distracter stimuli. This is consistent with a preferential engagement of the dorsal stream pathway in the perception of the standard and target stimuli in contrast to a stronger engagement of the ventral pathway in the perception of the black-and-white checkerboard distracter. The N1 was shown to be of greater amplitude in response to the target stimuli than the standards in keeping with the established finding that stimuli evoking increased attentional processing due to their behavioral relevance are associated with stronger N1 amplitudes (Naatanen, 1988).

The P3a and P3b components were both strongly inhibited in amplitude by psilocybin indicating decreased attentional resources allocated to the task. Furthermore, the latency of the P3a to the distracters was significantly increased indicating slower processing as well. The P3 to the standard was significantly decreased only at frontal locations by low dose psilocybin, but across frontal, central and parietal locations by high dose psilocybin. The P3b to the target showed a strong right-sided distribution and was decreased in amplitude to a greater extent than the P3 to the standards, consistent with the notion that psilocybin selectively interfered with the neural circuitry involved in P3b generation.

The P3 is known to be critically related to the cognitive process of context updating and although the precise neural contributions to the P3 component have not been definitively established, studies of patients with lesions as well as intracortical recordings and concurrent fMRI neuroimaging studies have implicated both the temporoparietal junction and regions in the frontal lobes. It is believed that these separate generators reflect the involvement of different cognitive processes, with temporoparietal generators being more involved in the P3b response related to target detection and response and frontal generators being more involved in the P3a arising from automatic orienting to distracting stimuli (Polich, 2003). In the present study we show that both of these processes are largely inhibited by psilocybin, leading to reduced P3a and P3b component amplitudes.

Serotonin has been shown to play a role in working memory; intracranial experiments on primate frontal cortex has demonstrated that 5-HT2A receptor function is

of relevance to spatial working memory (G. V. Williams, Rao, & Goldman-Rakic, 2002). Further, recent studies have demonstrated that serotonin depletion in humans disrupts measures of spatial working memory (Harrison et al., 2004). Given that the P3 component is known to be functionally related to the context updating of working memory the finding of psilocybin-induced inhibitions of P3a and P3b amplitudes may be related to serotonin's role in the normal functioning of the working memory circuits.

In contrast, we had initially hypothesized that we might observe increased P3 amplitudes to distracting stimuli despite some findings indicating decreases in P3 amplitude associated with worsening symptoms in schizophrenics. This hypothesis followed from subjective reports of greater distractibility in psilocybin states, the widely discussed decreased sensory gating model for the effects of hallucinogens (Nichols, 2004; Vollenweider, Csomor, Knappe, Geyer, & Quednow, 2007; Vollenweider & Geyer, 2001b), and neurophysiologic evidence involving the locus ceruleus supporting a candidate mechanism. Namely, phasic locus ceruleus activation has both been implicated in P3 generation and shown to increase after hallucinogen administration. An association between phasic locus ceruleus activation and P3 component generation has also been observed in the primate (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Pineda, Foote, & Neville, 1989; Swick, Pineda, & Foote, 1994; Swick, Pineda, Schacher, & Foote, 1994). Moreover, hallucinogens have been shown to decrease the spontaneous activity and increase the phasic activation of locus ceruleus cell bodies through 5HT2a receptor activation in the rat (Rasmussen & Aghajanian, 1986; Rasmussen, Glennon, & Aghajanian, 1986), leading to speculation that the increased distractibility and/or

decreased sensory filtering induced by hallucinogens might be mediated through such a mechanism . The locus ceruleus has been conceived of as a "novelty detector" for salient external stimuli (Aston-Jones & Bloom, 1981a, 1981b; Cedarbaum & Aghajanian, 1978) in support of the integral role of the locus ceruleus in the generation of the P3 and its associated cognitive operations (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005).

Given this discussion, the greatly reduced amplitude of the P3 component to both distracting and target stimuli in the current findings was unexpected, although it was consistent with a reasonable extrapolation of the model psychosis predictions. One explanation might be the related use of visual stimuli in the current experiment as opposed to the somatosensory stimuli which were used in the animal experiments demonstrating potentiation of LC phasic excitability by way of hallucinogen action at 5HT-2a receptors. It is also possible that the interactions of psilocybin with the locus ceruleus would have lent strength to the P3 amplitude if not for competing interactions of psilocybin with other brain areas which had a greater inhibitory effect. For example, the dysregulation of the normal serotonergic circuitry involving phasic inhibition of serotonin release by dorsal raphe neurons at moments of attentional orienting (B. L. Jacobs & Fornal, 1991; B. L. Jacobs, Wilkinson, & Fornal, 1990) or some other supervening effect of the altered serotonergic tone provided by the presence of the psilocybin may have overridden a potential psilocybin-induced increase in phasic LC excitability. It is also possible that truly novel stimuli would have evoked greater P3 amplitudes that can not be assessed with the use of the visual oddball paradigm we used here.

In regards to the effects of psilocybin on the LC, it is possible that the enhancing effects of psilocybin on medial P1 amplitudes described above may be mediated in part through a locus ceruleus – lateral geniculate pathway. This may follow from the fact LC activation has been shown to enhance the synaptic excitability of lateral geniculate neurons (Rogawski & Aghajanian, 1980), the primary input source to V1 which, in turn, has been shown to be of primary importance in the generation the P1 component.

The late effect on the N600 potential is consistent with an effect of psilocybin on decreasing the prolonged sensory processing of the visual stimuli. This late potential has not been previously described but may be related to the tendency for an afterimage to be perceived in the present study due to the very dark room and black background for the computer screen. The fact that it was not observed in the target trials might be related to a decrease in visual cortex post-processing after the execution of the motor command to respond to the target and the associated widespread activity this entails. The psilocybin-induced decrease in stimulus encoding evidenced by the decreased N1 amplitude to the distracter and the decreased frontal engagement evidenced by the reduced P3 and theta power activations may not be specifically related to this reduced late occipital negativity given the lack of correlation between the effects. The N600 finding is, however, consistent with the notion that psilocybin may decrease the tendency of the visual cortex to engage in prolonged post-processing of stimuli. Interestingly, the low dose psilocybin condition only moderately decreased the N600 amplitude to the distracter stimuli while it strongly decreased the N600 amplitude to the standard stimuli. This is consistent with the view that psilocybin decreases the visual post-processing of stimuli to which processes of

habituation are more active more readily than to distracting visual input. When considered in concert with the increased P1 component amplitude it appears that psilocybin may biases the visual system towards greater early cortical responsivity to stimuli but that mechanisms as yet not understood interfere with the extended processivity induced in the normally functioning visuospatial attentional system.

The findings reviewed herein indicate that psilocybin dramatically alters the neurophysiologic processing of the visual oddball paradigm. The earliest observed effects are seen to the P1 component where increased medial amplitudes are seen, an effect most strongly associated with the response to distracter stimuli. The N1 component is not greatly affected to the standard and target stimuli but is strongly increased in latency and decreased in amplitude in response to the distracter stimuli which is processed preferentially through the ventral stream. Both the P3a amplitude to the distracter and the P3b amplitude to the target are greatly reduced by psilocybin to the point where under the high dose condition there is no significant difference in amplitude of P3 response to the standard vs. target vs. distracter stimulus. Lastly, the increase in theta power observed to the target and especially distracter stimuli was strongly reduced by psilocybin.

There was a correlation between the baseline level of theta power induced by the distracter stimuli and the degree of positive altered state experienced as indexed by the OB score on the 5D-ASC. Further, the baseline level of theta power was also positively correlated with the degree of P3 reduction seen in response to the high dose psilocybin. Lastly, the low dose psilocybin-induced decreases in P3 amplitude to the standard stimuli

were associated with the degree of altered state experienced. Given the fact that numerous multiple regression calculations were executed, this pattern of correlations may have arisen from type I errors. Arguing against this possibility is the fact that of the three correlational patterns held for a number of related measures, but further validation would be required to have confidence. The strongest pattern of correlations was that observed between the distracter-induced theta power in the placebo states and the degree of altered state experienced in the oceanic boundlessness and visionary restructuralization domains. This association gives rise to the hypothesis that theta power induction to distracting stimuli, possibly a marker for some aspect of frontal attentional system functioning, is a trait marker for susceptibility to positively experienced altered state under the effect of serotonergic hallucinogens.

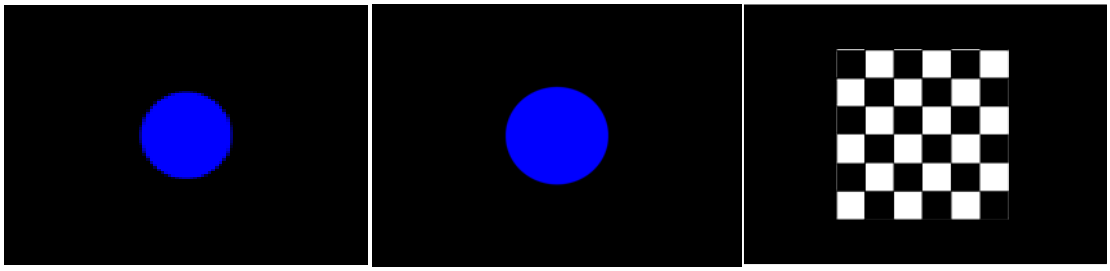
In sum, the findings obtained indicate that psilocybin induces a state of neurophysiologic processing with some increases in early visual processing, possibly at the level of V1. Later effects on N1 and P3a and P3b amplitudes indicate that psilocybin slows the processing of visual distracter stimuli as well as decreasing the strength of processing by the attentional networks involved in visuospatial operations. The decreased attentional engagement may be related to the degree of altered state experienced, mirroring findings in schizophrenia that P3 amplitude decrements are related to schizophrenic symptomatology.

Chapter 3, in part, is in preparation for submission for publication with Franz Vollenweider as co-author. The dissertation author is the primary investigator and author of this paper.

Chapter 3 Table 1. Percent correct response and reaction time for the three psilocybin dose conditions. Mean ± S.E.M. is indicated in each case.

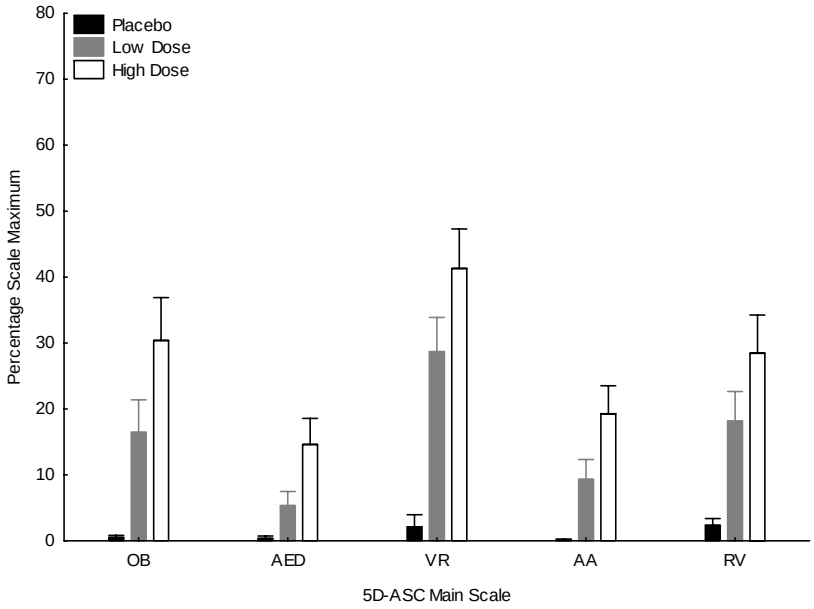
Dose	Percentage correct - Standards	Percentage correct - Targets	Target Reaction Time
Placebo	99.4 ± 0.16 %	90.9 ± 1.9 %	455.0 ± 20.7
Low Dose	98.8 ± 0.32 %	80.7 ± 2.5 %	513.6 ± 21.7
High Dose	97.0 ± 0.89 %	82.1 ± 3.3 %	550.8 ± 28.8

1.

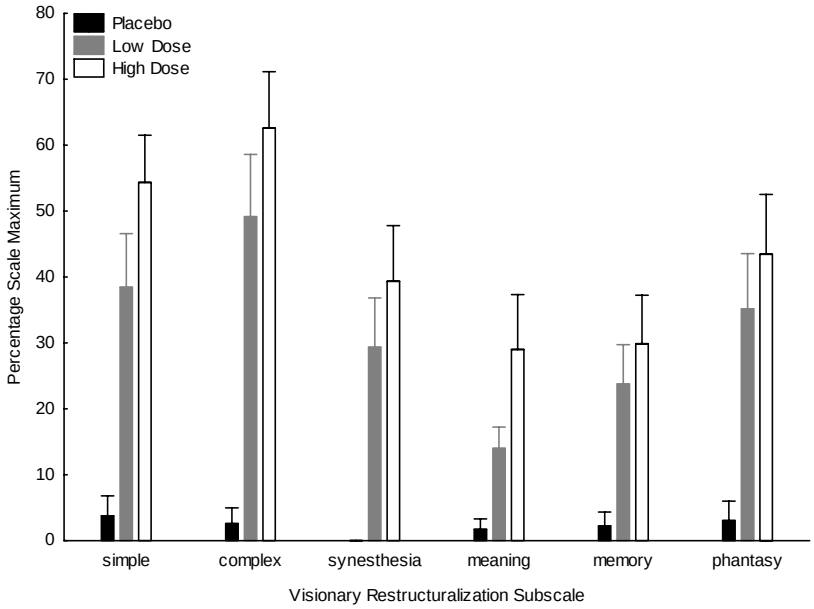


Chapter 3 Figure 1 legend. Standard (left), target (middle) and distracter (right) stimuli employed in the visual oddball paradigm. Subjects were required to respond to the smaller-diameter target blue circle only.

2a.

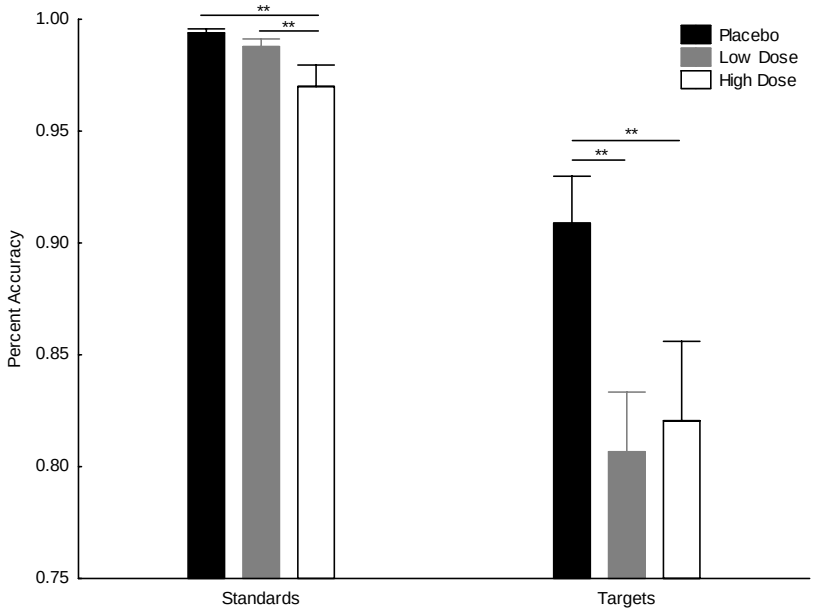


2b.

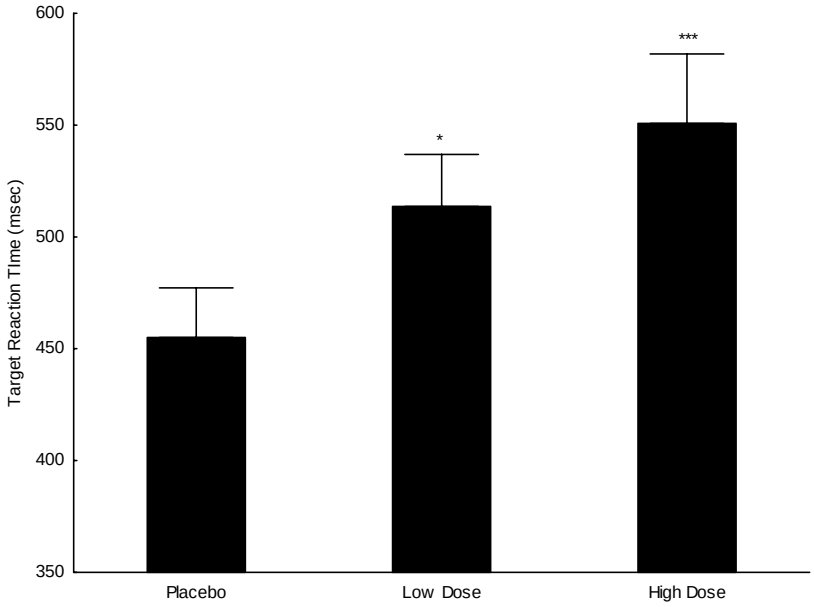


Chapter 3 Figure 2 legend. Mean percentage scores ± SEM of the Altered States of Consciousness Rating Scale (5D-ASC) main scales (2a) and subscales of the Visionary Restructuralization scale (2b) during placebo, low dose psilocybin (125 µg/kg), and high dose psilocybin (250 µg/kg) conditions. OB = Oceanic Boundlessness, AED = Anxious Ego Dissolution, VR = Visionary Restructuralization, AA = Auditory Alterations, RV = Reduction of Vigilance.

3a.

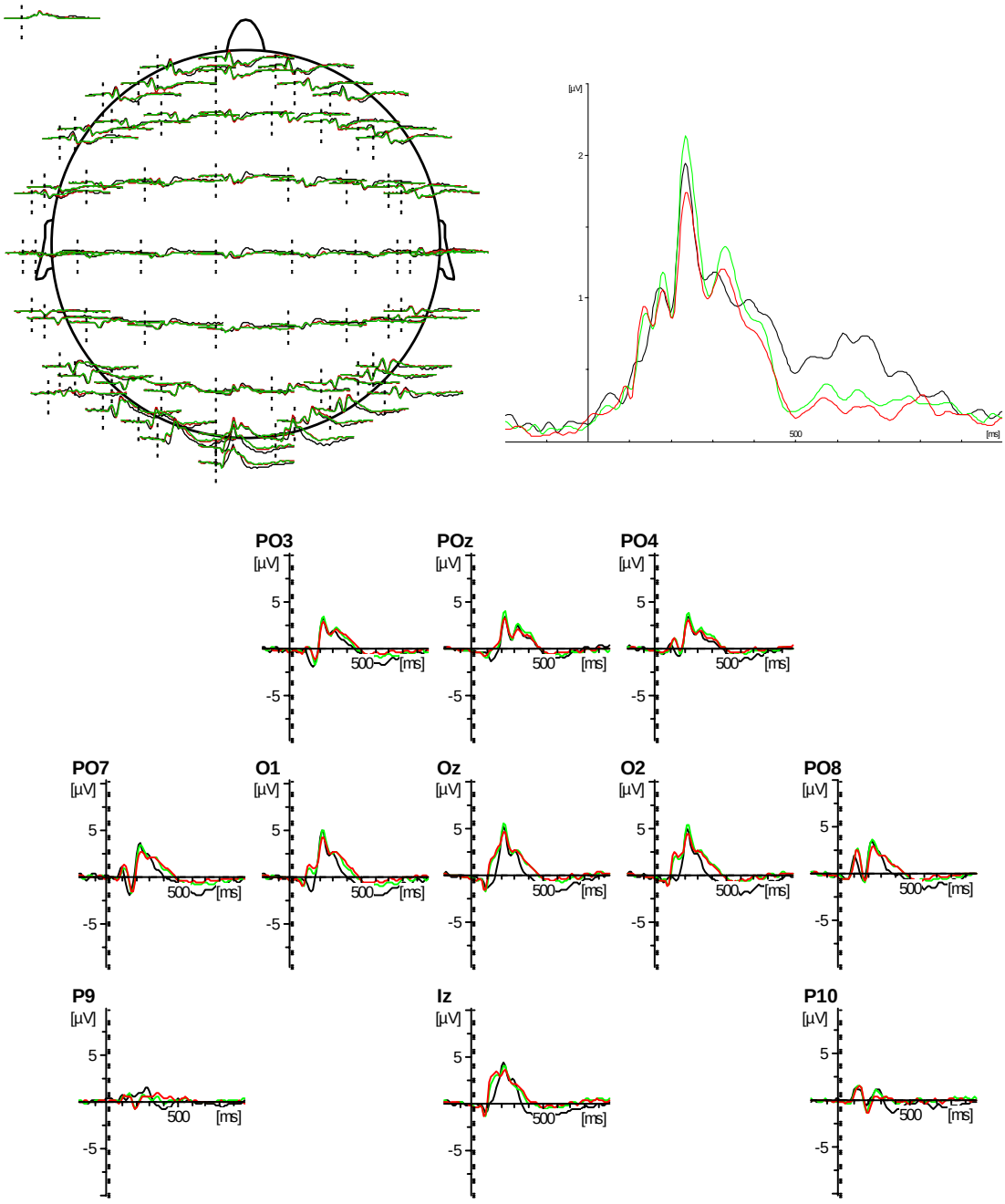


3b.



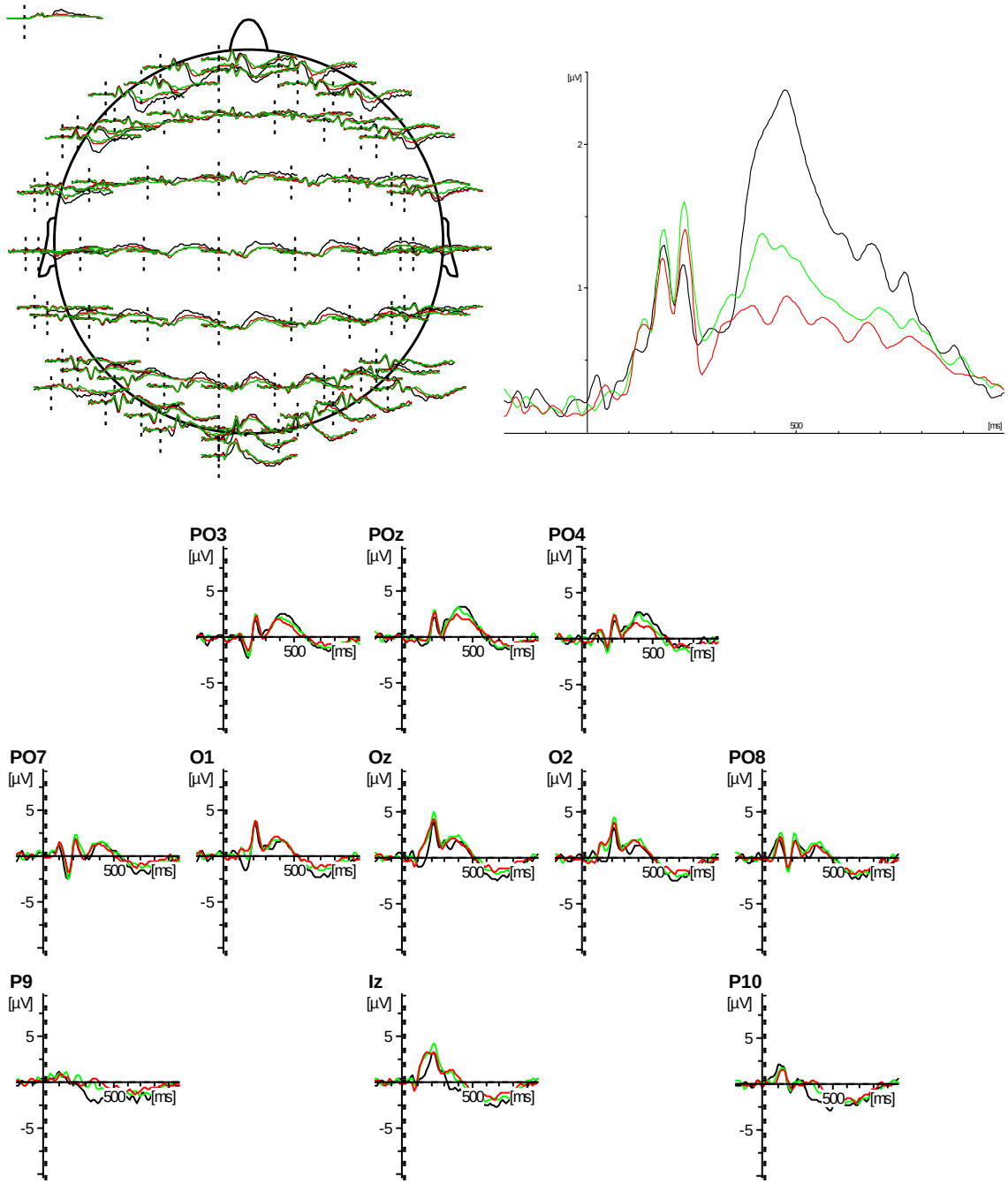
Chapter 3 Figure 3 legend. Accuracy (3a) and reaction time (3b) performance on the visual oddball task. Psilocybin causes decreases in accuracy and increases in reaction time. *, **,*** indicate significant difference with placebo condition at the $p < 0.05$, $p < 0.01$ and $p < 0.001$ significance level.

4a.



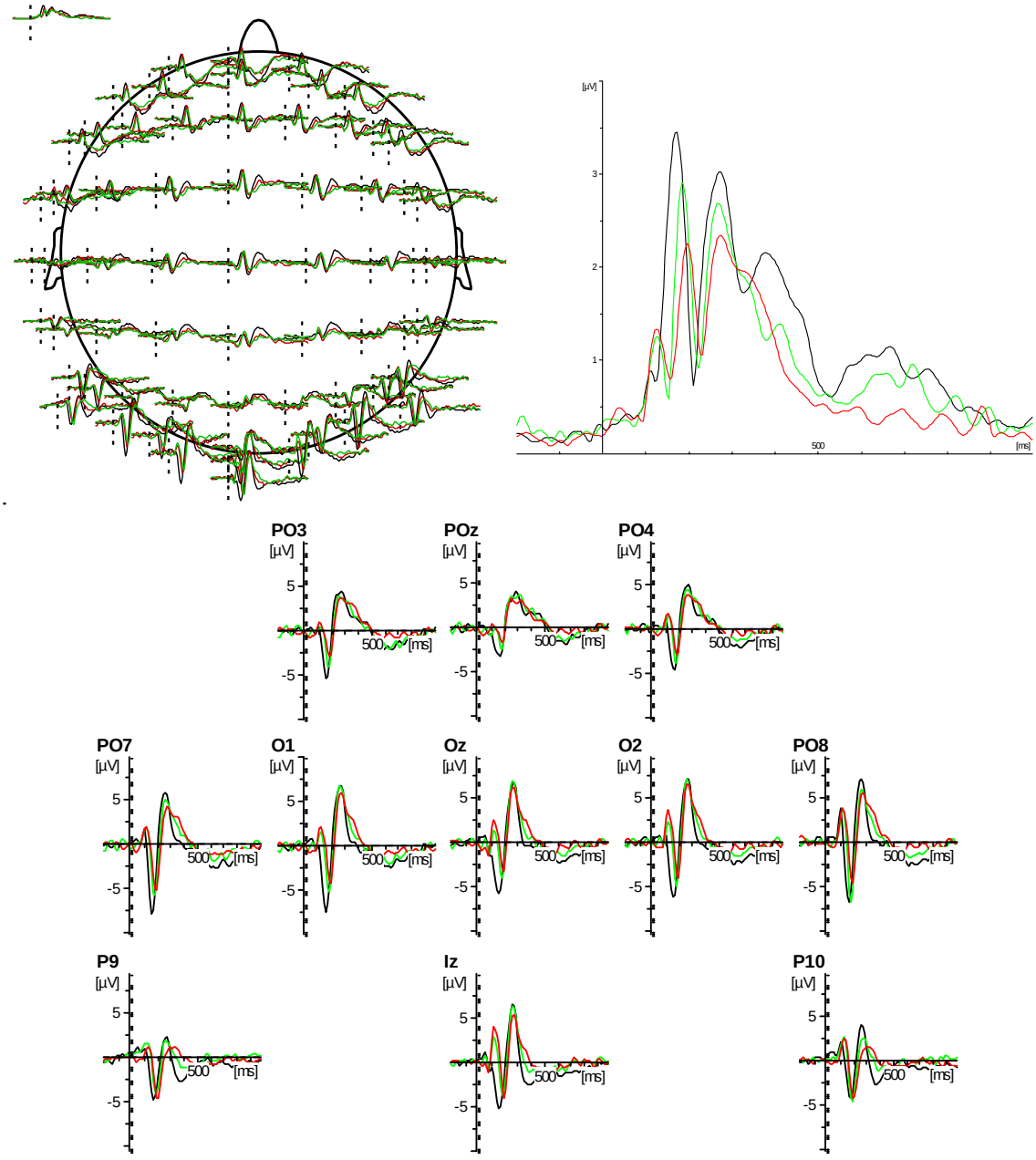
Chapter 3 Figure 4 legend. Grand average waveforms for the Standard, Target and Distracter trials. Black lines indicate placebo condition, red lines indicate low dose psilocybin condition, green lines indicate high dose psilocybin condition. The global field power map is indicated in the upper right quadrant for each condition. 4a, Standard waveforms under placebo, low dose, and high dose conditions; 4b, Target waveforms under placebo, low dose, and high dose conditions; 4c, Distracter waveforms under placebo, low dose, and high dose conditions.

4b.



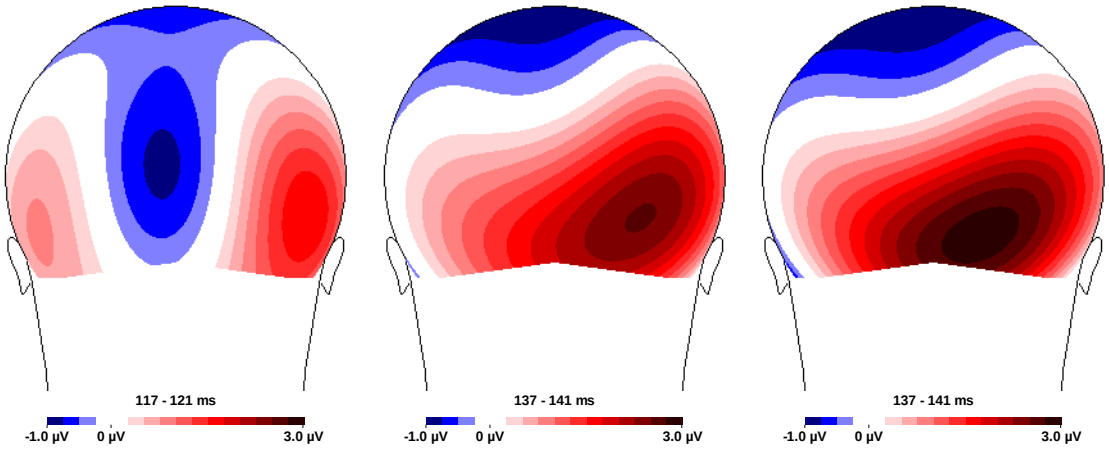
Chapter 3 Figure 4 continued. Grand average waveforms for the Standard, Target and Distracter trials. 4b, Target waveforms under placebo, low dose, and high dose conditions.

4c.



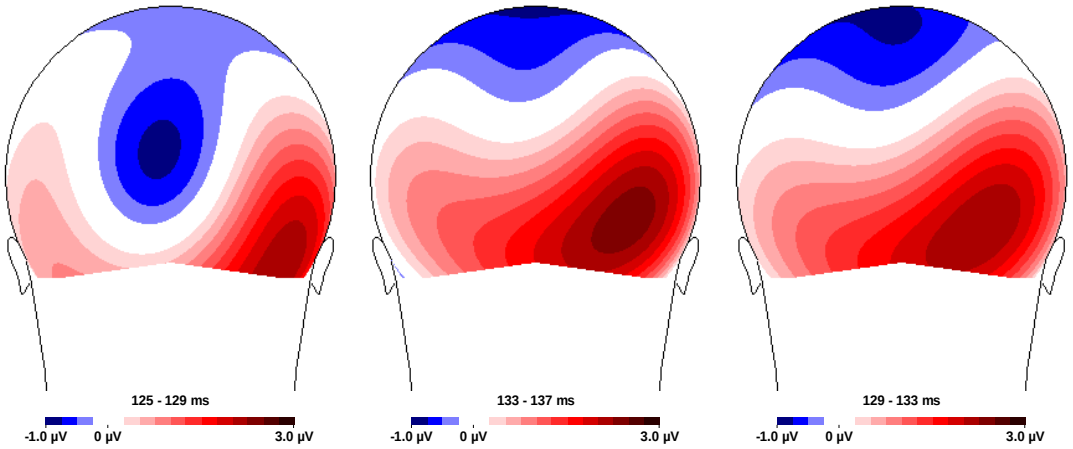
Chapter 3 Figure 4 continued. Grand average waveforms for the Standard, Target and Distracter trials. 4c, Distracter waveforms under placebo, low dose, and high dose conditions.

5a. 5b. 5c.



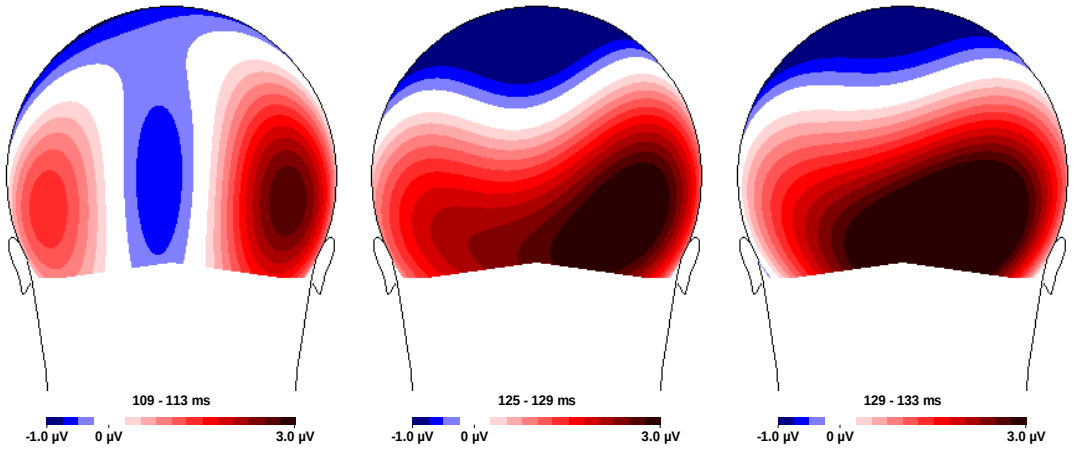
Chapter 3 Figure 5 legend. Scalp distribution at the peak of the global field power for the P1 component to the Standard stimuli in placebo (5a), low dose psilocybin (5b), and high dose psilocybin (5c) conditions

6a. 6b. 6c.

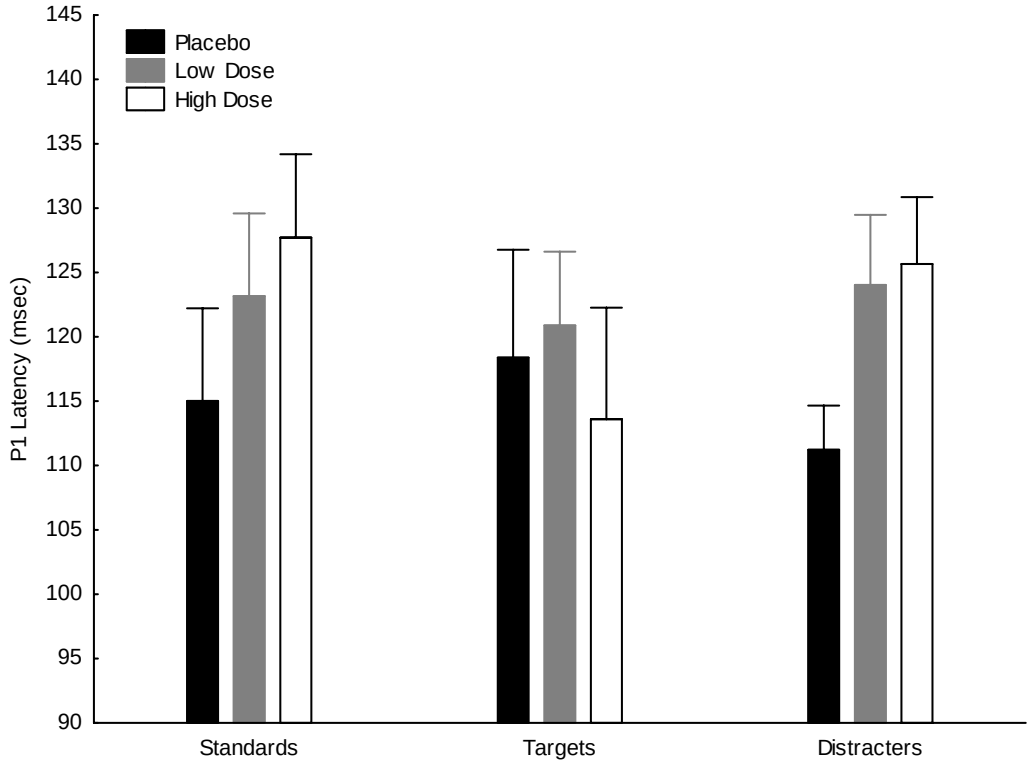


Chapter 3 Figure 6 legend. Scalp distribution at the peak of the global field power for the P1 component to the Target stimuli in placebo (6a), low dose psilocybin (6b), and high dose psilocybin (6c) conditions

7a. 7b. 7c.

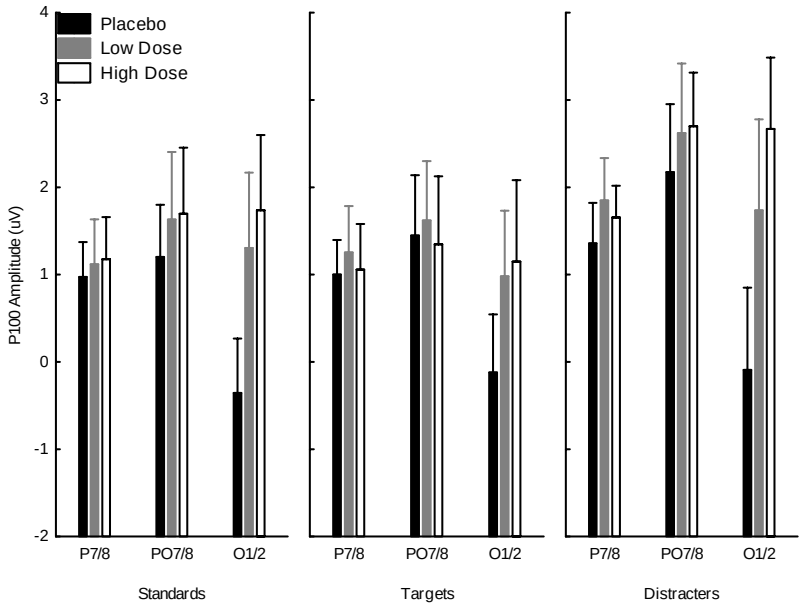


7d.

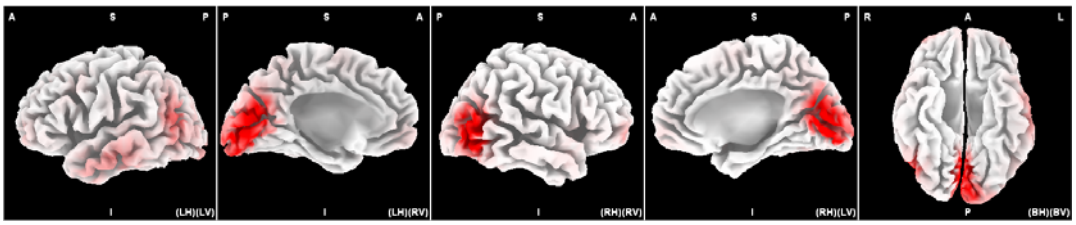


Chapter 3 Figure 7 legend. Scalp distribution for the P1 component at the peak of the global field power for the Distracter stimuli in placebo (7a), low dose psilocybin (7b), and high dose psilocybin (7c) conditions. P1 latency (7d) and amplitude (7e) values for the Standards, Targets and Distracters in placebo, low dose, and high dose conditions. 7f, LORETA grand average difference map for the high dose distracter trials – placebo distracter trials.

7e.

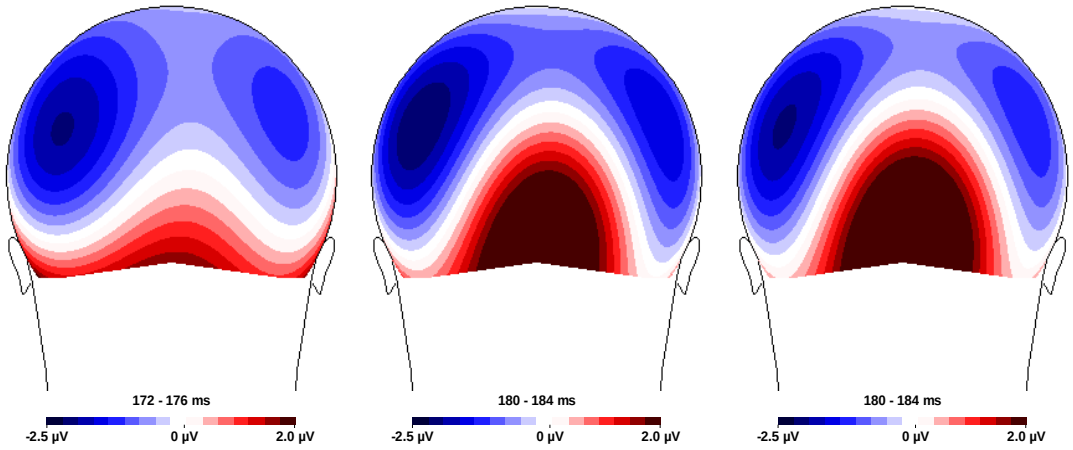


7f.



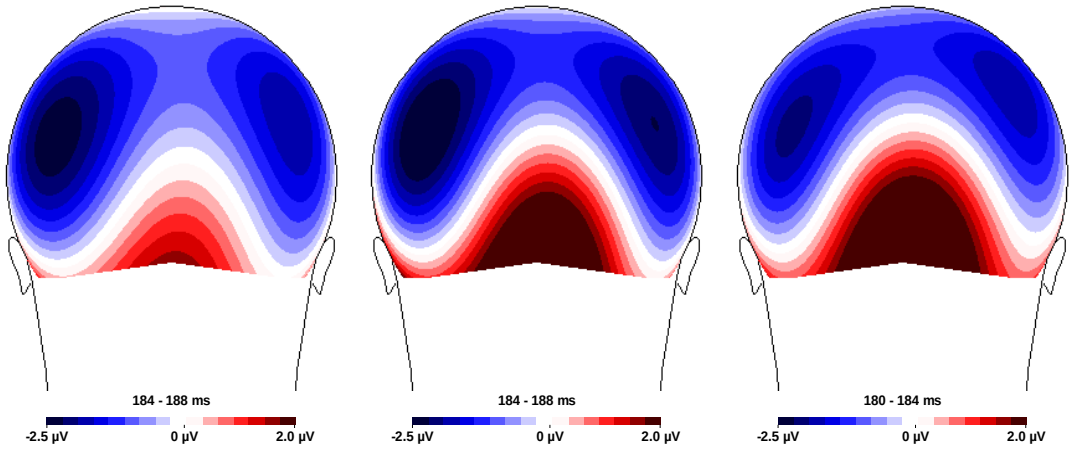
Chapter 3 Figure 7 continued. 7e, P1 amplitude values for the Standards, Targets and Distracters in placebo, low dose, and high dose conditions; 7f, LORETA grand average difference map for the high dose distracter trials – placebo distracter trials

8a. 8b. 8c.



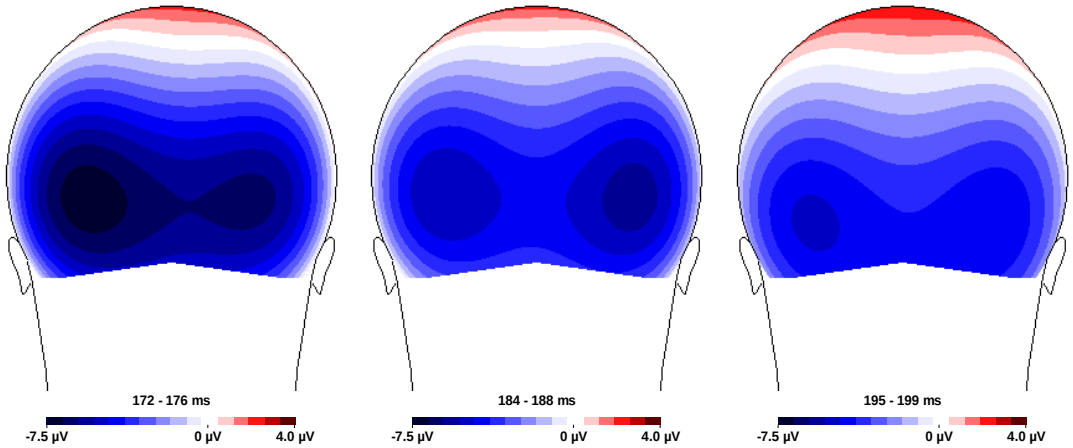
Chapter 3 Figure 8 legend. Scalp distribution for the N1 at the peak of the global field power to the Standard stimuli in placebo (8a), low dose psilocybin (8b), and high dose psilocybin (8c) conditions.

9a. 9b. 9c.

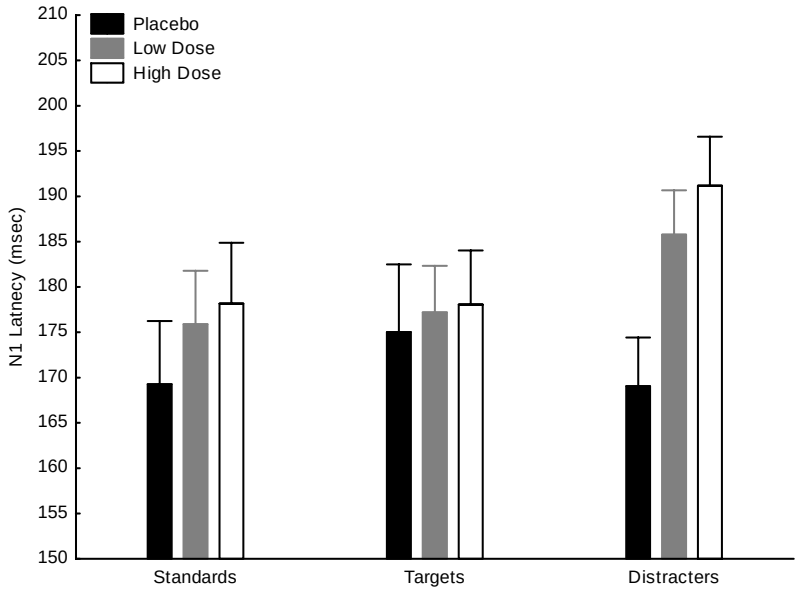


Chapter 3 Figure 9 legend. Scalp distribution for the N1 at the peak of the global field power to the Target stimuli in placebo (7a), low dose psilocybin (7b), and high dose psilocybin (7c) conditions

10a. 10b. 10c.

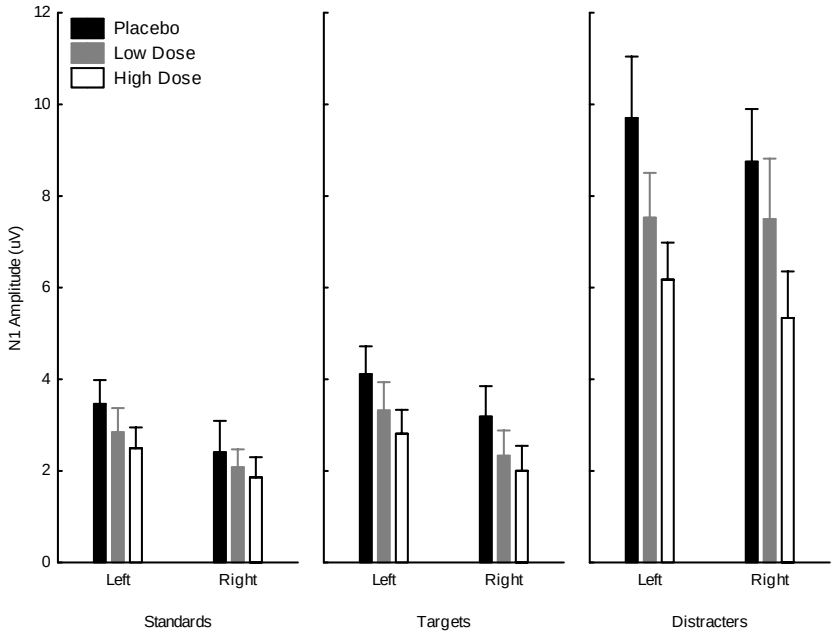


10d.



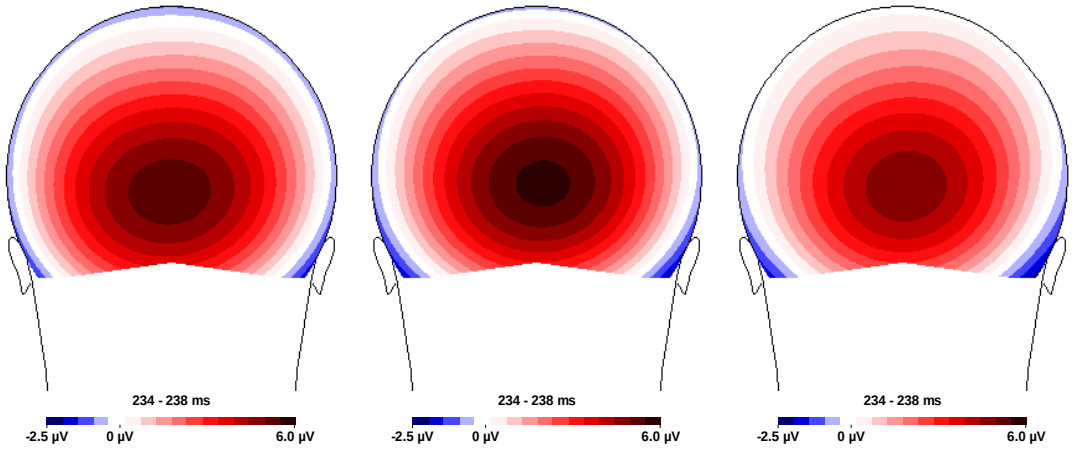
Chapter 3 Figure 10 legend. Scalp distribution for the N1 at the peak of the global field power to the Distracter stimuli in placebo (10a), low dose psilocybin (10b), and high dose psilocybin (10c) conditions. Note that the scale is greater than figures 8 and 9 due to the much stronger N1 amplitude to Distracters. 10d, N1 latency amplitude to all stimuli in placebo, low dose and high dose conditions. 10e, N1 amplitude to all stimuli in placebo, low dose and high dose conditions.

10e.



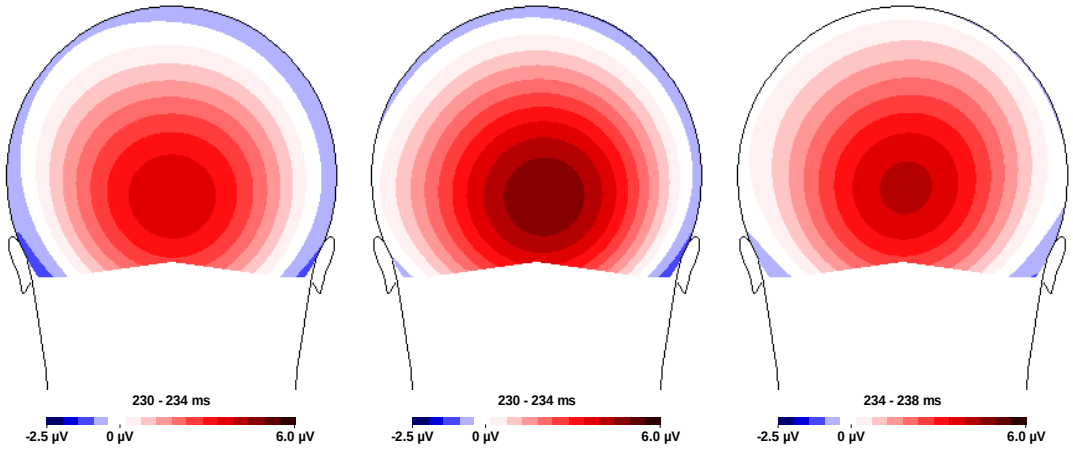
Chapter 3 Figure 10 continued. 10e, N1 amplitude to all stimuli in placebo, low dose and high dose conditions.

11a. 11b. 11c.



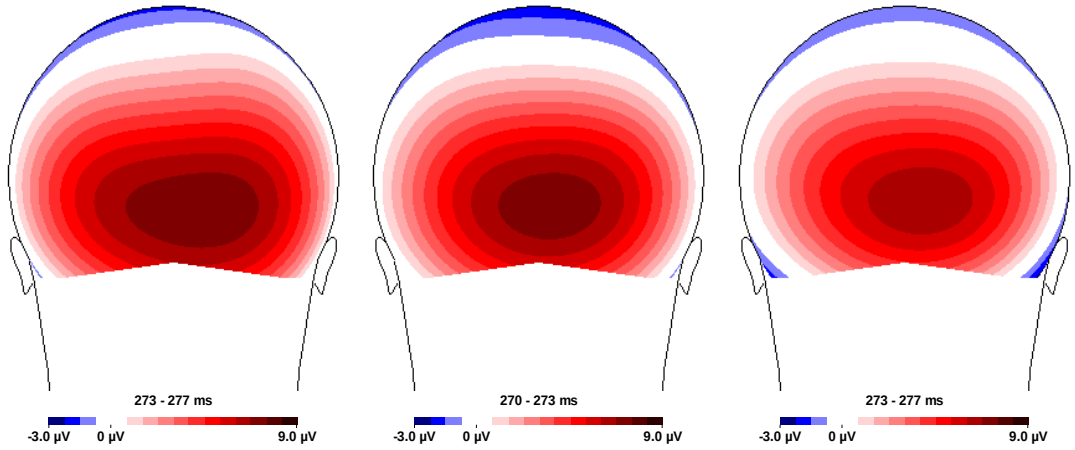
Chapter 3 Figure 11 legend. Scalp distribution for the P2 at the peak of the global field power to the Standard stimuli in placebo (11a), low dose psilocybin (11b), and high dose psilocybin (11c) conditions

12a. 12b. 12c.

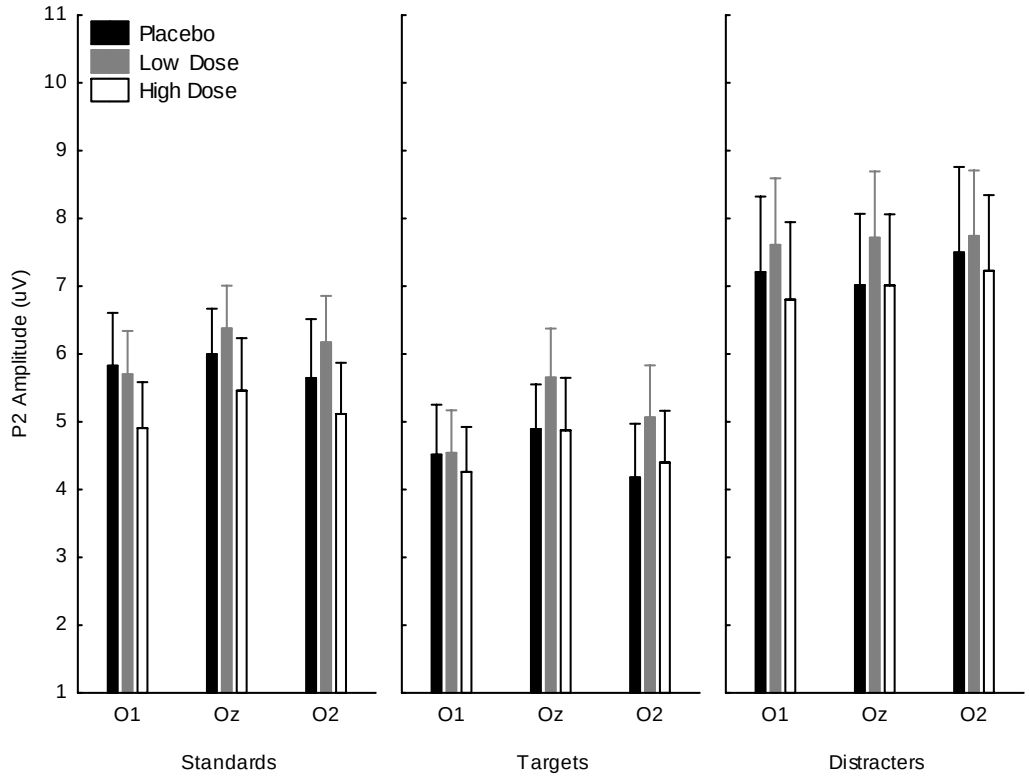


Chapter 3 Figure 12 legend. Scalp distribution for the P2 at the peak of the global field power to the Target stimuli in placebo (12a), low dose psilocybin (12b), and high dose psilocybin (12c) conditions.

13a. 13b. 13c.

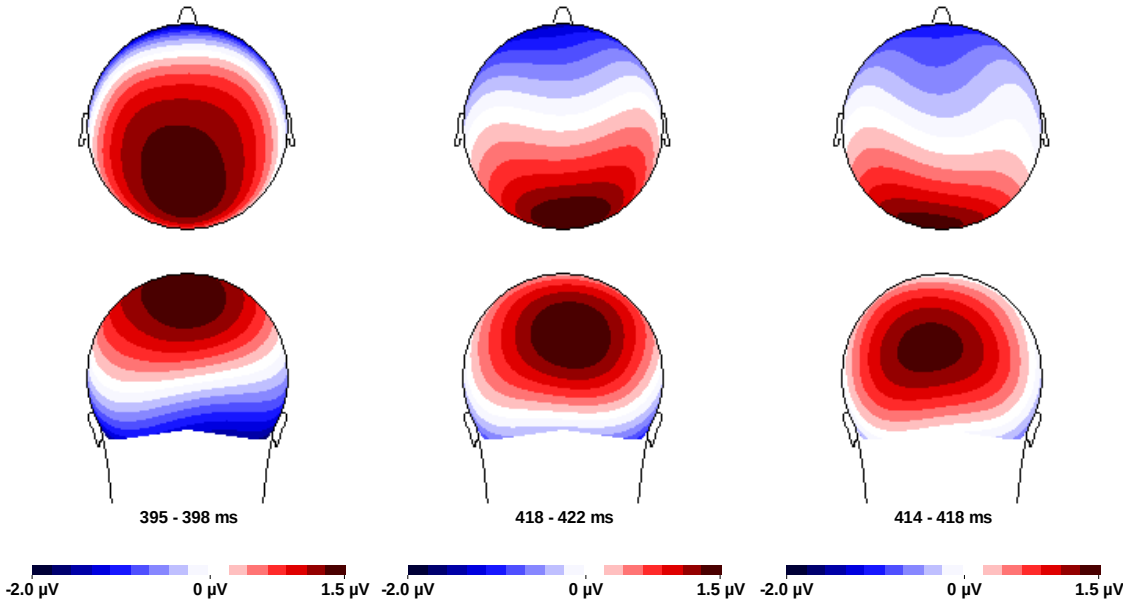


13d.

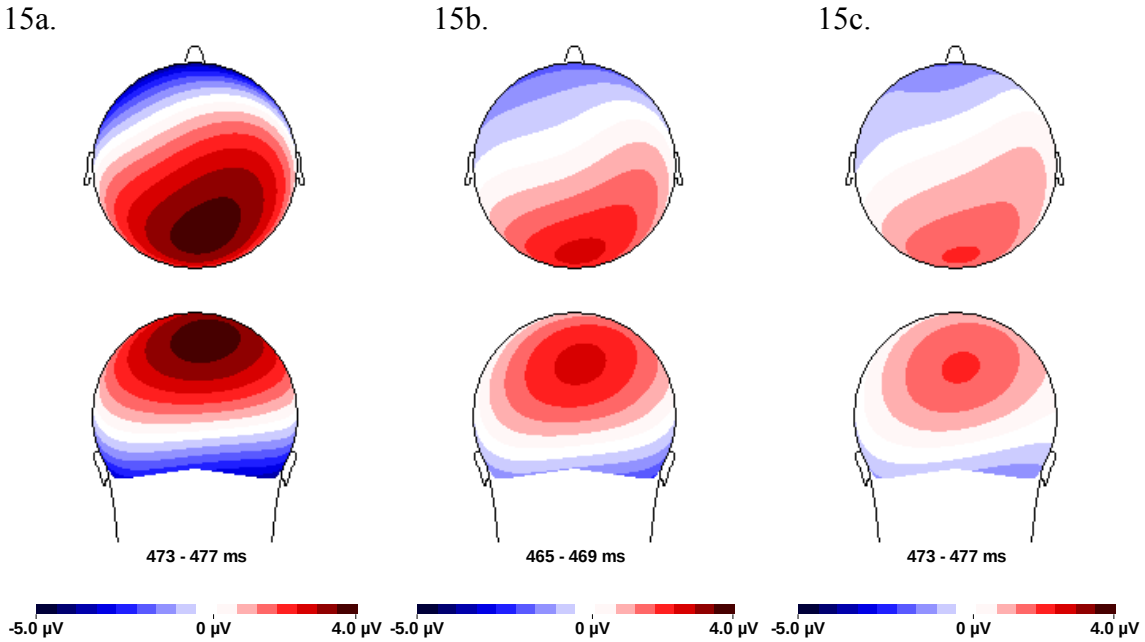


Chapter 3 Figure 13 legend. Scalp distribution for the P2 at the peak of the global field power to the Distracter stimuli in placebo (13a), low dose psilocybin (13b), and high dose psilocybin (13c) conditions. Note that the scale is greater than figures 11 and 12 due to the much stronger N1 amplitude to Distracters. 13d shows the P2 amplitudes to each of the stimuli under placebo, low dose, and high dose conditions

14a. 14b. 14c.

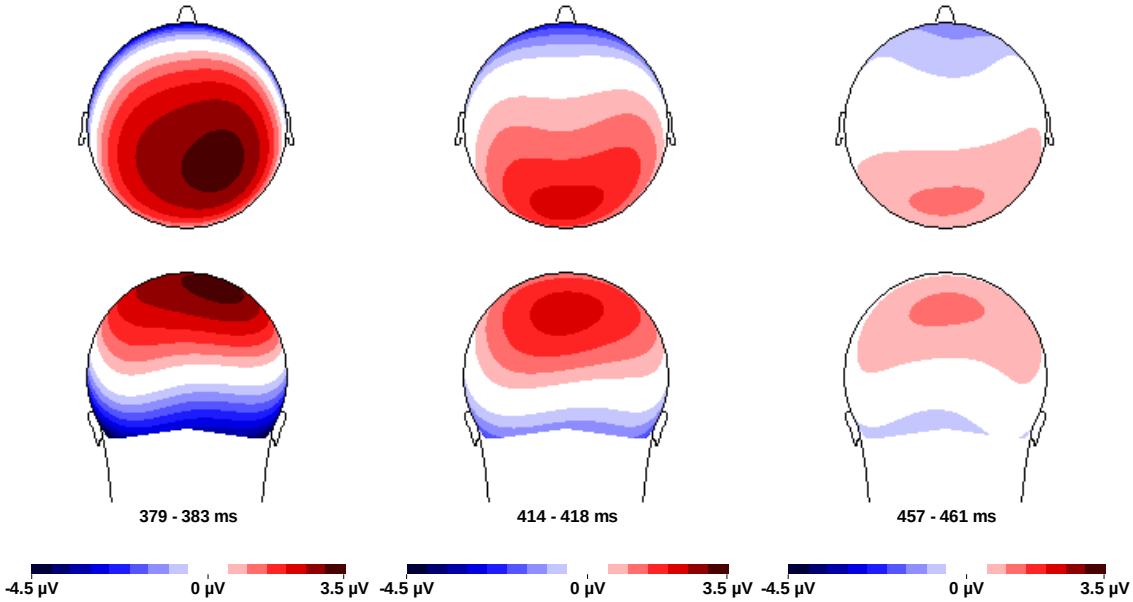


Chapter 3 Figure 14 legend. Scalp distribution for the P3 at the peak of the global field power to the Standard stimuli in placebo (14a), low dose psilocybin (14b), and high dose psilocybin (14c) conditions

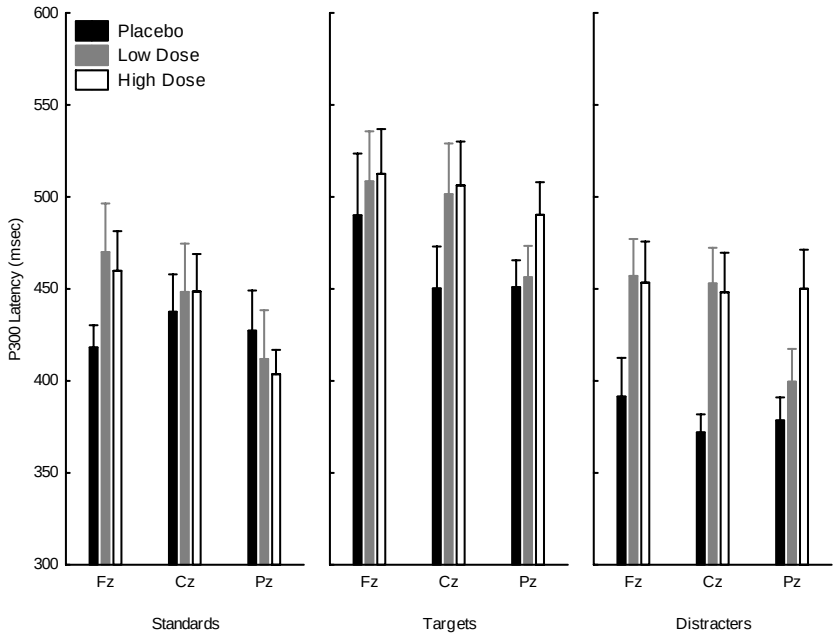


Chapter 3 Figure 15 legend. Scalp distribution for the P3 at the peak of the global field power to the Target stimuli in placebo (15a), low dose psilocybin (15b), and high dose psilocybin (15c) conditions

16a. 16b. 16c.

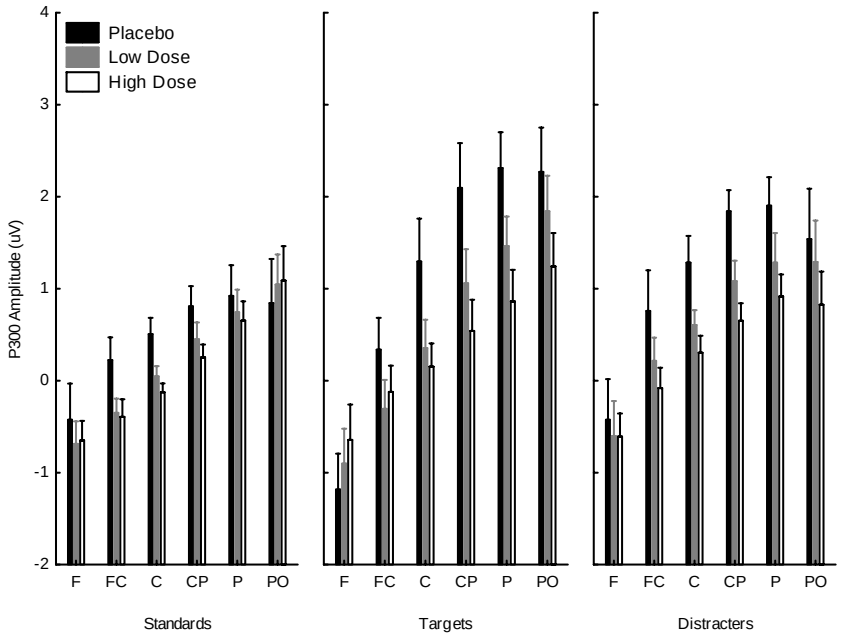


16d.

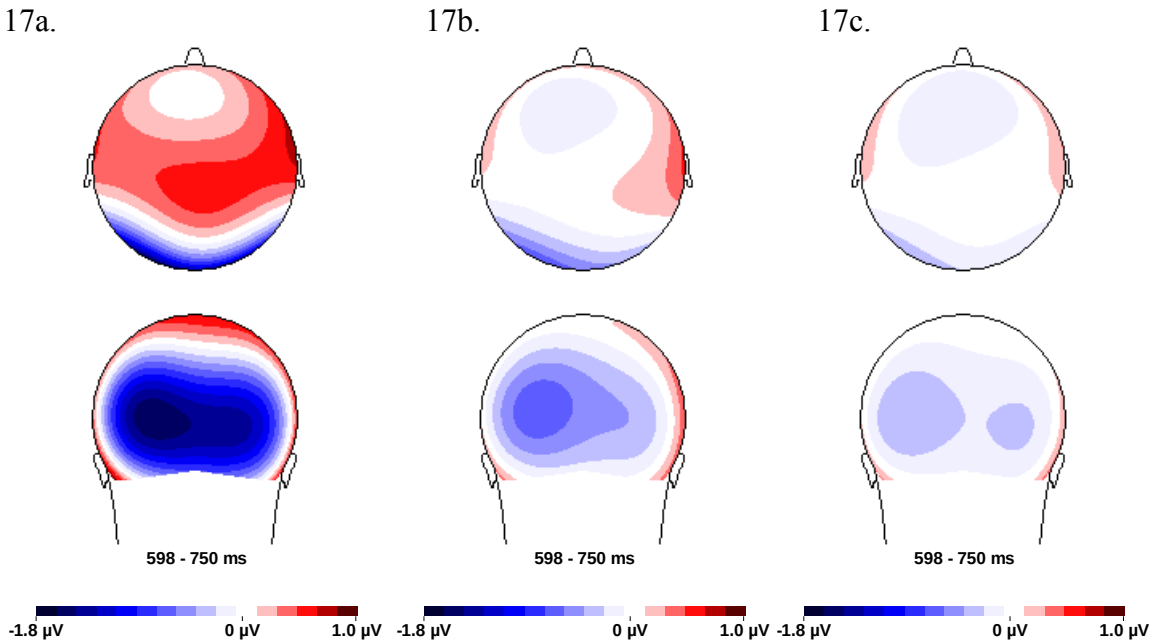


Chapter 3 Figure 16 legend. Scalp distribution for the P3 at the peak of the global field power to the Distracter stimuli in placebo (16a), low dose psilocybin (16b), and high dose psilocybin (16c) conditions. P300 latency (16d) and amplitude (16e) to Standard, Target, and Distracter Stimuli under Placebo, Low Dose, and High Dose conditions.

16e.

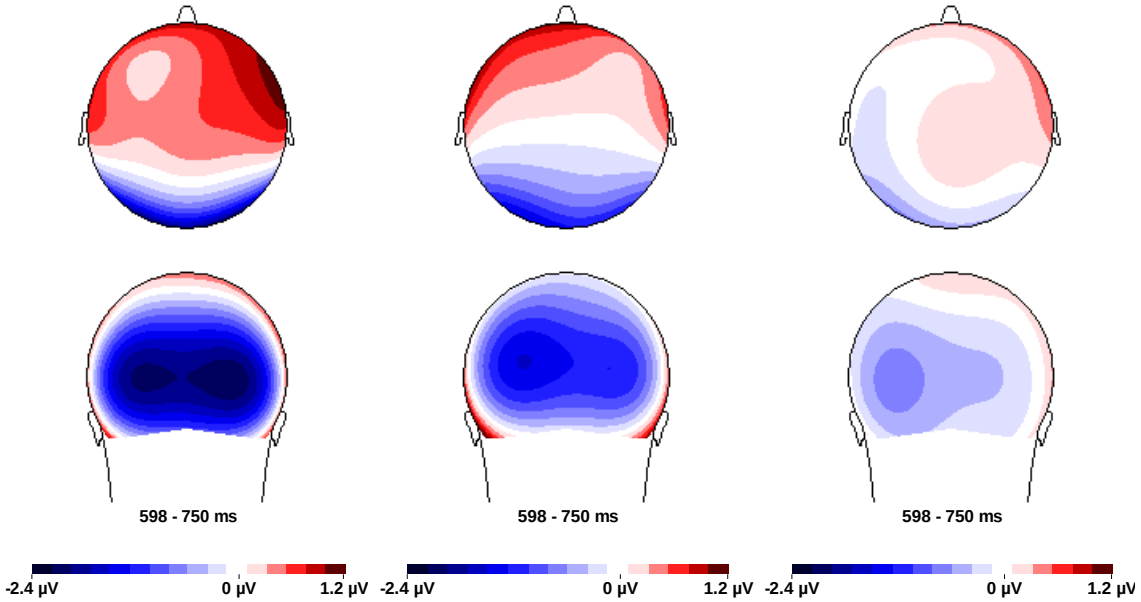


Chapter 3 Figure 16 continued. 16e, P300 amplitude to Standard, Target, and Distracter Stimuli under Placebo, Low Dose, and High Dose conditions

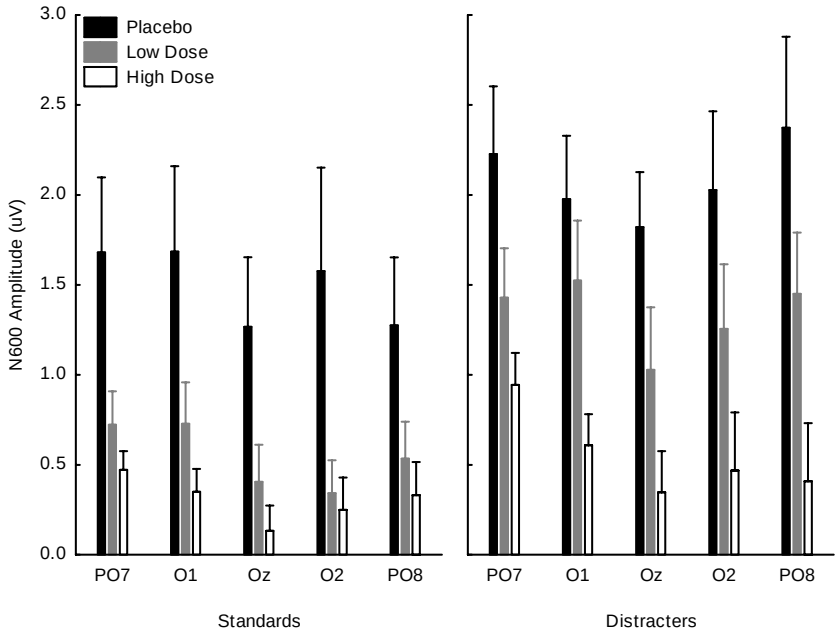


Chapter 3 Figure 17 legend. Scalp distribution for the N600 for the Standard stimuli in placebo (17a), low dose psilocybin (17b), and high dose psilocybin (17c) conditions

18a. 18b. 18c.

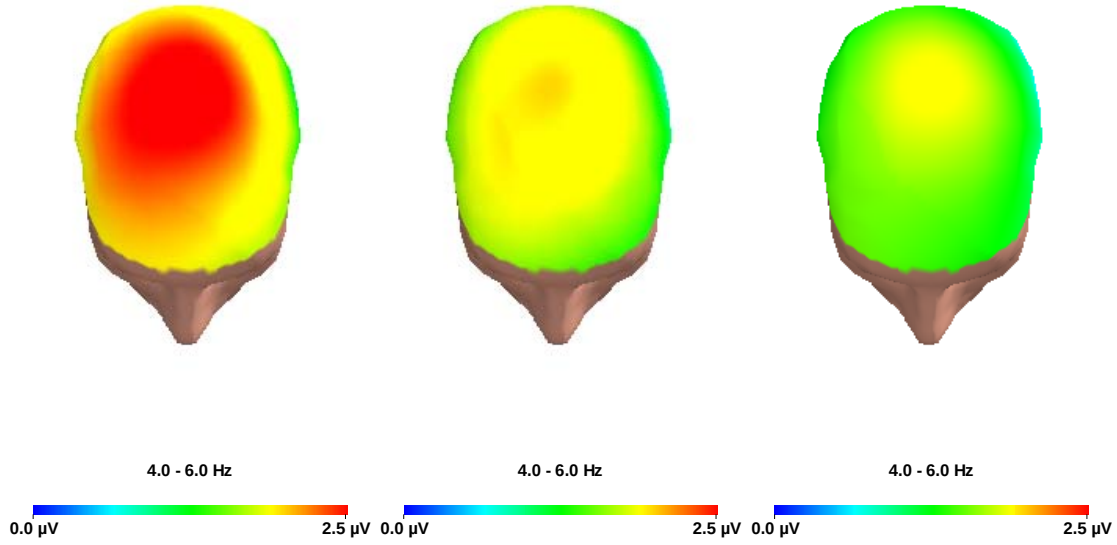


18d.



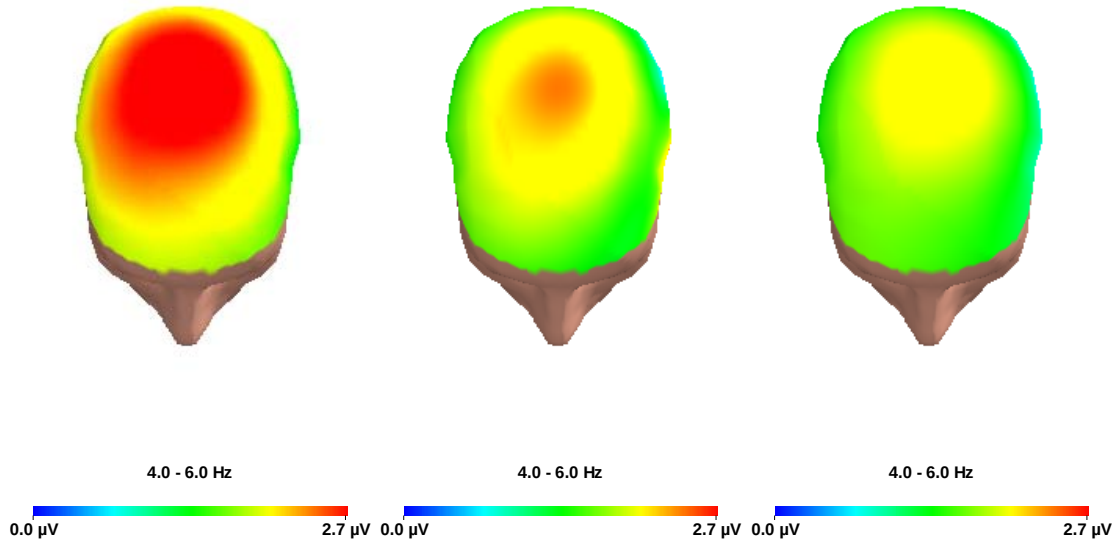
Chapter 3 Figure 18 legend. Scalp distribution for the N600 for the Distracter stimuli in placebo (18a), low dose psilocybin (18b), and high dose psilocybin (18c) conditions. 18d depicts the N600 amplitude to the Standard and Distracter Stimuli under placebo, low dose, and high dose conditions at occipital channels.

19a. 19b. 19c.



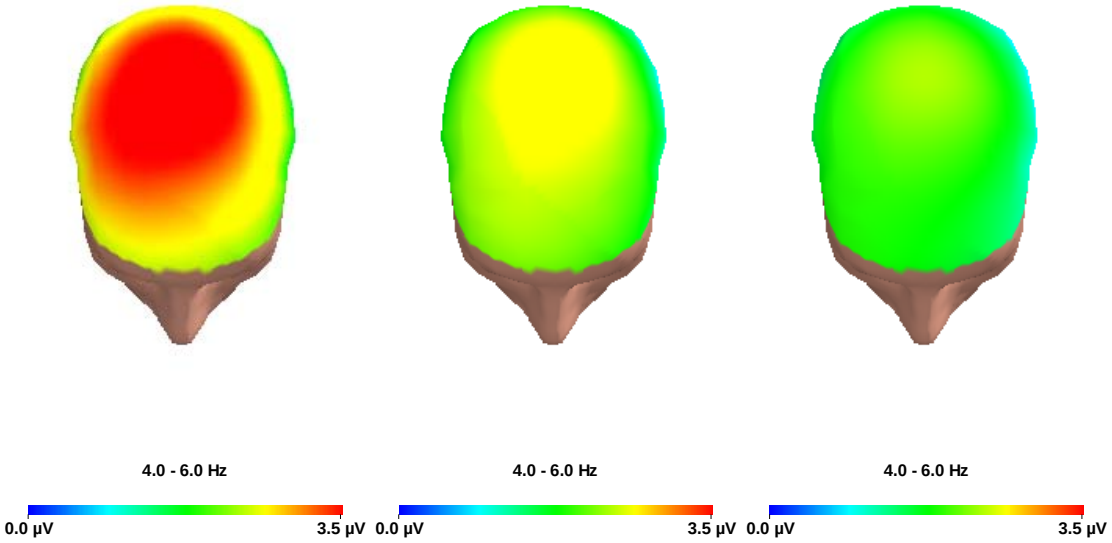
Chapter 3 Figure 19 legend. Theta power scalp distribution for the Standard stimuli in placebo (19a), low dose psilocybin (19b), and high dose psilocybin (19c) conditions.

20a. 20b. 20c.

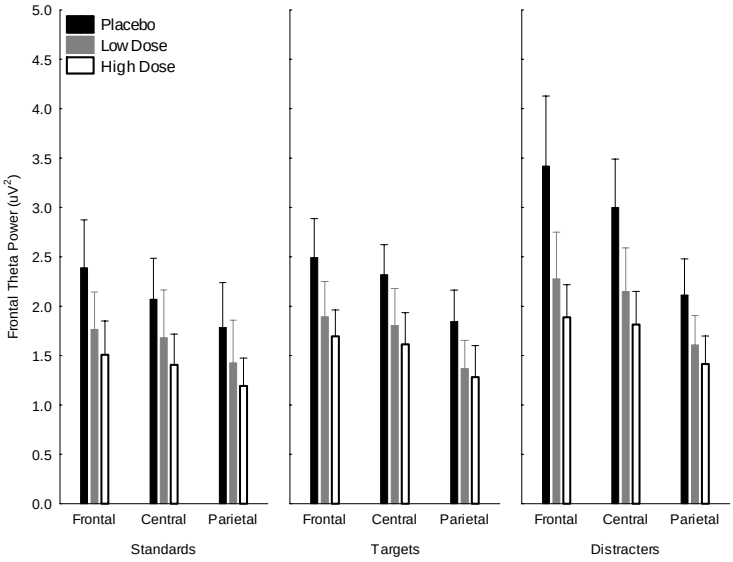


Chapter 3 Figure 20 legend. Scalp map of Theta Power (4-6 Hz) scalp distribution for the Target stimuli in placebo (20a), low dose (20b), and high dose (20c) conditions

21a. 21b. 21c.

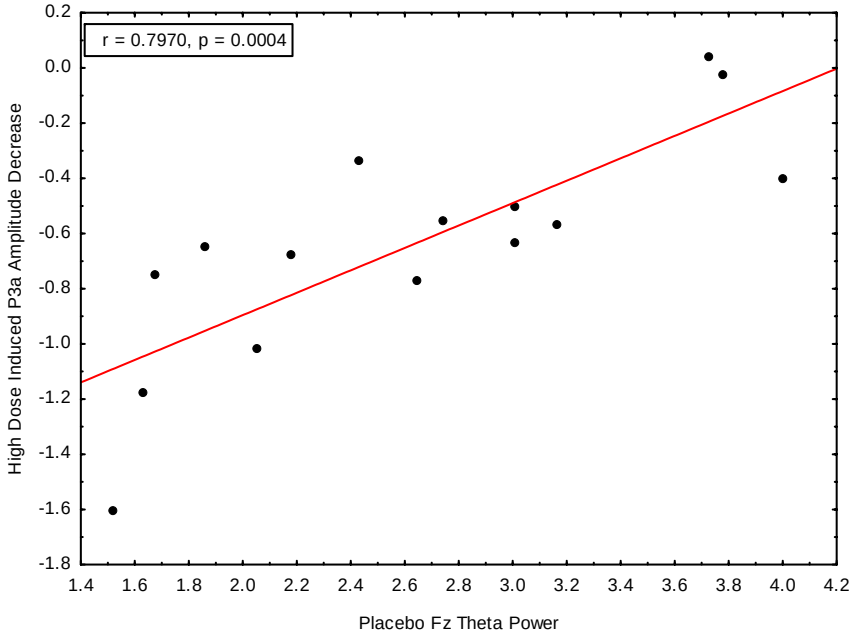


21d.

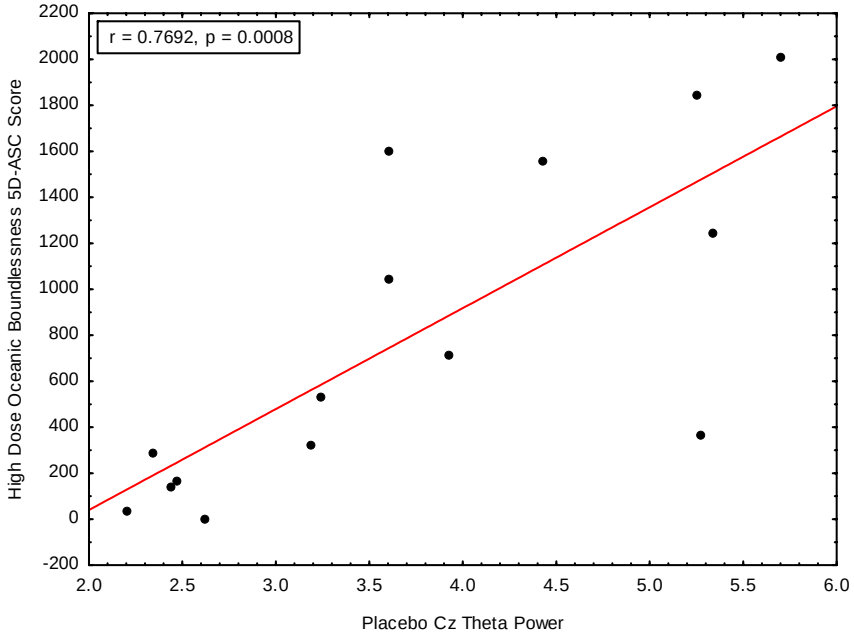


Chapter 3 Figure 21 legend. Scalp map of Theta Power scalp distribution for the Distracter stimuli in placebo (21a), low dose psilocybin (21b), and high dose psilocybin (21c) conditions. 21d Theta (4-6 Hz) power at frontal, central, and parietal locations to the Standards, Targets, and Distracters.

22a.

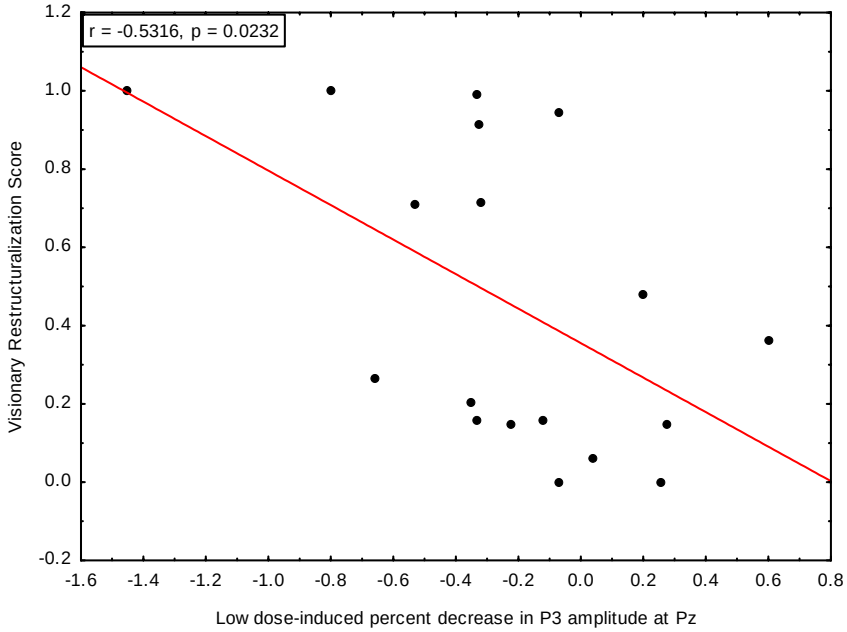


22b.



Chapter 3 Figure 22 legend. Correlation of theta power with reported psychometric scales. 22a, correlation between frontal theta power under placebo conditions and the decrease of P3a amplitude to high dose psilocybin; 22b, correlation between theta power at Cz under placebo conditions and Oceanic Boundlessness scores; 22c, correlation between low dose psilocybin reduction in standard P3 amplitude and Visionary Restructuralization-like score reported during ERP recording session.

22c.



Chapter 3 Figure 22 continued. 22c, correlation between low dose psilocybin reduction in standard P3 amplitude and Visionary Restructuralization-like score reported during ERP recording session.

CHAPTER 4

Psilocybin and illusory contour processing: Altered spatiotemporal brain dynamics during the perception of a visual illusion

Abstract

The hallucinogenic serotonin1A/2A agonist psilocybin is known for its ability to induce an altered state of consciousness associated with visual illusions that mimics some of the signs and symptoms of psychosis. Recent studies of visual processing in schizophrenia have indicated disturbances in visual evoked responses in these subjects, including disruptions of the sensory P100 ERP component, the N170 component known to be involved in object recognition, as well as the P300 component associated with context-updating cognitive processes. Kanizsa triangles are stimuli that have been shown to cause significantly increased N170 amplitude responses relative to control stimuli due to the presence of illusory contours and the induced gestalt perception of form. Further, the processing of illusory contours and Kanizsa figures has been found to be degraded in schizophrenic subjects. This study investigates the effect of psilocybin on brain processing of Kanizsa triangles using both an ERP paradigm composed of the presentation of Kanizsa figures and control stimuli and a visual detection task wherein Kanizsa triangles and real triangles were embedded within fields of distracters. We demonstrate that psilocybin enhances amplitude at the occipital midline for the early P100 component and strongly decreases the N170 amplitude. Additionally, psilocybin

preferentially inhibited the N170 amplitude to the Kanizsa stimuli relative to control stimuli. The decrease in N170 amplitude was correlated with the decreased performance on the visual detection task, indicating a possible functional significance. This result is discussed in relation to previous findings in schizophrenia and supports the notion that some aspects of visual processing in psychosis may be modeled by the use of hallucinogens such as psilocybin.

Introduction

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a mixed 5HT1a/2a agonist that has been shown to induce an altered state of consciousness marked by visual disturbances varying from simple patterns to complex visual hallucinations. Kanizsa figures are visual stimuli that induce the perception of illusory contours in normal subjects and have been shown to activate lateral occipital cortical areas and engage visuospatial attention. The current study assesses how psilocybin influences the different stages of visual perception and cognition with similarities and differences to the ways in which the brains of schizophrenic patients might be altered noted.

Psilocybin may be used to induce transient and predictable changes in neurotransmitter activity so as to gain insight into the mechanisms responsible for visual distortions and by extension, into visual functioning generally. Further, given the relationship between the hallucinogenic drug action and naturally occurring schizophrenia, observed alterations may be of relevance to the pathophysiology of schizophrenia. This is of particular relevance with the recent genetic observation of a

relationship between the 5HT2a serotonin receptor most closely associated with the psychological alterations due to the classic hallucinogens (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998) and schizophrenia (Abdolmaleky, Faraone, Glatt, & Tsuang, 2004; Dean & Hayes, 1996; Joober et al., 1999).

Psilocybin interacts mainly with serotonergic neurotransmission including prominent activity at 5-HT1A, 5-HT2A, and 5-HT2C receptor subtypes (Nichols, 2004). In contrast to lysergic acid diethylamide (LSD), psilocybin and its active metabolite psilocin have no affinity for dopamine D2 receptors (Creese, Burt, & Snyder, 1975). In a receptor-blocking study, it was shown that the psychotropic effects of psilocybin could be blocked completely by pretreatment with the 5-HT2A preferential antagonist ketanserin (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998) suggesting that psilocybin-induced effects are mediated primarily via activation of 5-HT2A receptor subtypes, with multiple downstream effects on other neurotransmitter systems including dopamine and glutamate identified (Aghajanian & Marek, 1997; Vollenweider, Vontobel, Hell, & Leenders, 1999).

Aside from the use of psilocybin as a model for schizophrenia (Vollenweider et al. 1997; Gouzoulis-Mayfrank et al. 1998; Vollenweider et al. 1999; Vollenweider and Geyer 2001), psilocybin can serve as an experimental tool in neurosciences to study the neurobiological basis of altered states of consciousness (ASC). Recent investigations revealed that the serotonin (5-HT) receptor system is of basic importance also in the modulation of cognitive functions such as memory and attention (Meneses 1998; Buhot et al. 2000; Ellis and Nathan 2001). Hence, the 5-HT2 receptor agonistic mode of action

of psilocin (4-hydroxy-N,N,-dimethyltryptamine), the first and pharmacologically active metabolite of psilocybin (Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997), makes this "classic" visual hallucinogen an interesting compound to investigate brain mechanisms underlying visual perception.

The primary aim of this study was to determine how psilocybin influences illusory contour processing. A secondary aim was to investigate whether it does so with a selectivity similar to that seen in schizophrenic individuals, as this population has been shown to have deficits in gestalt processing (Spencer et al., 2003; Spencer et al., 2004; Uhlhaas et al., 2006; Vianin et al., 2002). Independent of clinical relevance, the final aim of this study was to use psilocybin's primary and preferential mode of action at 5-HT2A receptors to investigate the role of the serotonergic system in visual perception.

Kanizsa stimuli such as those employed in the present study (figure 1) induce the perception of an illusory figure due to the presence of co-aligned inducer lines that, if completed, would define a geometric shape such as a triangle or square. V1 and V2 cells in the macaque monkey respond to stimuli which contain perceptually completed contours in the absence of luminance-defined edges (illusory contours (ICs)) such as those present in Kanizsa stimuli (Grosof, Shapley, & Hawken, 1993; T. S. Lee & Nguyen, 2001; von der Heydt, Peterhans, & Baumgartner, 1984)

The contribution of serotonergic circuits to visual processing are not well understood but some preliminary findings have begun to unravel them. Recent work in our lab (Carter et al., 2004) demonstrated that a 215 mg/kg dose of psilocybin selectively impaired global motion perception, thought to be dependent on processing in higher

visual areas such as MT, but not local motion processing, thought to be resolved at the level of V1. Concurrent work outlined in Chapter 3 with the visual oddball paradigm and psilocybin indicated that some neurophysiologic effects of psilocybin on visual processing (the P1) are affected already at the level of V1. We sought to assess the impact of psilocybin at an intermediate stage of processing – that involved in the increased N170 component amplitude to Kanizsa stimuli. Current findings implicate the intermediate lateral occipital cortical areas in this processing, with feedback to earlier V1/V2 areas.

A number of studies have assessed the differential response to Kanizsa stimuli using neuroimaging methods and one highly replicable finding is that Kanizsa stimuli evoke greater brain activity relative to control stimuli consisting of the same elements but not aligned to induce a figure perception in early visual areas such as V2 and LOC (Ffytche & Zeki, 1996). At the ERP level this has been observed as an increase in N170 amplitude (C. S. Herrmann & Bosch, 2001; Kruggel, Herrmann, Wiggins, & von Cramon, 2001; Murray, Foxe, Javitt, & Foxe, 2004; Pegna, Khateb, Murray, Landis, & Michel, 2002). Data indicates that the illusory-figure stimuli actually cause greater activation than similarly designed stimuli with contours filled-in as assessed by measurements of both blood flow (Ffytche & Zeki, 1996) and ERPs (Pegna, Khateb, Murray, Landis, & Michel, 2002).

Von der Heydt et al. (1984) reported that in macaque monkeys some V1 and many V2 cells are responsive to illusory contours. Recent findings from intracranial recordings of monkey cortex have shown that responses to illusory contours occur first in

V2 (70–95 ms) and then in V1 (100–200 ms) (T. S. Lee & Nguyen, 2001). In sum, the animal literature supports the notion that V1 activity is modulated by illusory contours, but due the feedback from higher areas, V2 and possibly beyond. The human neuroimaging literature suggests that the first major visual area to respond preferentially to illusory contours is the lateral occipital complex, and that increased signaling there then results in feedback increases in earlier visual areas as well (Halgren, Mendola, Chong, & Dale, 2003).

Regardless of the exact locus of the neural effects (including the N170 component) differentiating the processing of Kanizsa figures with illusory contours from control figures, this is a useful paradigm in the assessment of the brain's tendency to perceptually "fill-in" the sensory surround. Given the profound impact of drugs like psilocybin on perceptual processing, greatly increasing the amount of filling-in that most users experience to the point of filling-in whole patterns and scenes not truly present in the sensory field, we felt that an empirical investigation of the effects of psilocybin on the neural processing underlying the gestalt processing of illusory contours would be instructive.

Methods

Substance and dosing

Psilocybin was obtained through the Swiss Federal Office for Public Health. Psilocybin capsules (1mg) were prepared at the pharmacy of the Cantonal Hospital of Aarau, Switzerland and quality was controlled through tests for identity, purity and

uniformity of content. The psilocybin high-dose (HD, 250 ug/kg), low-dose (LD, 125 ug/kg), and lactose placebo were administered in gelatin capsules of identical number and appearance.

Participant recruitment

18 healthy right-handed subjects (age 28.8 +/- 3.6 y.o., 8 male) were recruited through advertisement from the local University. Two of the subjects evidenced data too noisy to interpret on one of the experimental days and were excluded from further analysis. All subjects had normal or corrected-to-normal vision and a medical examination including EKG, hematogram and detailed clinical-chemical blood analysis indicated no health disturbance. The DIA-X diagnostic expert system (Wittchen, 1997) was used to assess present or antecedent psychiatric disorders. History of major psychiatric disorder or disorder in first degree relatives, as revealed in the explorative clinical interview, were used as exclusion criteria as was personal history of drug or alcohol abuse. The screening procedure was supplemented by standard psychometric instruments (Freiburg Personality Inventory FPI (Fahrenberg et al., 1984), Hopkins Symptom Checklist SCL-90 (Derogatis, Rickels, & Rock, 1976), the Cloninger Temperament and Character Inventory self-transcendence subscale (Cloninger, 1994; Cloninger, Svrakic, & Przybeck, 1993) and the Tellegen Absorption Scale (Tellegen & Atkinson, 1974). Since the personality trait factors “rigidity” and “emotional lability” were identified to be predictors of negative experiences during ASC (Dittrich, 1994), scores exceeding two SD from the mean value of normative data in the respective subscales of the FPI (i.e., “openness” and “neuroticism”) were used as exclusion criteria.

After being informed by written and oral description of the aims, procedures and associated possible risks of the study, all volunteers gave their written consent as requirement for participation. Twelve of the participants reported having previous experience with psilocybin or other hallucinogens the other four were hallucinogen-naive. Subjects were reimbursed for their time and they were instructed that at any time they were free to withdraw from the study. The study was approved by the ethics committee of the University Hospital of Psychiatry, Zurich, and the use of psilocybin in humans was authorized by the Swiss Federal Office for public health.

Experimental protocol

On three experimental days separated from each other by two weeks or more the subjects came to the lab at 9 AM and confirmed they had not eaten breakfast or taken caffeine that morning. The subjects were then given pills with placebo, 125 ug/kg psilocybin, or 250 ug/kg psilocybin and a protein drink. After 40 minutes of unstructured free time for relaxation the subjects were brought to an EEG room and a headcap with 64 active electrodes (Biosemi) was applied. EEG and ERP data was recorded in addition to time for rest and psychometric assessment starting at 80 minutes post-ingestion of drug (some of this data will be presented elsewhere). Starting at 120 min post-drug ingestion the Kanizsa triangle paradigm was begun. The distance from the subject's eyes to a 17" Sony Trinitron Multiscan E215 computer monitor was set to 1 meter.

During the paradigm a 0.2° x 0.2° black fixation cross was kept constant in the middle of a white screen and Kanizsa triangles or a control figure were presented centered on the fixation cross with an intertribal interval of 3 seconds. The Kanizsa

triangle and control figure were each composed of three black pac-men figures of 1.3°-visual arc-diameter and a sector defined by an arc of 60 degrees removed. The removed sectors were aligned such that the Kanizsa triangle stimulus types induced the perception of an illusory triangle and the control figure consisted of the same three pac-men stimuli each rotated by 180 degrees so as not to induce the illusory triangle percept (figure 1a-b). In the Kanizsa triangle stimuli the sides of the induced illusory triangle percept were 2.7° of visual arc and the support ratio describing the ratio of the real contours of the pac-men to the perceived triangle side length was 0.49.

A total of 88 Kanizsa triangle stimuli and 88 control figure stimuli were shown across two blocks of 88 presentations in pseudorandom order with each block of 88 trials containing an equal number of Kanizsa triangles and control figures. Because illusory contours can fade and disappear with continued fixation (Ffytche & Zeki, 1996), we presented our stimuli in one of four orientations so as to reduce visual habituation. Twenty-two presentations of the Kanizsa triangle and the control figure were shown in each of four orientations rotated 0°, 90°, 180°, and 270° from the traditional upright Kanizsa triangle figure. Subject had to respond as fast as possible by pressing “1” (using the forefinger or middle finger of their dominant hand) for Kanizsa triangle stimuli, and by pressing “2” (using their forefinger or middle finger) for control stimuli. The required response to the stimuli was counterbalanced across the subjects to control for faster reaction times with forefinger compared to middle finger. Subjects were given a practice session with the paradigm consisting of 15 stimuli prior to the ingestion of placebo/drug on experimental day 1 to ensure familiarity with the task.

Approximately 1 hr and 40 minutes post-drug ingestion, after the removal of the EEG electrodes (see ERP setup) and a short break, subjects were presented with a visual search paradigm also involving Kanizsa triangles. This paradigm was composed of 240 trials with each visual stimulus comprising a field of 9.6° x 14.6° with a semi-random arrangement of pac-men with a diameter of 1.5° for trials with set size 15 and 1.2° for trials with set size 28 (figure 1c-d). Three trial categories were presented in an equiprobable pseudorandomized order: one-third with three of the pac-men forming a Kanizsa triangle with support ratio of 0.7 embedded within the field, one-third with a real equilateral triangle replacing one of the pac-men elements, and one-third with neither a Kanizsa triangle or a real triangle (figure 1 depicts only the two stimulus types containing a target). The lengths of the side for the Kanizsa triangle and real triangle in the trials of set size 15 were 2.2° and 1.8° respectively. In trials of set size 28 the lengths were 1.7° and 1.4°.

The real triangle, illusory triangle, and no target trials were each presented as part of a set size of 15 or 28 and at stimulus durations of 140 msec and 280 msec for a total of 12 trial types, each presented 20 times. For each set-size target category a total of 10 stimuli were constructed and these were each shown two times at 140 msec and two times at 280 msec, thus comprising the 240 total presentations. The 240 trials were presented as 6 blocks of 40 stimuli with each block of 40 consisting of a pseudorandomized presentation of the three trial types in an approximately equiprobable ratio (13:13:14). The inter-trial interval was 2 seconds and half the subjects were instructed to press a “1” with their index finger if they saw an illusory triangle and a “2”

with their middle finger if they saw a real triangle and not to press a button if they saw neither. As in the ERP Kanizsa paradigm, to control for the quicker reaction times seen with index finger response, half the subjects responded with the assignment of button-presses for illusory vs. real triangle perception reversed.

Altered State of Consciousness Quantification

The Altered States of Consciousness rating scale 5D-ASC (A. Dittrich, 1998; A. Dittrich, von Arx, S., Staub, S., 1985) consists of 94 items that are visual-analogue scales of 10 cm length. These items measure alterations in mood, perception, experience of self in relation to environment, and thought disorder. Scores of each item range between zero ('No, not more than usually') and ten ('Yes, much more than usually'). The ASC items are grouped into five main factors comprising several items. (1) Oceanic Boundlessness (OB) measures derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria and alterations in the sense of time. The component subscales are positive derealization, positive depersonalization, altered perception of time and space, positive mood, and mania-like experience. (2) Anxious Ego Dissolution (AED) measures ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. The component subscales are anxious derealization, thought disorder, paranoid ideation, fear of loss of self control, and fear of loss of body control. (3) Visual Restructuralization (VR) includes the item clusters elementary hallucinations, complex hallucinations, synesthesia, changed meaning of percepts, facilitated recollection, and facilitated imagination. (4) Auditory Alterations

(AA) refers to acoustic hallucinations and distortions in auditory experiences and (5) the dimension Reduction of Vigilance (RV) relates to states of drowsiness, reduced alertness, and related impairment of cognitive function. Prior to the beginning of the experiment the participants were introduced to the language of the 5D-ASC and given some of the exemplar statements for the dimensions oceanic boundlessness and visual restructuralization. During the EEG recording just prior to the beginning of the ERP paradigm they were asked to rate their experience on each of these dimensions as well as their experience of thought disorder using a mouse to move a cursor from left (no change in the dimension from normal) to right (maximal change from normal) and the position of the cursor was recorded as a coarse measure of their experienced alteration of consciousness along the 3 primary dimensions of the 5-D ASC.

Personality Trait Assessment

SCL-90-R

In the SCL-90-R (Derogatis, 1983; Derogatis, Rickels, & Rock, 1976), subjects rate 90 symptoms of distress on a 5-step Likert-scale with 0 being ‘not at all’ and 4 being ‘extremely’. Subjects are instructed to indicate the amount they were bothered by each of the symptoms during the preceding week. The statements are assigned to 9 dimensions or factors reflecting various types of psychopathology: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism.

FPI

The Freiburg Personality Inventory (FPI) (Fahrenberg, 1973) is a comprehensive personality inventory with 105 true/false statements. Twelve subscales correlating to dimensions of the personality are identified: Nervousness, Aggression, Depression, Excitability, Sociability, Calmness, Dominance, Inhibition, Openness, Extraversion, Emotional Lability, and Masculinity.

TAS

The Tellegen Absorption Scale (Tellegen & Atkinson, 1974) was developed to measure the extent to which people become involved in everyday events, or the tendency to totally immerse oneself with attentional objects. Subjects rated 34 statements on a 5-step Likert-scale with 0 being 'not at all' and 4 being 'extremely.' The overall score is a measure of absorptive tendency and five factors have been identified, representing subscores of the TAS: Responsiveness to engaging stimuli, synesthesia, enhanced cognition, oblivious/dissociative involvement, vivid reminiscence, and enhanced awareness. It has been recently been found that higher absorption correlates with greater 5HT-2a binding potential (Ott, Reuter, Hennig, & Vaitl, 2005) and was assessed for its possible correlation with the electrophysiological and/or psychological changes induced by psilocybin.

TCI-ST

The Cloninger Temperament and Character Inventory Self-Transcendence (TCI-ST) scale is a subset of the TCI (Cloninger, Svrakic, & Przybeck, 1993), a self-report questionnaire widely used in psychological and psychiatric research. Subjects rated 33 statements regarding their orientation to the world their sense of self on a 5-step Likert-

scale with 0 being ‘not at all’ and 4 being ‘extremely’. “Self-transcendence” is one of the three character dimensions identified within the TCI and is related to the extent to which an individual identifies himself with his environment. Three subscales are differentiated within the TCI self-transcendence score: self-forgetfulness, transpersonal identification, and spiritual acceptance. Previous work has demonstrated an association between self-transcendence as identified through the TCI and serotonin 5-HT1a and 5-HT2a receptor expression and activity (Borg, Andree, Soderstrom, & Farde, 2003; Ham et al., 2004; Lorenzi et al., 2005).

EEG Data acquisition

EEG data was collected EEG was recorded from 64 standard scalp locations according to the International 10-10 System using active Ag-AgCl electrodes (BioSemi, Active 2) mounted in an elastic cap: Fp1, Fp2, Fpz, AF7, AF3, AF4, AF8, F7, F5, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P9, P7, P5, P3, P1, Pz, P2, P4, P6, P8, P10, PO7, PO3, POz, PO4, PO8, O1, Oz, O2, Iz. Additionally single active Ag-AgCl electrodes were applied to the left mastoid, the outer canthi of both eyes (for horizontal EOG monitoring) and the infraorbital and supraorbital regions of the left eye in line with the pupil (for vertical EOG monitoring EEG signals were sampled at 256 Hz, amplified and band-pass filtered between 0.01 and 67 Hz by the amplifier system. The Biosemi electrode-amplifier system uses a common-mode reference for on-line data acquisition so testing for impedances was unnecessary.

ERP Analysis

Offline the data were imported into BrainVision Analyzer V1.05 for ERP analysis and re-referenced to left mastoid. Subsequently, data were band-pass filtered using zero-phase butterworth filters (1–20 Hz, 48 dB/octave), and correct-response trials were epoched from -200 to +800 ms relative to stimulus presentation. Single trials were investigated for signs of artifact and those trials containing voltages of greater magnitude than 100uV were rejected resulting in the rejection of 2.6% of the placebo trials, 6.6% of the low-dose trials, and 12.2 % of the high-dose trials. Subsequently, EOG artifacts were corrected according to the procedure described by Gratton and Coles (Gratton, Coles, & Donchin, 1983). ERPs were then averaged separately for the Kanizsa triangle and non-triangle trials with all conditions containing at least 60 averaged epochs.

Inspection of the data indicated a clear maximum for both P1 and N170 components at the parieto-occipital sites PO7 and PO8. Peaks were thus picked for these two electrodes using a semi-automatic routine with visual inspection for the most positive peak within the 90 – 140 msec range (P100) and the most negative peak within the 150 – 210 msec range (N170). As it was noticed that the scalp distribution for the P100 was different in the grand averages for the psilocybin conditions peaks were picked in the 90-140 msec range for electrodes O1, O2, Iz, and Oz as well. Latency and amplitude values for the respective peaks were recorded and subsequently analyzed for statistical significance between condition (triangle vs. non-triangle percept) and dosage (placebo vs. low-dose vs. high-dose psilocybin). To confirm the significant *dose* x *contour* finding of the peak-picking analysis, a separate analysis of the data assessing the global field power

of each condition was conducted, picking the peak of global field power in the 80 – 140 msec (P100) and 140 – 250 msec (N170) time ranges. These average peak latencies were then used in a secondary analysis of the P100 and N170 component over the average global field power peak latency. For this analysis the average activity over a 30 msec window centered on the global field power peak latency was extracted from the electrodes showing maximal amplitudes for the P100 (P7, PO7, O1, P8, PO8, O2) and N170 (PO7, O1, PO3, PO8, O2, PO3) components. The findings for the P100 component are presented herein as they revealed the change in scalp distribution for the P100. The findings for this analysis for the N170 component revealed the same pattern of findings as the analysis on the PO7 and PO8 electrodes and will not be further reported upon. Analysis of the P300 component was facilitated by picking the maximal peak in channels Fz, Cz, and Pz in a 300 – 700 msec time window for each subject and trial-type. So as to assess the laterality of the P300 component a secondary analysis was conducted on the average voltage over 3 bilateral scalp areas – frontal left (F1, F3), frontal right (F2, F4), central left (C1, C3, C5), central right (C2, C4, C6), parietal left (P1, P3, P5), and parietal right (P2, P4, P6). The average amplitude over the 300-500 millisecond time range was extracted for each of these 6 groups of channels and used in subsequent ANOVA analyses.

Stimulus-related perturbations in alpha and theta power were assessed in the pre- and post stimulus interval by means of a fast Fourier-transform spectral decomposition. Prior to averaging, the data from each trial type was subjected to a fast Fourier transform algorithm over the -750 to -250 msec (pre) and 0 to +500 msec (post) time frames. The

epochs were then averaged and the average power at 4-6 Hz (theta) and 8-10 Hz (alpha) was calculated. The scalp distribution of alpha effects indicated that strong decreases in alpha power were observed over parieto-occipital areas while significant increases in theta power were observed over frontocentral areas. In keeping with the observed maxima for these effects, pre and post stimulus alpha power was obtained for channels PO3, O1, POz, Oz, PO4, and O1 and pre and post stimulus theta power was extracted for channels F1, FC1, C1, Fz, FCz, Cz, F2, FC2, and C2. Inspection of the data indicated a wide range of alpha power values so alpha power was first log-transformed and then both alpha and theta power values were entered into ANOVA analysis with factors dose, pre vs. post stimulus, and electrode location.

Statistical methods

Repeated measures ANOVA analyses were conducted (reported p-values are Greenhouse-Geisser epsilon corrected for multiple comparisons) followed by Tukey post-hoc tests on all variables of interest – psychometric, behavioral and electrophysiological. Relevant factors for each statistical test are included in the text describing the results. To assess the correlation between the changes induced by psilocybin among and between the electrophysiological, psychometric, and behavioral domains Pearson's product moment regression analyses were conducted, using each participant's change scores from the PY low-dose and high-dose experimental days relative to placebo as separate data points.

Results

Altered State of Consciousness

The 94-item 5D-ASC Altered State of Consciousness questionnaire with 5 main scales was used to quantify the change in consciousness in this study. An ANOVA analysis was conducted on each of the scale and subscale scores as a percentage of maximum. Analysis of the main scale percent maximum scores with factors dose and main scale (Figure 2a) revealed a main effect of dose ($F(2, 30)=24.74$, $p < 0.00001$), main scale ($F(4,60) = 13.81$, $p < 0.0001$), and a dose X main scale interaction ($F(8,120) = 6.475$, $p < 0.001$). Post-hoc analysis of the main effect of dose indicated that each of the three dose conditions was significantly different from each other: high-dose vs. placebo ($p < 0.0001$); high-dose vs. low-dose, $p < 0.05$; low-dose vs. placebo, $p < 0.001$). Post-hoc analysis of the dose X main scale interaction indicated that high-dose psilocybin induced significantly higher ratings for all five main scales: Oceanic Boundlessness (OB), $p < 0.001$; Anxious Ego Dissolution (AED), $p < 0.01$; Visionary Restructuralization (VR), $p < 0.001$; Auditory Alterations (AA), $p < 0.001$; and Reduction of Vigilance (RV), $p < 0.001$. Low-dose psilocybin induced 5D-ASC ratings significantly higher than placebo for only the main scales Oceanic Boundlessness ($p < 0.001$), Visionary Restructuralization ($p < 0.001$), and Reduction of Vigilance ($p < 0.01$). High dose relative to low dose scores on the 5D-ASC were not significantly different although a trend was seen for the OB ($p = 0.090$) and VR ($p = 0.079$) subscales.

The main contributing subscale for the effect on Oceanic Boundlessness was the "altered perception of time and space" subscale with low-dose and high-dose psilocybin inducing 30.5 ± 27.0 % and 46.6 ± 30.4 % of the scale maximum, respectively. The main contributing subscale for the effect on Anxiety of Ego Dissolution was the "thought

disorder" subscale with low-dose and high-dose psilocybin inducing 13.8 ± 14.2 and 28.1 ±19.9% of the scale maximum, respectively. The two subscales contributing most to the increase in the Visionary Restructuralization scale were complex hallucinations (LD, 51.5 ± 35.5%; HD, 62.9 ± 31.0% scale maximum) and elementary hallucinations (LD, 41.2 ± 30.1%; HD, 55.3 ± 26.2% scale maximum). Of the 16 research subjects, all experienced moderate to marked alterations in their subjective state on the low dose psilocybin day. Fourteen subjects experienced strong alterations in their subjective state on the high dose psilocybin day but 2 felt that they may not have had any drug on that day. Indeed, the lack of a significant difference between the low dose and high dose data was largely driven by the anomalous response of the two research subjects who reported very little subjective alteration in consciousness on the high dose administration days despite moderate to strong subjective alterations in state on low dose administration (an assessment of the data without these subjects revealed a significant increase in the VR and OB scales between low and high dose at $p < 0.01$). Of the two high dose non-responders, one experienced a subjective alteration in consciousness on the placebo day, accounting for virtually all of the small increases above zero seen in the placebo 5D-ASC data.

As we were particularly interested in the visual changes induced by psilocybin and their relation to changes in electrophysiology we assessed the dose-related effects on the subscales of the Visionary Restructuralization (VR) main scale with factors dose and subscale (Figure 2b). ANOVA analysis indicated a main effect of dose ($F(2,30) = 24.39$, $p < 0.00001$) and subscale ($F(5,75) = 13.94$, $p < 0.00001$) as well as a dose X subscale

interaction ($F(10,150) = 4.220$, $p < 0.01$). Post-hoc analysis of the significant dose effect revealed that both low- and high-dose conditions evoked greater scores than placebo (LD, $p < 0.001$; HD, $p < 0.0001$) but that the two doses were not significantly different from each other (LD vs. HD, $p = 0.19$). Post-hoc testing of the significant dose X VR subscale effect showed that both high and low-dose psilocybin induced greater scores than placebo on the VR subscales elementary hallucinations (LD and HD both $p < 0.0001$), complex hallucinations (LD and HD both $p < 0.0001$), synesthesia (LD and HD both $p < 0.0001$), facilitated recollection (LD, $p < 0.01$; HD, $p < 0.001$) and facilitated imagination (LD, $p < 0.05$; HD, $p < 0.001$). On the subscale changed meaning of percepts, HD psilocybin induced greater scores than placebo ($p < 0.0001$) but LD psilocybin did not ($p = 0.713$) and the scores at the two different doses were significantly different from each other ($p < 0.05$).

The results of the computerized short ASC assessment done during the EEG recording just prior to the ERP paradigm (while the subjects were still feeling the acute effects of psilocybin) indicated a similar pattern of results in that the visual restructuralization-like scale showed the largest response to psilocybin with the oceanic boundlessness-like scale close behind, with each well above the anxious ego dissociation-related scales. ANOVA analysis with factors dose and scale indicated a main effect of dose ($F(2,30) = 28.03$, $p < 0.00001$), scale ($F(3,45) = 26.14$, $p < 0.00001$), and a significant dose X scale interaction ($F(6,90) = 10.77$, $p < 0.00001$). Post-hoc analysis of the *dose* x *scale* effect indicated that the OB-like score was significantly different comparing placebo to low dose ($p < 0,001$) and high dose (0.001) and that low and high

dose were not significantly different ($p = 0.76$). The VR-like score was also significantly increased above placebo by both low ($p < 0.001$) and high dose ($p < 0.001$) was not different comparing high dose to low dose condition ($p = 0.18$). The AED-like scale was not affected by psilocybin ($p = 1.0$ for all comparisons) but the thought disorder scale was increased from placebo by both low ($p < 0.05$) and high dose ($p < 0.01$), though again was not different comparing low vs. high dose ($p = 0.97$). The short form ratings for the low dose psilocybin correlated well with each other: OB-like to OB, $r = 0.70$, $p < 0.01$; VR-like to VR, $r = 0.63$, $p < 0.01$, thought disorder to AED subscale thought disorder, $r = 0.54$, $p < 0.05$. However, the short form ratings for the high dose psilocybin condition showed much less correlation with the scale scores as assessed by the 5D-ASC with only the OB score showing a trend towards significance: OB-like to OB, $r = 0.38$, $p < 0.05$; VR-like to VR, $r = 0.09$, $p = 0.46$; thought disorder to AED subscale thought disorder, $r = -0.23$, $p = 0.79$). The AED-like subscale was not correlated with the AED scores on either the low or high dose days, largely driven by the fact that subjects endorsed very little experience of this kind on the computerized short form report (average percent maximum scores for LD and HD were 0.44 + 0.21 and 1.25 + 0.73 for the short AED-like scores vs. 5.83 + 2.39 and 16.17 + 4.30 on the AED scale).

Visual Search Paradigm

3-way ANOVA analyses with factors dose, time (140 ms vs. 280 ms stimulus duration), set size (15 vs. 28 elements) was conducted separately on the accuracy data for the real triangle, Kanizsa triangle, and no target trials. A dose effect reflecting decreased

accuracy was found for the performance on the Kanizsa triangle trials ($F(2, 30) = 4.87$, $p<0.05$), but not for the real triangle ($p = 0.68$) or non-target ($p = 0.1$) trials. Post-hoc analysis of the effect of dose on accuracy for the Kanizsa trials indicated that high dose psilocybin caused decreased performance relative to placebo ($p < 0.01$) but that low dose was not different from placebo ($p = 0.22$) or high dose ($p = 0.33$). Generally, decreased stimulus duration and increased set size caused decreases in visual detection performance. For the Kanizsa trials main effects were observed for stimulus duration ($p < 0.01$) and set size ($p < 0.001$) whereas the real triangle trials evoked only a trend effect of stimulus duration ($p = 0.07$) and a significant effect of set size ($p < 0.01$).

For both the Kanizsa and real triangle trials there was a *time* x *set size* interaction (($F(1, 15) = 20.05$, $p<0.001$), ($F(1, 15) = 4.55$, $p<0.05$), respectively) indicating that the error-inducing (missed visual detection) effect due to increased number of distracters was greater than the one due to shortening of stimulus duration. This interaction indicated that the error-inducing effect of increasing distracter number was significant on both short and long duration trials but that the error-inducing effect of decreasing stimulus duration was only significant on the trials with the large set size. Specifically, post-hoc analysis of the Kanizsa trial data indicated that the performance was worse on the large set size trials than on the small set size trials at both 140 msec ($p < 0.001$) and 280 msec ($p < 0.001$) presentation times. Similarly, there was worse performance on the short vs. long stimulus duration trials for the large set sizes ($p < 0.001$). For the small 15-element set size the performance was not made worse by the decrease in stimulus duration ($p = 0.27$). For the real triangle data a similar pattern of post-hoc findings was obtained: there

was worse performance on the large vs. small set size trials at 140 msec duration ($p < 0.001$) and a trend at 280 msec duration ($p = 0.08$), and there was worse performance on the short vs. long stimulus duration for the large set size ($p < 0.05$) but not the smaller set size ($p = 1.0$).

The non-target trials exhibited a main effect for stimulus duration ($p < 0.0001$) and set size ($p < 0.00001$). As with the target trials the effect of shorter stimulus duration was a decrease in accuracy. However, in contrast to the target trials, the effect of increased set size was increased accuracy as the false positive rate went down with increased set sizes. The data for the non-target trials also contained a *time* x *set* size interaction ($F(1, 15) = 31.87$, $p<0.00005$). The error-inducing effect (increase in false positives) of short presentation times was significant for the smaller set size trials ($p < 0.001$) but did not effect the performance on the large set size trials ($p = 0.50$) which was very close to 100% for both stimulus durations (mean, S.E.M., short duration = 96.6 $\pm$ 2.3 %, long duration = 97.8 + 1.5 %). Further, the decrease in false positive rate on large vs. small set size trials was only significant for the short stimulus duration trials ($p < 0.001$) whereas the long duration trials showed no significant difference due to set size ($p = 0.11$) and the accuracy was close to 100% for both set sizes (mean, S.E.M., small = 95.8 $\pm$ 1.6 %, large = 97.8 + 1.5 %).

In order to assess the differential effect of psilocybin on the processing of the real triangle vs. illusory Kanizsa triangle targets in a more comprehensive manner, 4-way ANOVA analysis was conducted on the percentage correct and reaction time data of the visual search paradigm using factors dose (placebo, low-dose, high-dose), contour

(Kanizsa illusory contour vs. real contour triangle), time, and set size. As with the analysis of the target trial types individually, main effects were found for time ($F(1, 15) = 12.406$, $p<0.01$) and set size ($F(1, 15) = 33.366$, $p < 0.0001$) reflecting decreases in visual detection with decreased stimulus duration and increased set size. The main effect of dose ($F(2, 30) = 3.5407$, $p < 0.05$) revealed that there was a dose-related decrease in accuracy driven by the significant effect of psilocybin on the Kanizsa trials as seen above. Further, there was a significant main effect of illusory vs. real contour on accuracy ($F(1, 15)=44.474$, $p < 0.00001$) reflecting the fact that the detection of the real triangle was higher than the detection of the illusory contour Kanizsa triangle.

The ANOVA analysis of accuracy indicated significant *dose* x *contour* ($F(2, 30) = 4.8926$, $p < 0.05$) and *dose* x *time* ($F(2, 30) = 3.5472$, $p < 0.05$) interactions. The *dose* x *contour* interaction indicated that psilocybin caused greater decrements in performance on the illusory triangle visual detection. Post-hoc analysis of the *dose* x *contour* interaction revealed that while there was a significant decrease in accuracy comparing real vs. Kanizsa triangle detection at all three dose levels ($p < 0.0005$ in all cases), there was no significant difference in accuracy performance on the real triangle between doses and the difference in accuracy on the Kanizsa triangle trials were significant comparing high-dose to placebo ($p < 0.0005$) and but insignificant comparing high-dose to low-dose ($p = 0.20$) and only a trend comparing low-dose to placebo ($p = 0.09$). Post-hoc analysis of the *dose* x *time* interaction showed that while there was no difference in accuracy performance for the short vs. long stimulus duration under placebo, there was a significantly worse performance for the short stimulus duration under low-dose

psilocybin ($p < 0.005$). There was only a trend towards reduced performance under high-dose psilocybin ($p = 0.10$) as the performance at both stimulus durations was largely degraded. Further, the performance under low-dose psilocybin was worse than placebo for the short stimulus durations ($p < 0.001$) but not the long stimulus durations whereas the performance under high-dose psilocybin was worse than placebo for both short ($p < 0.0001$) and long ($p < 0.05$) stimulus durations. Comparing the low and high-dose performance revealed no significance at short stimulus durations but a trend towards worse performance with high dose at the long stimulus durations ($p = 0.07$).

3-way ANOVA analyses with factors dose, time (stimulus duration), and set size conducted on the reaction time data indicated main effects of dose ($F(2,30) = 7.064$, $p < 0.01$), time ($F(1,15) = 513.7$, $p < 0.00001$), and set size ($F(1,15) = 80.33$, $p < 0.00001$) on the real triangle trials as well as the Kanizsa triangle trials (dose, $F(2,30) = 13.23$, $p < 0.0001$; time, $F(1,15) = 731.5$, $p < 0.00001$; set size, $F(1,15) = 24.92$, $p < 0.001$). The effects of psilocybin, decreased stimulus duration, and increased set size were all increases in reaction time. For both the Kanizsa and real triangle trials the reaction time increases were significant comparing placebo to high dose (real, $p < 0.01$; Kanizsa, $p < 0.001$) and low dose (real, $p < 0.05$; Kanizsa, $p < 0.01$). There was a more significant slowing of reaction time induced by shorter stimulus durations than increased set sizes (see F-values), in contrast to the pattern of more significant decreases of accuracy due to increased set sizes than short stimulus durations seen above.

A 4-way ANOVA analysis on the reaction time data with factors contour, dose, time, and set size indicated significant main effects of dose ($F(2, 30)=12.318$, $p < 0.001$),

time ($F(1, 15) = 1165.4$, $p < 0.00001$), set size ($F(1, 15)=73.142$, $p < 0.00001$), as well as contour ($F(1, 15) = 48.054$, $p < 0.00001$). Just as accuracy to the illusory contour trials was worse, the reaction time to the illusory contour trials was significantly slower than to the real contour trials. A significant *dose* x *contour* interaction ($F(2,30) = 3.364$, $p < 0.05$) was obtained with a similar pattern to that seen with the accuracy data – again psilocybin caused greater decrements in performance (increases in reaction time) to illusory than real contour targets. Post-hoc analysis of the *dose* x *contour* interaction indicated that psilocybin at high dose caused increased reaction times on both the illusory contour (vs. placebo, $p < 0.001$; vs. low dose, $p < 0.001$) and real contour targets (vs. placebo, $p < 0.001$; vs. low dose, $p < 0.01$). In contrast, low dose did not cause increased reaction times relative to placebo for either the illusory ($p = 0.80$) or real ($p = 0.63$) contour targets.

Kanizsa ERP Paradigm

Behavioral data

ANOVA analyses were conducted on both the percentage correct and reaction time data using the factors contour (Kanizsa triangle vs. control figure) and dose. Analysis of the percentage of correct answers revealed no main effects or interactions for dose or gestalt condition on accuracy, although a trend toward a dose-related decrease was observed ($F(2, 30) = 2.324$, $p = 0.1152$). The average accuracy $\pm$ SEM on the task was 99.0 + 0.4% for placebo, 99.1 + 0.5% for low-dose, and 98.3 + 0.7% for high-dose conditions. ANOVA analysis of the reaction time data revealed a main effect of dose

such that psilocybin induced slower RTs ($F(2,30) = 16.847$, $p < 0.00001$), and a main effect of contour condition such that the Kanizsa triangles elicited faster RTs ($F(1,15) = 42.31$ $p < 0.00001$). Post-hoc analysis of the dose effect indicated that the high-dose psilocybin induced significantly slower RT than placebo ($p < 0.0001$) and low-dose ($p < 0.001$) but that low-dose RT was not significantly different than placebo RT ($p = 0.2424$). There was a significant *dose* x *contour* interaction in the RT data ($F(2,30) = 4.470$, $p < 0.05$) reflecting that psilocybin induced greater slowing of RT for the control figures than the Kanizsa triangles. Specifically, the reaction time difference between contour conditions with placebo was not significant ($p = 0.12$), but for both low-dose ($p < 0.001$ and high-dose ($p < 0.001$) the RT difference between contour conditions was significant.

Electrophysiological data

Both stimuli under all 3 drug conditions elicited prominent P100, N170, and P300 components. The P100 component peaked with an average latency of about 115 ms at the lateral occipital scalp areas, maximal at electrodes PO7 and PO8, whereas the N170 component peaked with an average latency of about 185 ms, also at electrodes PO7 and PO8. Figure shows the average event-related potential to the Kanizsa triangle for all 64 electrodes of the montage with global field power indicated in the upper left corner. Figures 4a-c show the scalp distribution of the P100 component in response to the Kanizsa triangle under all three drug conditions – each scalp map is presented at the latency where the amplitude of the P100 was maximal. P100 scalp distribution was highly similar to N170 scalp distribution with an inversion of sign. Figures 5a-f show the

scalp distribution of the N170 component for the Kanizsa triangle and control figure at the three dose levels. A response-related P300 component was elicited over occipito-parietal areas with maximum over the time frame of 300 - 500 msec post stimulus to both the Kanizsa triangle and control figure stimuli. Figure 6a-c shows the average scalp distribution of the P300 component to the Kanizsa triangle at each dose.

P100

The initial analysis of latency and amplitude values for channels PO7 and PO8 revealed no main effects for dose ($F(2,30) = 1.37$, $p = 0.269$) or illusory contour condition for P100 latency ($F(1,15) = 1.17$, $p = 0.296$) and a trend towards a shorter latency in the left hemisphere ($F(1, 15) = 3.87$, $p = 0.068$). The average $\pm$ SEM latencies obtained for the left and right hemisphere were 116.2 $\pm$ 3.8 msec and 120.8 $\pm$ 6.8 msec, respectively. P100 amplitudes were not significantly different in the different contour conditions ($F(1, 15) = 0.002$, $p=.967$) although there was a trend towards greater amplitude on the right side ($F(1,15) = 3.53$, $p = 0.080$) and a trend towards a reduced amplitude with psilocybin ($F(2, 30) = 2.54$, $p = 0.095$). As figure 3 suggests, the P100 scalp distribution was altered by psilocybin to a more medially-focused maximum. Thus, an analysis of the average P100 amplitudes at electrodes P7, PO7, O1, P8, PO8, and O2 over the P100 peak from 105 – 135 msec was conducted.

Factors in the four-way ANOVA were dose, hemisphere, laterality (from lateral P7/P8 to medial O1/O2), and illusory contour condition. This more extensive analysis of P100 amplitude again yielded no main effect of dose ($F(2,30) = 0.429$, $p = 0.655$), but

significant main effects of hemisphere ($F(1, 15) = 4.81$, $p < 0.05$) and laterality of scalp position ($F(1, 15) = 14.00$, $p < 0.0001$). Post-hoc analysis of the significant effect of occipital laterality indicated that the amplitude at PO7/PO8 was greater than that at P7/P8 ($p < 0.001$) and greater than O1/O2 at trend significance ($p = 0.057$) while the amplitude at O1/O2 was greater than at P7/P8 ($p < 0.05$). A significant interaction between hemisphere and laterality was found ($F(2, 30) = 4.79$, $p < 0.05$) indicating that the right-sided dominance of the P100 component was true for the more lateral sites but not the medial O1 and O2 sites. Specifically, greater amplitudes were seen at P8 compared to P7 ($p < 0.01$) and PO8 compared to PO7 ($p < 0.001$) but the amplitudes at O1 and O2 were not significantly different ($p = 0.296$).

A highly significant interaction was found between dose and laterality of scalp location ($F(4, 60) = 10.64$, $p < 0.00001$) reflecting the changed scalp distribution for the P100 component. This interaction was consistent with the finding that the amplitude at the lateral sites was not different between dose conditions (as found in the initial analysis of the individually-picked peaks at PO7 and PO8 above) but at medial sites was significantly greater in the psilocybin conditions than placebo (see figure 9). Post-hoc analysis indicated that the psilocybin-induced increase in amplitude at medial electrodes (O1 and O2) was significant comparing placebo to both low dose ($p < 0.001$) and high dose ($p < 0.001$) conditions. A significant *dose* x *hemisphere* x *contour* interaction was obtained ($F(2, 30) = 4.93$, $p < 0.05$) reflecting specific changes due to the psilocybin-related increased medial P100 amplitudes. Post-hoc analysis for this effect indicated that greater P100 amplitudes were obtained for the Kanizsa triangle on the right side in the

high dose condition compared to placebo ($p < 0.01$) and low dose ($p < 0.05$) conditions and for the control figure on the left side comparing the low dose and placebo conditions ($p < 0.01$).

N170

An ANOVA analysis of the latency values of the N170 component at electrodes PO7 and PO8 was conducted with factors dose, hemisphere and illusory contour condition. Main effects of hemisphere ($F(1, 15) = 13.548$, $p < 0.005$) and dose ($F(2, 30) = 4.855$, $p < 0.01$) indicated that N170 latency was shorter on the left compared to right hemisphere and slowed by psilocybin. Post-hoc analysis indicated that the placebo latency was significantly shorter than high dose latency ($p < 0.01$) but that the differences between low dose and placebo ($p = 0.136$) and between low dose and high dose ($p = 0.521$) were not significant.

ANOVA analysis of N170 amplitude values indicated, as previously reported, a significant increase in N170 amplitude for the illusory contour-containing Kanizsa triangle stimulus relative to the control figure ($F(1, 15) = 43.995$, $p < 0.00001$). Further, a reduction in N170 amplitude due to psilocybin was obtained ($F(2, 30) = 5.325$, $p < 0.01$). Post-hoc analysis revealed that there was a difference in N170 amplitude comparing placebo to high dose conditions ($p < 0.01$) but not between placebo and low dose ($p = 0.223$) or low dose and high dose ($p = 0.276$). While there was no main effect of hemisphere effect on N170 amplitude ($F(1, 15) = 0.353$, $p = 0.561$), there was a significant *hemisphere* x *illusory* contour interaction ($F(1, 15) = 4.141$, $p < 0.05$),

indicating that the Kanizsa triangle induced stronger right hemisphere processing while the control figure did not. Post-hoc analysis revealed that the control figure did not evoke different N170 amplitudes in right vs. left hemisphere ($p = 0.875$) but the illusory contour stimulus did evoke greater right vs. left N170 amplitude ($p < 0.05$). Lastly, there was a significant *dose* x *illusory* contour interaction ($F(2, 30) = 11.460$, $p < 0.001$) indicating that the psilocybin-induced reduction of N170 amplitude was greater for the illusory contour condition than the control figure condition (See Figure 10). Post-hoc analysis of this interaction indicated that the N170 amplitude to both the Kanizsa triangle and the control figure stimulus was significantly reduced from placebo for both the low dose and high dose conditions ($p < 0.001$ for all four comparisons). Further, the Kanizsa and control figure N170 amplitudes were lower in amplitude in high dose than low dose conditions (Kanizsa, $p < 0.001$; control figure, $p < 0.01$). The percentage relative decrease of the grand average N170 amplitude comparing the illusory contour to control figure conditions was 20.5% under placebo, 19.1% with low-dose psilocybin, and 14.3% with high-dose psilocybin. Despite the tendency for the N170 amplitude to be reduced relative to placebo following psilocybin, some subjects showed increased N170 amplitudes on the psilocybin days. Assessment of the average Kanizsa and non-Kanizsa N170 amplitudes for each subject on the 16 low dose and 16 high dose days revealed that there were 6 instances of slightly increased Kanizsa triangle trial N170 amplitudes (5 under low dose and 1 under high dose conditions) and 16 instances of slightly increased control figure trial N170 amplitudes (8 under low dose and 8 under high dose conditions).

P300

The ERP paradigm required a behavioral response classifying the two classes of stimuli as triangle or non-triangle on each trial so that each stimulus was of equal importance according to task demands. ANOVA analysis of P300 latency with factors dose, anterior-posterior location (Fz, Cz, Pz), and illusory contour indicated main effects for dose, anteriority, and illusory contour. Location caused an effect on P300 latency ($F(2, 30) = 6.999$, $p < 0.01$) such that Pz exhibited shorter latency than Cz ($p < 0.05$) or Fz ($p < 0.01$) in accordance with the expected arising of this response-related P300 at the temporal-parietal junction. Additionally, psilocybin caused an increase in P300 latency ($F(2, 30) = 5.964$, $p < 0.01$) and illusory contour presence in the Kanizsa triangle figure caused a decrease in P300 latency ($F(1, 15) = 4.586$, $p < 0.05$). Mean P300 latencies at Pz for placebo, low dose and high dose conditions ($\pm$ SEM) was found to be 383.7 $\pm$ 12.4, 397.8 $\pm$ 17.9, and 404.8 $\pm$ 18.4. Post-hoc analysis indicated that placebo P300 latency was shorter than both low dose ($p < 0.05$) and high dose ($p < 0.01$) conditions and that low dose and high dose were not significantly different ($p = 0.8495$).

ANOVA analysis of P300 peak amplitude at Fz, Cz, and Pz with factors dose, location, and illusory contour condition indicated main effects of dose ($F(2, 30) = 24.503$, $p < 0.00001$) and location ($F(2, 30) = 59.921$, $p < 0.00001$) and a trend effect of illusory contour condition ($F(1, 15) = 3.507$, $p = 0.081$). The main effect of dose indicated psilocybin-induced strong reductions in P300 amplitude and post-hoc analysis revealed that placebo amplitude was greater than both low dose ($p < 0.001$)and high dose ($p< 0.001$) and that low dose was greater than high dose ($p < 0.05$). The main effect of

location indicated that amplitudes at Pz were greater than amplitudes at Fz ($p < 0.01$) and Cz ($p < 0.05$) but that amplitudes at Fz and Cz were not differentiable ($p = 0.866$). As it was observed that the scalp distribution of P300 tended to be right lateralized, as was the difference map comparing the Kanizsa triangle and control figure P300 a secondary analysis of average P300 amplitude at left and right sites in frontal, central, and parietal areas over the 300 – 500 msec time range was carried out.

ANOVA analysis of the average P300 amplitude at the six regions of interest with factors dose, hemisphere, anterior-posterior location, and illusory contour condition revealed again a main effect of dose ($F(2, 30) = 24.707$, $p < 0.00001$) and anterior-posterior location ($F(2, 30) = 40.370$, $p < 0.00001$) as well as a strong main effect of hemisphere ($F(2, 30) = 46.676$, $p < 0.00001$) and trend effect of illusory contour condition ($F(1, 15) = 3.984$, $p = 0.062$). Post-hoc analysis again indicated that placebo P300 amplitude was greater than low dose ($p < 0.001$) and high dose ($p < 0.001$) amplitudes and that low dose amplitude was greater than high dose amplitude ($p < 0.05$). The amplitude at parietal locations was found to be greater than frontal ($p < 0.001$) and central ($p < 0.001$) locations and central amplitude was greater than frontal amplitude ($p < 0.01$).

A significant interaction between hemisphere and anterior-posterior location ($F(2, 30) = 6.411$, $p < 0.01$) as well as between illusory contour by anterior-posterior location ($F(2, 30) = 6.856$, $p < 0.01$) indicated that parietal locations showed greater right-lateralization of P300 distribution than frontal locations and also showed greater P300 amplitudes to the illusory contour condition. Specifically, post-hoc analysis

indicated that the comparison between left and right hemisphere P300 amplitudes was significant at frontal locations ($p < 0.01$) and of greater significance at central ($p < 0.001$) and parietal ($p < 0.001$) locations. Further, the comparison between P300 amplitude to the Kanizsa triangle vs. control figure were not significant at frontal locations ($p = 0.179$) but were significant at central ($p < 0.01$) and parietal ($p < 0.001$) locations.

A triple *dose* x *A-P location* x *contour* interaction was found as well ($F(4, 60) = 2.710$, $p < 0.05$) reflecting that while the P300 amplitude to both stimuli was greatly reduced by psilocybin, the increased P300 amplitude to the illusory contour condition was somewhat accentuated by psilocybin (see figures 11a-c and 12). In particular, post-hoc analysis of this interaction indicated that in the placebo condition the difference in P300 amplitude to the Kanizsa triangle vs. control stimulus was insignificant at frontal locations ($p = 0.81$) and was significant at central ($p < 0.05$) and parietal ($p < 0.001$) locations. In the low dose condition the contrast was again insignificant at frontal locations ($p = 1.00$) and significant at central ($p < 0.01$) and parietal ($p < 0.001$) locations. In contrast, the high dose condition showed significant increases in P300 amplitude due to illusory contour at frontal ($p < 0.001$), central ($p < 0.001$), and parietal ($p < 0.001$) locations.

Stimulus-induced changes in alpha and theta rhythms

The presentation of visual stimuli caused occipital alpha power to decrease and frontal midline theta power to increase. Figures 13a-c show the stimulus-induced increases in theta power at 6-8 Hz and figures 14a-c show the stimulus-induced decreases

in alpha power at 10-12 Hz. ANOVA analysis of the pre and post stimulus occipital alpha and frontocentral theta power examined these effects.

ANOVA analysis of the pre and post stimulus frontal theta power over channels F1, FC1, C1, Fz, FCz, Cz, F2, FC2, and C2 with factors dose, laterality (left, midline, right), frontality (frontal, frontocentral, and central), pre vs. post stimulus and contour indicated a main effect of pre/post stimulus ($F(1, 15) = 31.699$, $p < 0.0001$), indicating that frontal theta power was higher after stimulus presentation than before. Further main effects were found for dose ($F(2, 30) = 35.902$, $p < 0.00001$), lateral location ($F(2, 30) = 21.279$, $p < 0.00001$), frontal location ($F(2, 30) = 10.167$, $p < 0.001$), and illusory contour ($F(1, 15) = 6.100$, $p < 0.05$). The dose effect indicated that psilocybin decreased frontal theta power as seen in figures 13a-c. Post-hoc analysis demonstrated that theta power was greater in the placebo condition than low dose ($p < 0.001$) or high dose ($p < 0.001$) psilocybin condition but that low dose theta power was not significantly greater than high dose ($p = 0.10$). Central locations (Fz, FCz, Cz) were found to show greater magnitude theta power than left ($p < 0.001$) and right ($p < 0.001$) locations and right locations exhibited a trend towards greater power than left ($p = 0.065$). Frontal and frontocentral locations exhibited higher magnitude theta power than central locations (F vs. C, $p < 0.05$; FC vs. C, $p < 0.001$). Further, a significant interaction between pre/post stimulus and lateral location ($F(2, 30) = 11.134$, $p < 0.001$) indicated that while the post stimulus theta power was greater than pre stimulus power at left, central, and right locations (all $p < 0.001$), the greater increases were induced at the midline Fz, FCz, Cz locations.

A significant interaction on the frontal theta power effect was found between dose

and pre/post stimulus ($F(2, 30) = 19.318$, $p < 0.00001$) indicative of a stronger inhibition of the post vs. pre stimulus theta power. Post-hoc analysis indicated that at all three dose conditions the post stimulus theta power was greater than prestimulus theta power (all $p < 0.001$) and that pre stimulus theta power in the placebo condition was greater than pre stimulus theta power in the low and high dose conditions (both $p < 0.001$) but not greater than low dose ($p = 0.85$) or high dose ($p = 0.33$) post stimulus theta power. Low dose pre stimulus theta power was greater than high dose pre stimulus power at trend significance ($p = 0.052$) and low dose post stimulus theta power was significantly greater than high dose post stimulus power ($p < 0.05$).

A significant interaction between the effect of psilocybin and illusory contour was obtained ($F(2, 30) = 35.902$, $p < 0.00001$) indicating that psilocybin caused greater decreases in frontal theta power to the illusory contour condition than the control condition. Post-hoc analysis of this effect indicated that in the placebo condition the Kanizsa triangle trials evoked greater theta power than the control figure trials ($p < 0.001$) but that no such difference was seen in low dose ($p = 0.927$) or high dose ($p = 0.987$) conditions.

ANOVA analysis of the occipital alpha reduction in response to the stimuli with factors pre vs. post stimulus, occipital vs. occipito-parietal location, left/midline/right location and dose yielded main effects for pre/post stimulus (($F(1, 15) = 15.354$, $p < 0.01$), occipital vs. parieto-occipital location (($F(1, 15) = 28.590$, $p < 0.00001$), lateral location (($F(2, 30) = 21.869$, $p < 0.00001$), and dose ($F(2, 30) = 12.005$, $p < 0.001$). The main effect of pre vs. post stimulus reflected the decrease in alpha power in the post

stimulus period induced by visual processing. No effect of Kanizsa figure was obtained indicating that the stimulus-induced decrease in alpha power was unrelated to the presence of illusory contour. The main effects of location indicated that the parieto-occipital locations (PO3, POz, PO4) showed greater alpha power than the occipital locations (O1, Oz, O2) and the right locations showed greater alpha power than the left ($p < 0.001$) and midline ($p < 0.001$) locations. The main effect of dose indicated the decrease in alpha power induced by psilocybin wherein both high dose ($p < 0.001$) and low dose ($p < 0.01$) caused decreases in alpha power relative to placebo but were not different from each other ($p = 0.23$). A significant *dose* x *pre/post* interaction was obtained as well ($F(2, 30) = 21.209$, $p < 0.00001$) indicating that psilocybin caused a greater inhibition of the baseline prestimulus alpha than the poststimulus alpha. Despite this highly significant interaction, the pre vs. post stimulus alpha power was still significantly different for placebo ($p < 0.01$), low dose ($p < 0.01$), and high dose ($p < 0.01$) conditions.

Correlations

Personality Structure and Altered State

Under the LD psilocybin condition, a positive correlation between the SCL-90 global severity index (GSI) reflecting subclinical psychiatric disturbance and the degree of induced altered state as measured by the 5D-ASC was significant for the main scale of greatest interest, Visionary Restructuralization ($p < 0.05$, $r = 0.59$). The VR subscale contributing most to the correlation between visual changes and the SCL-90 Global

Severity Index was the elementary hallucinations subscale ($p < 0.001$, $r = 0.80$), followed by the facilitated recollection subscale ($p < 0.05$, $r = 0.57$). In the HD psilocybin condition the SCL-90 5D-ASC correlations were not significant.

A positive association was found between aspects of the Cloninger's Temperament and Character Inventory self-transcendence construct and the degree of altered state induced as well. There were significant correlations between the Self-Transcendence score and the Oceanic Boundlessness (OB) ($p < 0.05$, $r = 0.49$) and Visionary Restructuralization (VR) ($p < 0.05$, $r = 0.49$) scales for the low-dose condition. Under the HD condition there was a trend for these correlations that just missed significance (OB, $p = 0.074$, $r = 0.46$; VR, $p = 0.09$, $r = 0.44$).

Correlation between N170 and P300

Correlational analysis indicated that in all three dose conditions the average (of Kanizsa and non-Kanizsa trials) N170 amplitude was correlated with the average P300 amplitude (placebo, $p < 0.01$, $r = 0.65$; LD, $p < 0.05$, $r = 0.59$; HD, $p < 0.05$, $r = 0.55$). Moreover, when analyzing the low and high dose data points together the percentage average N170 amplitude reduction was significantly correlated with the percentage average P300 amplitude reduction due to psilocybin ($p < 0.05$, $r = 0.41$).

N170 reduction and altered state

The percent N170 amplitude reduction relative to placebo on each of the psilocybin experimental days was analyzed to assess whether this measure correlated

with personality scores, behavioral changes (increased reaction time), or the experienced altered state of consciousness. Linear regression analysis with the subscores of the Freiburg Personality Inventory (FPI) and the Symptom Checklist (SCL-90) indicated no significant correlations between these personality measures and the change in the N170 amplitude induced by psilocybin. The N170 reduction did, however, correlate with the one of the main scales of the 5D-ASC questionnaire: there was a significant positive correlation between the average N170 amplitude reduction (across conditions and hemispheres) and the visionary restructuralization (VR) score ($p < 0.05$, $r = 0.37$). Further analysis of the VR subscales showed that the only subscale significantly contributing to the correlation with the N170 amplitude reduction was the elementary hallucination subscale ($p < 0.01$, $r = 0.44$), corresponding to the appearance of simple patterns and light flashes. Subsequent analysis of the elementary hallucination score and the N170 reduction to Kanizsa vs. non-Kanizsa stimuli showed slightly stronger correlation with the non-Kanizsa stimuli N170 reduction ($p < 0.01$, $r = 0.46$ for non-Kanizsa vs. $p < 0.05$, $r = 0.39$ for Kanizsa).

P300 and behavior

Analysis of the P300 amplitudes in association with reaction times in the ERP paradigm revealed that larger average P300 amplitudes correlated with faster reaction times in the placebo condition ($p < 0.05$, $r = 0.53$) but not in the low-dose ($p = 0.60$) or high-dose ($p = 0.84$) conditions. Further, an assessment of the grouped low-dose and high-dose change scores for P300 amplitude and RT revealed that the reduction in P300

correlated with the increase in reaction time ($p < 0.01$, $r = 0.44$).

Visual Search

The average reduction in accuracy for the Kanizsa stimuli in the visual search experiment was seen to moderately correlate with the increase in reaction time ($p < 0.05$, $r = 0.36$). Further, the increase in reaction time on the Kanizsa trials was also seen to correlate with the decrease in N170 amplitude for the Kanizsa triangles in the ERP paradigm ($p < 0.05$, $r = 0.41$) – greater slowing of reaction time tended to occur on experimental days with psilocybin involving greater decreases of N170 amplitude to the Kanizsa triangles.

Discussion

In summary we have assayed the behavioral and neurophysiologic responses to illusory contours and the effect of psilocybin on these measures. We replicated the previously reported finding that the reaction time to Kanizsa figures tends to be faster than that to control figures composed of similar elements but not containing illusory contours. In the more sophisticated analysis of Kanizsa vs. real triangles in the visual search task, reaction times were faster for real triangles than Kanizsa triangles. Further, as expected, accuracy was decreased to the illusory contour stimuli as well as to faster presentation times and increased number of distracters. We also replicated the finding that N170 amplitudes are increased to Kanizsa stimuli relative to control stimuli not containing illusory contours. In addition we have shown that frontal theta activity is

increased by Kanizsa relative to control stimuli, likely reflecting the automatic attentional engagement stimulated by the perception of illusory contours. Occipital alpha activity was seen to decrease after visual stimulus presentation in a manner independent of the presence of illusory contours. Lastly, at the behavioral level we have shown that the reaction time to the Kanizsa figure is quicker than that for the control figure in the simple categorization task for which ERP's were recorded.

We found that psilocybin interacted with these neurophysiologic and behavioral measures in meaningful and significant ways. In the simple categorization task for the Kanizsa vs. control figure, reaction times were slowed by psilocybin but accuracy was not decreased. In contrast, in the visual search detection paradigm psilocybin slowed reaction times and decreased accuracy. Moreover, psilocybin interacted meaningfully with the presence of the illusory contours, causing greater slowing of reaction time and decrements in accuracy to the Kanizsa triangle trials than the real triangle trials. At the neurophysiologic level, the P100 component was shown to be increased in amplitude at midline electrodes by psilocybin. The N170 and P300 component amplitudes were both significantly decreased by psilocybin. Furthermore, both the alpha and theta power during this cognitive task were significantly decreased by psilocybin. Lastly, the psilocybin effects on N170, P300, and induced frontal theta power were all shown to interact meaningfully with the presence of the illusory contours of the Kanizsa stimuli as reflected by significant psilocybin dose x illusory contour interactions on ANOVA analysis.

The findings discussed here at both the behavioral and electrophysiological level

can be accounted for, at least in part, by the effects of psilocybin on attentive capacity. It is important to note, however, that there is clear evidence that the subjects were engaged in the tasks given that both the accuracy in the performance of the ERP task and the detection of the real triangle in the visual search task showed no decrement due to the psilocybin.

One of our primary hypotheses was that psilocybin would affect illusory contour processing in a manner reflected by the amplitude of the N170 component to the illusory triangle vs. control figure conditions. Given the significant *dose* X *contour* interaction and that the N170 amplitude to the Kanizsa triangle was rarely preserved relative to placebo after psilocybin while the N170 amplitude to the control figure was preserved or slightly enhanced in 50% of the observed measurements, it seems that one effect of psilocybin is to decrease the normally enhanced object-recognition processing for illusory contours indexed by the N170 component. The tendency for psilocybin to have a greater inhibitory effect on the N170 amplitude to the illusory triangle condition was thus partly due to the fact that there were few instances of preserved or slightly enhanced N170 amplitude under psilocybin conditions while half of the observed control figure N170 amplitudes under psilocybin conditions were slightly enhanced.

Interpretation of the greater inhibition of the Kanizsa figure N170 amplitude evokes the question as to what property(ies) of the Kanizsa figure exactly brings about this selectivity. By constructing Kanizsa-like stimuli with the same visual elements and an equal number inducing lines, it has been shown that N170 amplitude is increased not from the presence of inducing lines but the presence of inducing lines enclosing an

illusory figure (C. S. Herrmann & Bosch, 2001). Further, some investigators have focused on the notion of a "salience region" that such figures contain, which is not dependent on aligned inducing lines. At both the psychophysiological (Stanley & Rubin, 2005) and brain activation (Stanley & Rubin, 2003) levels it has been shown that such stimuli induce the same kind of increases in perceptual performance and blood flow that figures with illusory contours induce. Nonetheless, in a recent study that directly compared stimuli with salience regions to a stimulus with illusory contours enclosing salience regions the N170 amplitude was greater to the stimulus with illusory contours (Yoshino et al., 2006), leading to the conclusion that psilocybin is interfering with the normal processing of illusory contours per se in the experimental findings here.

The locus of psilocybin-induced activity giving rise to both the generally decreased N170 amplitude as well as the decreased additional illusory contour-driven activity in the Kanizsa condition is unknown. Evidence has supported the notion that low-to-moderate doses of LSD increased the spontaneous activity in the optic tract. Early work with hallucinogens such as LSD and psilocybin found that spontaneous and evoked activity of LGN neurons tended to be decreased in animals, especially as doses were increased (Evarts, 1957; Horn, 1973). Similar findings of decreased visual evoked activity were obtained with studies of single-cell responses in V1 (Connors, 1979; Fox, 1979), although it was also reported that lower doses sometimes induced increased responses while higher doses decreased V1 responses (Dray, 1980; Rose, 1977). Some investigators found only increases in the visual evoked response of cats with systemic and iontophoretically-applied LSD to the dorsal raphe, leading to the theory that visual

evoked potential increases may result from the disinhibition of the raphe on the LGN (Strahlendorf, Goldstein, Rossi, & Malseed, 1982). This early work is not directly relevant to our present-day work with human subjects due to the fact that the effects were observed in non-human, anesthetized animals and often only assessed in the first minutes or hour post-injection or iontophoresis. However, the bulk of the early local field potential and single-cell studies suggested that hallucinogens such as psilocybin and LSD do indeed decrease transmission of evoked activity to the visual cortex, at least at higher doses (Foote, 1982), leading us to expect a decrease in early visual evoked potentials recorded at the scalp including the P100 and N170.

In fact, if the transmission to the LGN or from LGN to V1 was the primary mechanism responsible for the decrease in early visual evoked potentials we would expect to see different results from those obtained, with a primary deficit in the early P100 component as well as a possible N170 deficit. Instead we find increase P100 component amplitudes.

It has been argued that the P100 potential is preferentially a metric of magnocellular dorsal stream processing whereas the N170 potential is more a metric of parvocellular ventral stream processing (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001). Further, evidence suggests that the N170 modulation in the Kanizsa paradigm is primarily a ventral stream processing effect due to activity in the lateral occipital complex (Foxe, Murray, & Javitt, 2005). Thus, the finding that the N170 is significantly reduced in amplitude by psilocybin whereas P100 is, if anything, increased, suggests a mechanism of psilocybin inhibition of ventral stream processing,

possibly through a top-down mechanism of action involving the role of the cortical areas receiving serotonergic input from the dorsal raphe and the known secondary alterations in glutamatergic neurotransmission (Aghajanian & Marek, 2000).

A number of studies have investigated schizophrenic patients to assess possible early visual disturbances (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005; M. J. Herrmann, Ellgring, & Fallgatter, 2004; Onitsuka et al., 2006; Spencer et al., 2003; Spencer et al., 2004). One of these groups has consistently reported decreased P1 and intact N1/N170 generation (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005). Unfortunately, only one such study has assessed psychotic individuals not taking medication so more direct comparisons to our data which possibly mimics the unmedicated early psychotic state is somewhat problematic. The previous findings in schizophrenia with greatest similarity to the findings we report here involved showing Kanizsa vs. non-Kanizsa triangles to schizophrenic patients vs. normal controls. In the first of these studies, it was reported that P1 amplitudes were decreased in the schizophrenia group and there was a trend towards decreased N170 amplitude (Spencer et al., 2003). The second study from the same group (Spencer et al., 2004) reported that schizophrenia patients relative to controls exhibited decreased P1 amplitudes only on the right hemisphere in the Kanizsa condition, and decreased N170 amplitude across conditions. Further, they reported a less significant difference in N170 amplitude between the two conditions in the schizophrenia group and that those patients with prominent visual hallucinations showed a dramatically reduced N170 amplitude (Spencer

et al., 2004). A more recent finding with Kanizsa squares comparing schizophrenia patients to normal controls found no difference in N170 amplitude for schizophrenics but a significant decrement in P1 amplitude and topography, which the authors interpreted as evidence for deficits in dorsal stream processing but intact ventral stream early visual processing (Foxe, Murray, & Javitt, 2005).

Comparing the visual N170 to faces and buildings, recent work has shown that chronic, medicated schizophrenic patients exhibit smaller N170 amplitudes to faces. This effect caused a smaller difference in N170 amplitude between the two stimuli, suggesting a deficit in the early visual processing similar to the one we describe here, but in the domain of face instead of illusory form perception (M. J. Herrmann, Ellgring, & Fallgatter, 2004). A second group has replicated the selective decrease in the normally increased N170 amplitude for faces comparing the N170 response to faces, hands, and cars (Onitsuka et al., 2006). However, a third group (Valkonen-Korhonen et al., 2005) has assessed N170 to face stimuli in unmedicated first-episode psychotic patients and found that patients had greater N170 amplitudes than control subjects, suggesting that the decreased facial N170 may be partly due to the effects of neuroleptics.

Using line drawings of animate and inanimate objects with progressively fragmented versions of the stimuli used to make their identification ambiguous, chronic medicated schizophrenics were shown to exhibit markedly decreased P1 amplitudes to both the intact and fragmented versions of the stimuli but not to show deficits in N170 responses (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001). Again, related recent findings with global-local stimuli contradict this selective P1

finding. This study used visual stimuli such as "H" stimuli composed of "T" elements with response required to global vs. local features of the visual stimuli and found that chronic medicated schizophrenic patients exhibited reduced N150 responses to the stimuli with P1 unaffected (S. C. Johnson, Lowery, Kohler, & Turetsky, 2005). In sum, it appears that the findings reported here that psilocybin decreases the N170 amplitude to both Kanizsa and control figures is consistent with some of the previous findings in schizophrenia and may relate to a similar relative disengagement of the attentional systems from the sensory surround. It is possible that in such states the brain's networks may become more internally active, generating rich meaningful internal landscapes that are less attuned to faithfully representing the external sensory world due to a shift in the balance of active corticostriatothalamic loops (Vollenweider & Geyer, 2001b). It is important to note, however, that the findings in schizophrenia are still equivocal with the preponderance of the data from Javitt's group supporting the view that the P1 and not the N1/N170 is more robustly decreased in amplitude in schizophrenics, reflecting a relatively selective deficit in dorsal stream processing. Testing a group of schizophrenics with the stimuli and paradigm used herein would provide useful comparison data.

Another possibly related finding was reported comparing Williams Syndrome patients to normal controls using Kanizsa square stimuli vs. control pac-men figures. Although there was no main effect of group, the N170 amplitude to the Kanizsa stimulus compared to control stimuli was highly similar in contrast with control subjects who exhibited the expected strong N170 differential response (Grice et al., 2003). While the effects of psilocybin are not reported to be phenomenologically similar to developmental

disabilities such as Williams Syndrome, the evidence suggests that in both cases there may be a relative deactivation of the lateral occipital complex as the brain becomes less engaged with the encoding of illusory contours in the service of interpreting the visual sensory surround.

The finding that psilocybin caused a greater slowing of reaction time to the non-triangle stimulus than the illusory triangle stimulus in the ERP experiment is somewhat at odds with the finding that the N170 amplitude in response to the stimuli became more similar. One might expect greater differential amplitude of N170 to the two stimuli, reflecting stronger differential stimulus feature encoding, would be accompanied by greater differential reaction time to the stimuli. Two lines of argument may help to make this finding more interpretable. On the one hand, reaction time data tend to be more highly correlated to later cognitive components such as P300 than early/mid-level components such as the N170, and we see no *dose* x *contour* interaction in the P300 response for our data. Further, in our visual search paradigm we find that the *dose* x *contour* interaction for both reaction time and error rates is in the direction we might expect given the electrophysiological findings. That is, for both accuracy and reaction time the performance on the illusory triangle trials is more greatly degraded due to psilocybin than the performance on the real triangle trials. This correspondence of electrophysiological and behavioral effects underscores the fact that stimulus encoding strength is important in the execution of visual detection tasks. The lack of the correspondence to the behavioral effect in the easy stimulus categorization task may be related to the ease of that task; because the cognitive system was not challenged by the

test, the weaker encoding strength of the illusory contours may not have been behaviorally relevant.

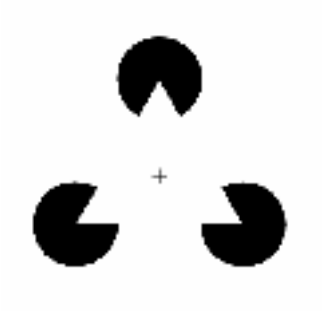
One aspect of the data with great relevance to the question of how psilocybin affects the neural processing of the illusory contours of the Kanizsa figures is the relative strength of the various ERP components and induced theta power to the Kanizsa *vs.* the control figure. The N170 amplitude, P300 amplitude, and theta power induction to the Kanizsa vs. control figure all showed significant psilocybin x illusory contour interactions. Both the N170 power and the illusory contour-induced frontal theta induction were found to be of a more similar magnitude after psilocybin than under placebo conditions. In contrast, the P300 amplitude was shown to be more markedly different in the psilocybin vs. placebo condition, specifically at the frontal Fz electrode. The fact that the N170 amplitude was more differentiated in the placebo state than the psilocybin state is in line with the theory that psilocybin inhibits the strength of the ventral stream object-recognition processing activity thought to underlie the generation of the N170 component to these stimuli. It follows from this that the engagement of the frontal attentional networks indexed by induced theta activity would be less differentially activated in the psilocybin state as well. It is of note that this disruption of induced theta activity parallels findings of decreased theta power inductions to cognitive tasks in schizophrenia (Gonzalez-Hernandez et al., 2003). It may be that the additional frontal power of the P300 component to the Kanizsa stimulus in the psilocybin state was related to the fact that extra frontal processing needed to be recruited in order to accomplish the categorization task of illusory triangle vs. control figure due to the degraded object-

recognition and attentional engagement activity induced by the psilocybin.

Chapter 4, in part, is in preparation for submission for publication with Franz Vollenweider as co-author. The dissertation author is the primary investigator and author of this paper. Thanks to David Andel for constructing the Kanizsa stimuli used in the ERP and visual search experiments. Thanks to Daniel Senkowski for providing us with the Kanizsa visual search stimuli which we adapted for the experiments herein.

1a.

1b.

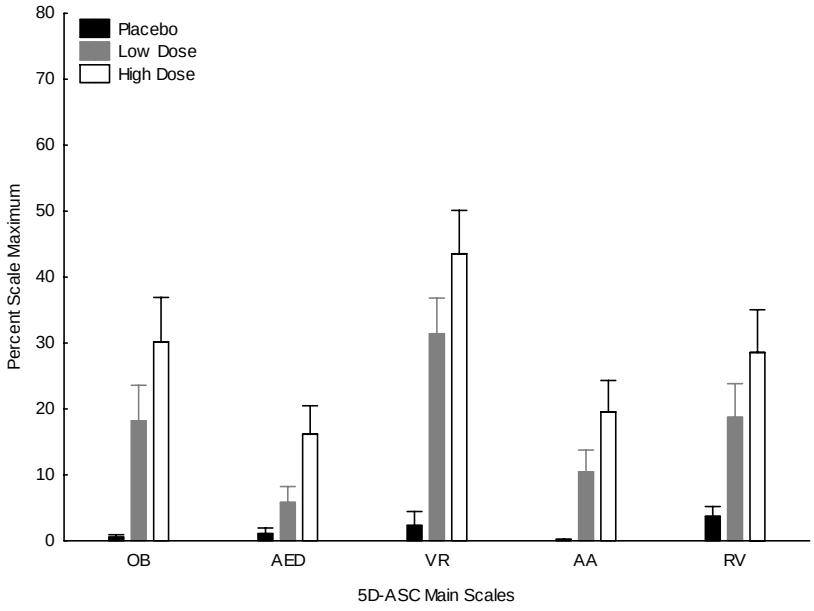


1c.

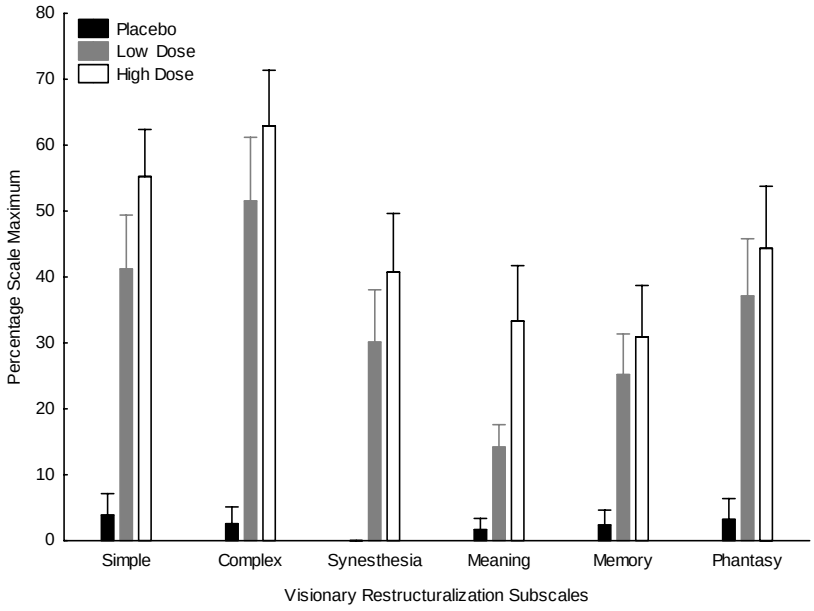
1d.

Chapter 4 Figure 1 legend. Kanizsa stimuli. Control figure (1a) and illusory contour-containing Kanizsa triangle (1b) stimulus used for the ERP paradigm, three additional stimuli of each class consisted of the rotated versions of these stimuli at +90, +180, and +270 degrees 1c-d., representative stimuli from the visual search paradigm. Each stimulus consisted of 15 or 28 total elements with either a real triangle (1c), a Kanizsa triangle (1d), or neither (not shown)

2a.

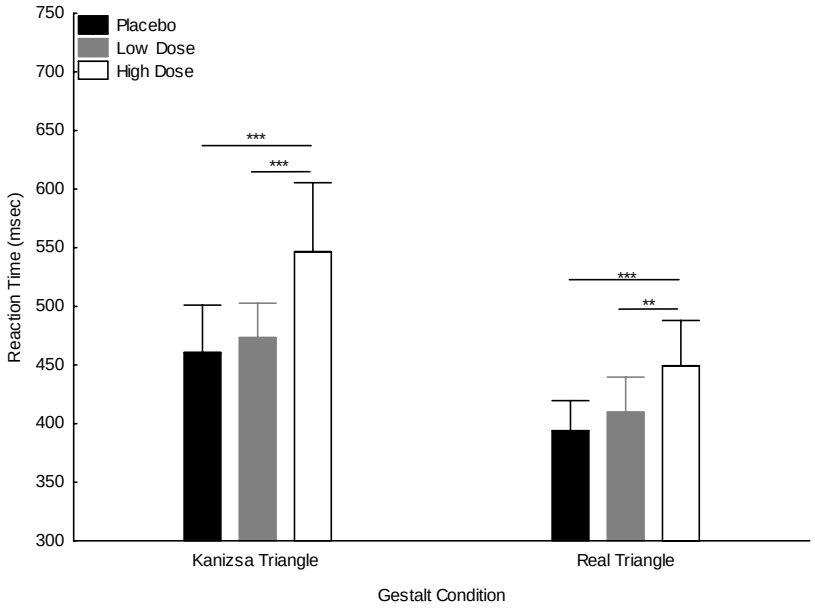


2b.

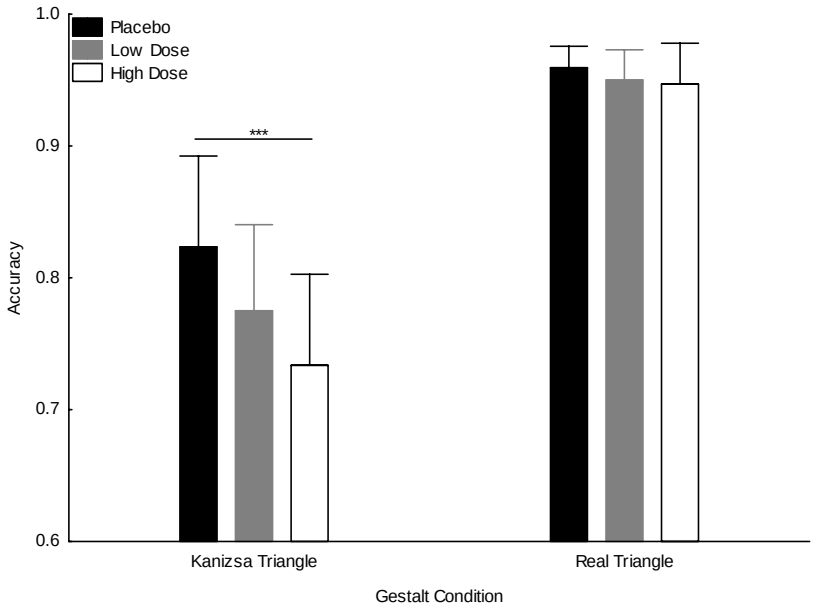


Chapter 4 Figure 2 legend. Mean percentage scores ± SEM of the Altered States of Consciousness Rating Scale (5D-ASC) main scales (2a) and subscales of the Visionary Restructuralization scale (2b) during placebo, low dose psilocybin (125 µg/kg), and high dose psilocybin (250 µg/kg) conditions. OB = Oceanic Boundlessness, AED = Anxious Ego Dissolution, VR = Visionary Restructuralization, AA = Auditory Alterations, RV = Reduction of Vigilance.

3a.

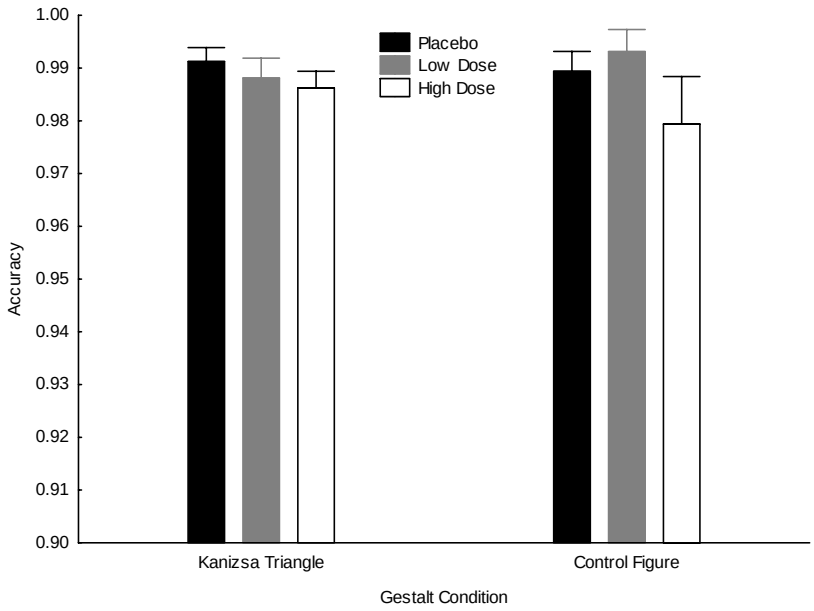


3b.

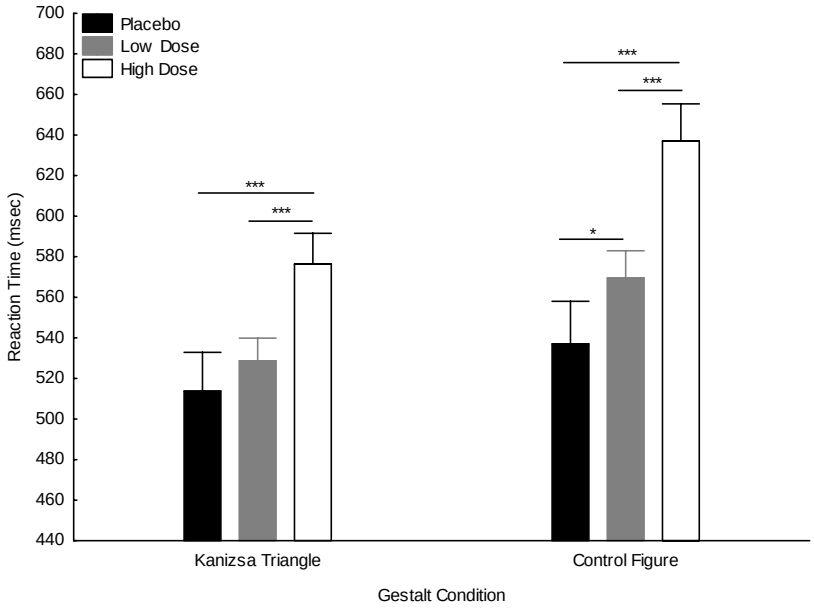


Chapter 4 Figure 3 legend. Accuracy (3a) and reaction time (3b) performance on the real and illusory contour (Kanizsa) visual detection task trials. Psilocybin cause decreases in accuracy and increases in reaction time especially for the illusory contour target trials. **, *** indicate significant difference between conditions at the $p < 0.01$ and $p < 0.001$ levels.

4a.

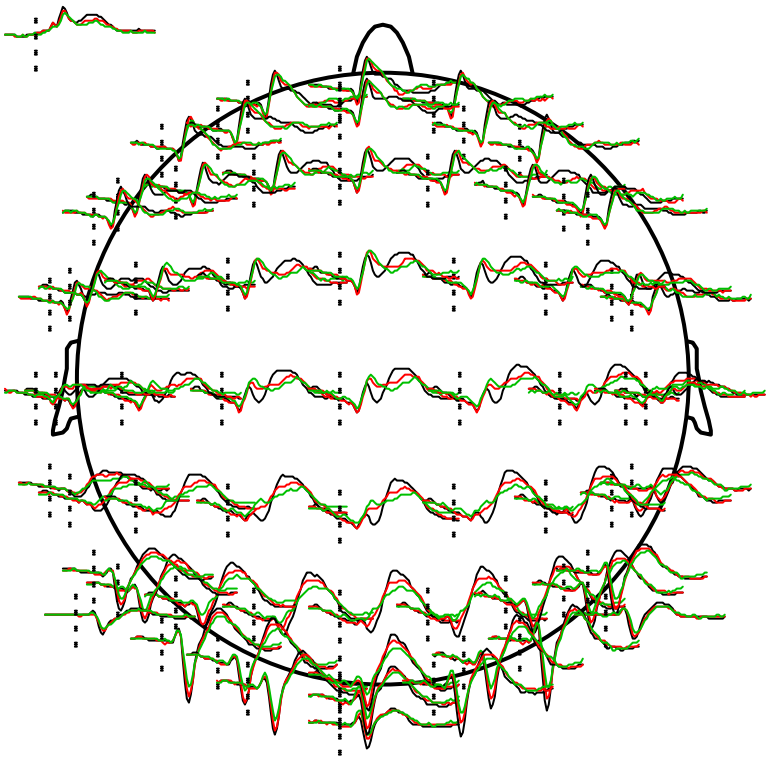


4b.

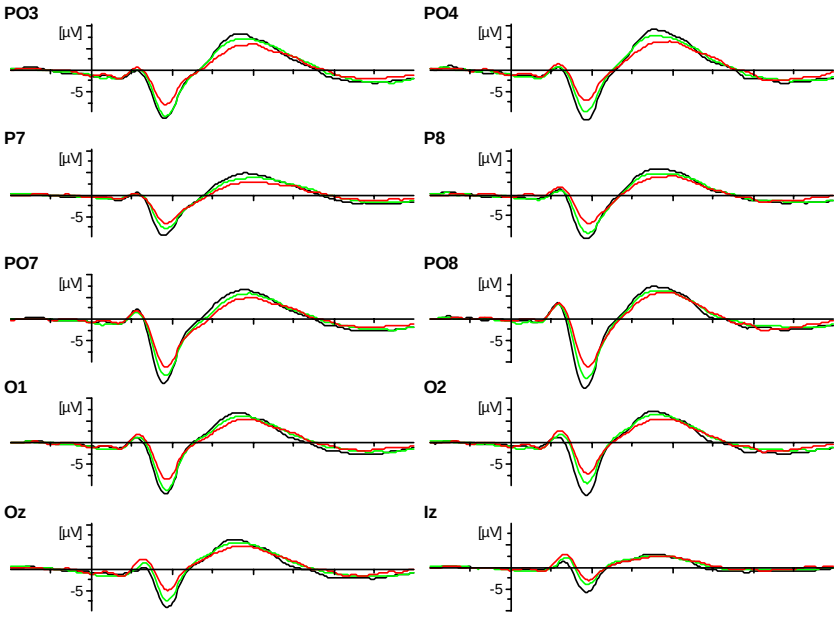


Chapter 4 Figure 4 legend. Accuracy (4a) and reaction time (4b) performance on the Kanizsa triangle and control figure trials for the ERP paradigm. There was no significant decrease in accuracy due to psilocybin but an increase in reaction time, especially for the control figure. *, *** indicate significant difference between conditions at the $p < 0.05$ and $p < 0.001$ levels.

5a.

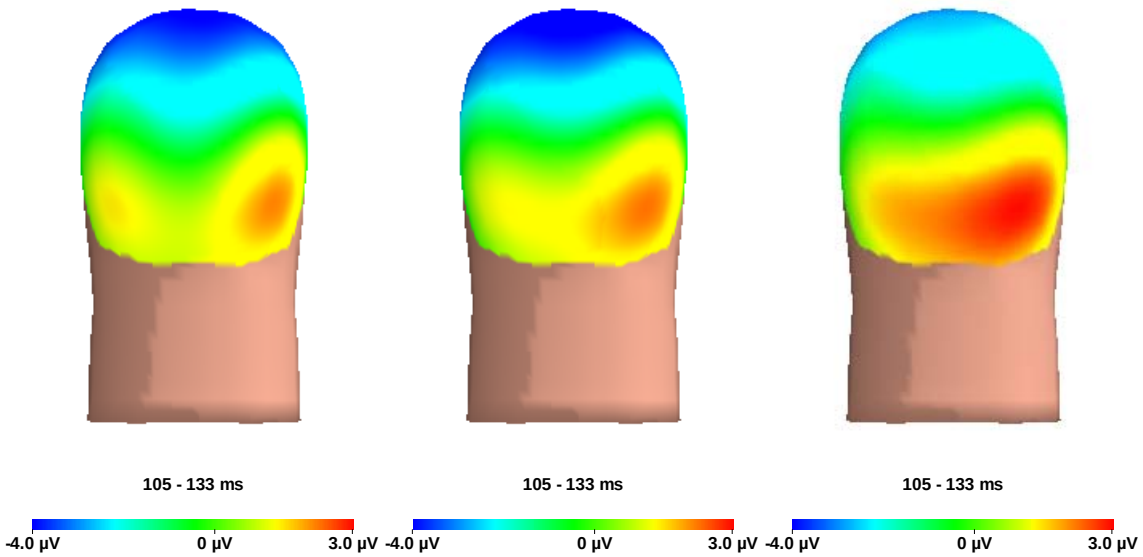


5b.

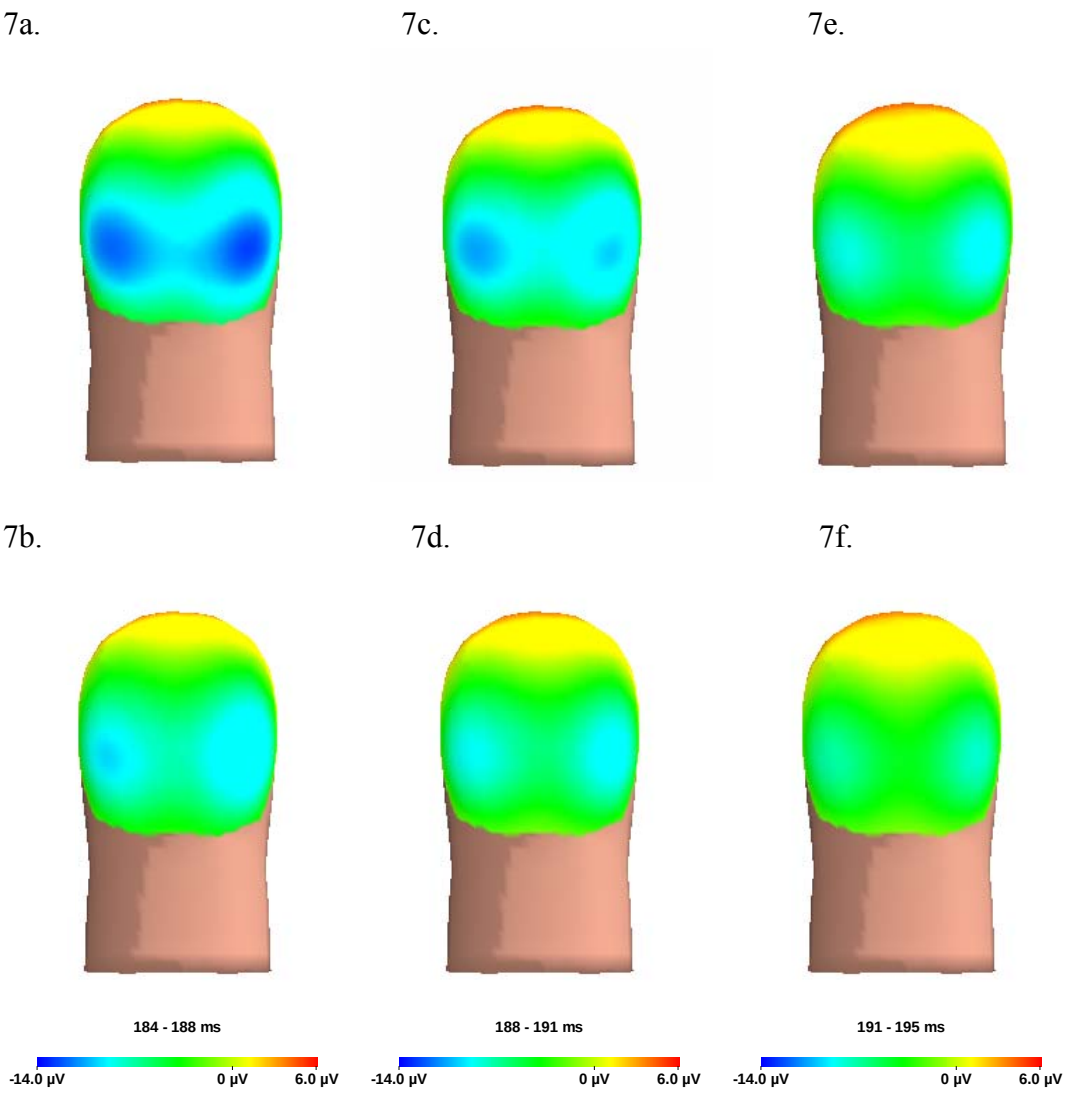


Chapter 4 Figure 5 legend. Grand average wave forms for the Kanizsa triangle trials. Black traces indicate placebo condition, green traces indicate low dose psilocybin condition, and red traces indicate high dose psilocybin condition. 5a, all scalp eclectrodes; 5b, close-up view of occipital electrodes only.

6a. 6b. 6c.

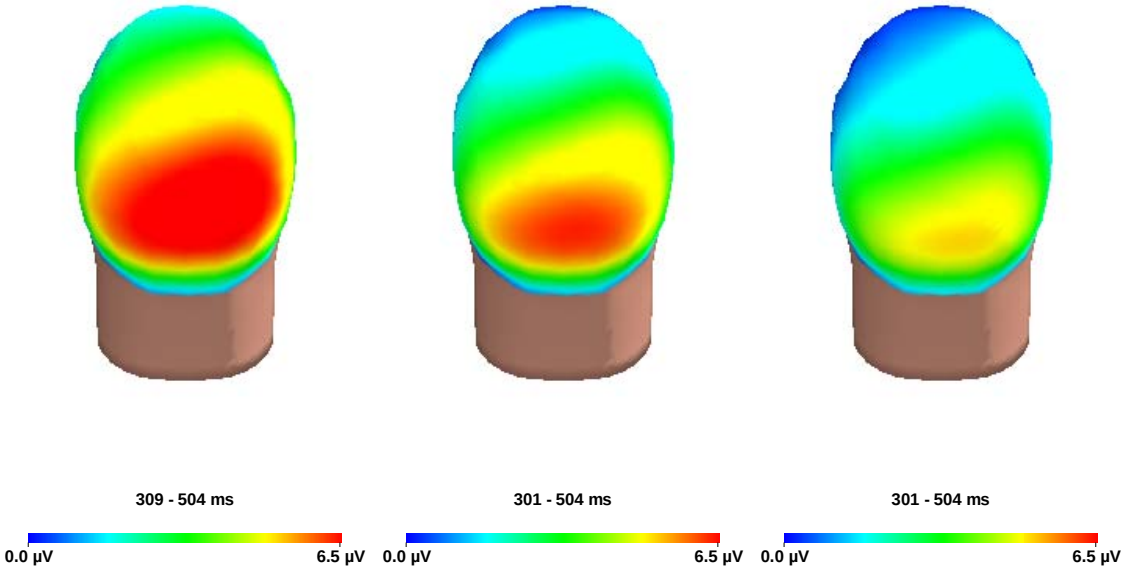


Chapter 4 Figure 6 legend. P100 scalp map to Kanizsa triangle. Scalp distribution over a 30 msec window centered on the global field power peak for the P100 component to the Kanizsa triangle stimulus in placebo (6a), low dose psilocybin (6b), and high dose psilocybin (6c) conditions.



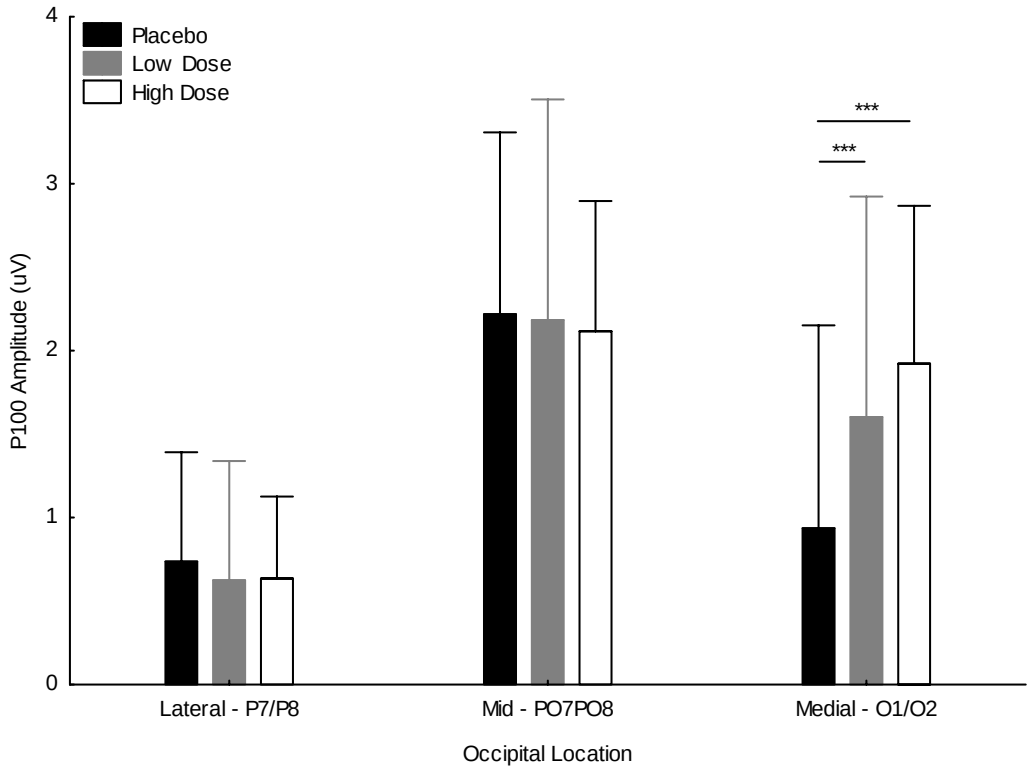
Chapter 4 Figure 7 legend. Scalp distribution for the N170 component at the peak latency for each of the dose conditions. 7a-b, placebo dose Kanizsa triangle (7a) and Control figure (7b) stimuli; 7c-d, low dose Kanizsa triangle (7c) and Control figure (7d) stimuli;7e-f, high dose Kanizsa triangle (7e) and Control figure (7f) stimuli.

8a. 8b. 8c.



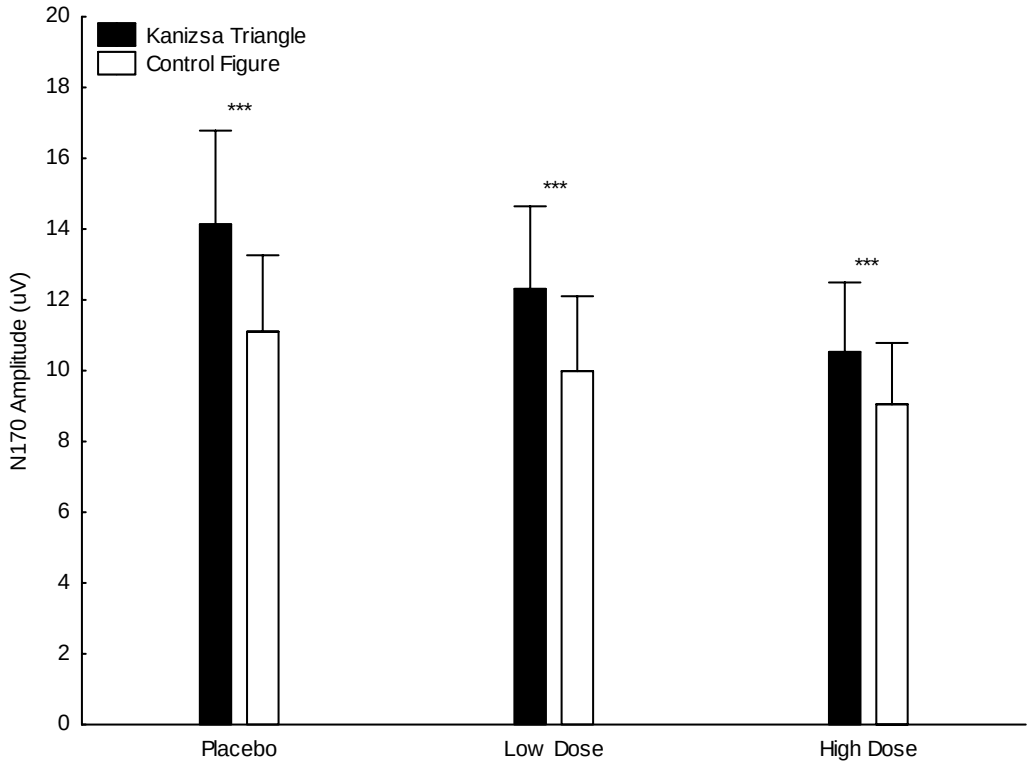
Chapter 4 Figure 8 legend. P300 scalp map to Kanizsa triangle. Scalp distribution for the P300 component for the Kanizsa triangle trials over the 300-500 msec latency for each of the dose conditions. 8a, placebo; 8b, low dose psilocybin; 8c, high dose psilocybin.

9.



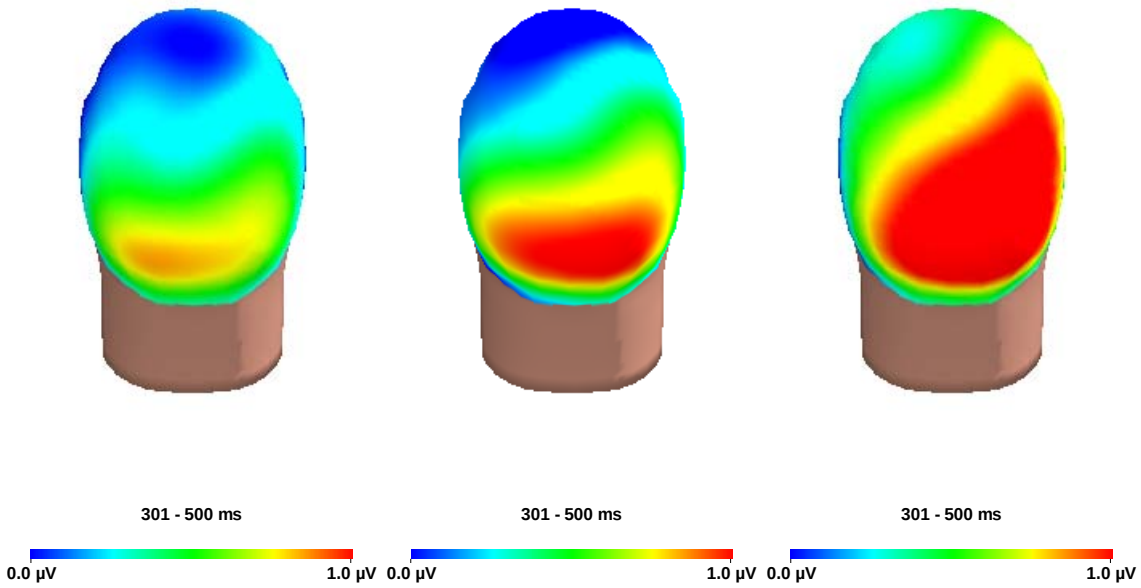
Chapter 4 Figure 9 legend. Psilocybin dose effect on P100 component amplitude. P100 Amplitude + SEM averaged over 105 – 135 msec at occipital channels. *** indicates the increase of medial occipital P100 amplitude for low dose (125 μg/kg) compared to placebo ($p < 0.001$) and high dose (250 μg/kg) compared to placebo ($p < 0.001$).

10.



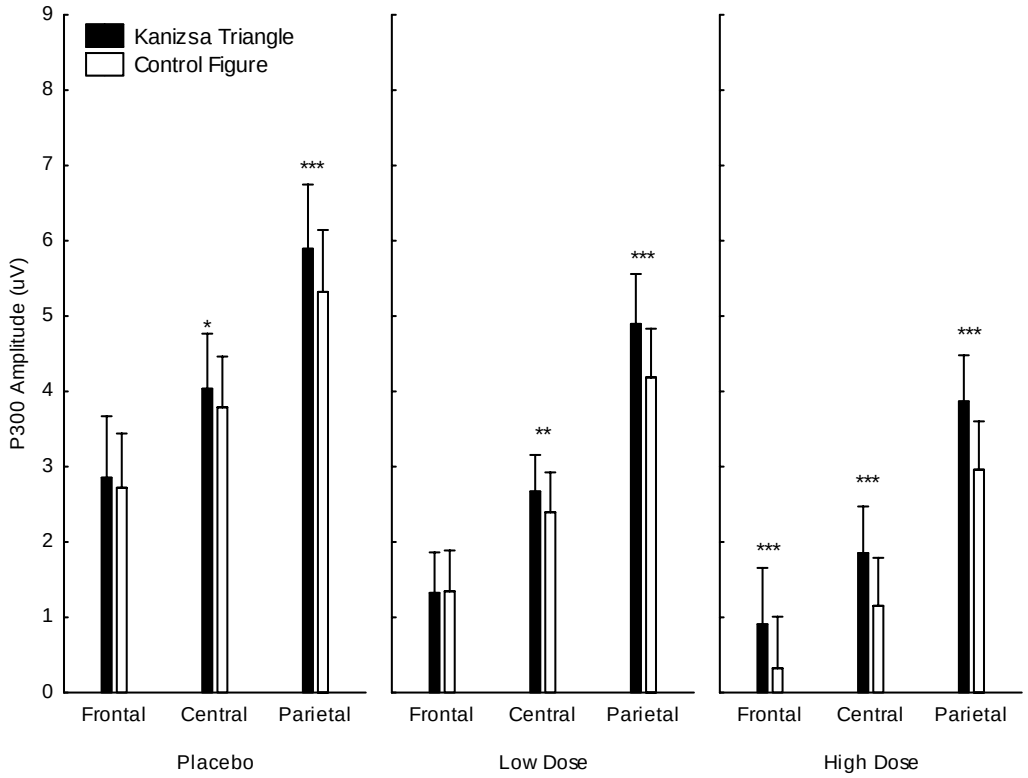
Chapter 4 Figure 10 legend. Psilocybin dose effect on N170 component amplitude. N170 Amplitude + SEM for Kanizsa illusory triangle trials compared to the control figure trials during placebo, low dose psilocybin, and high dose psilocybin.

11a. 11b. 11c.



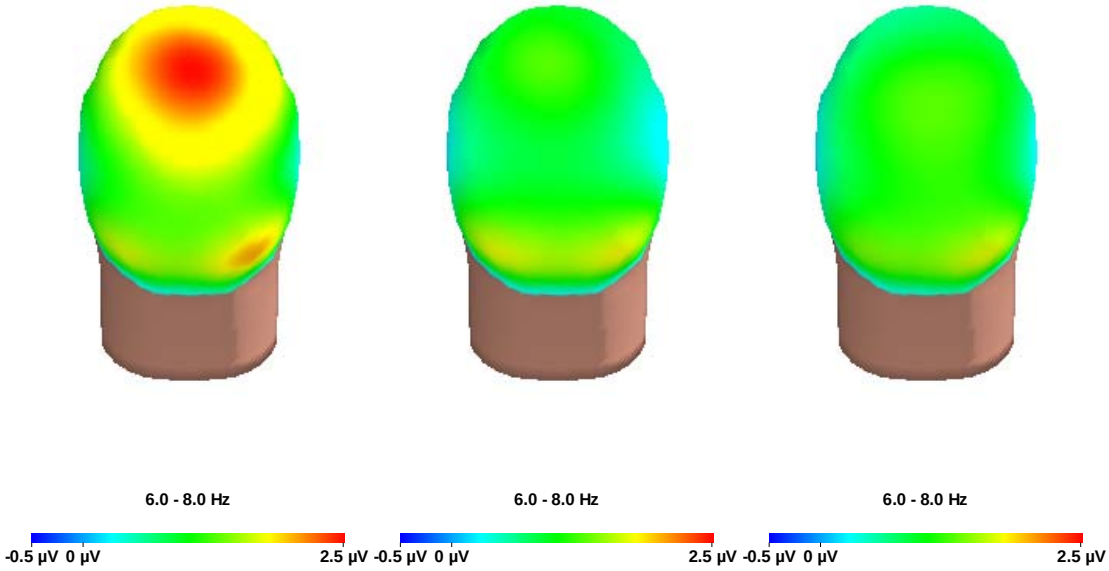
Chapter 4 Figure 11 legend. P300 component difference map. Grand average difference maps for the P300 component comparing Kanizsa triangle trials to control figure trials for the placebo (11a), low dose (11b), and high dose (11c) conditions. Note that despite psilocybin-induced decreased P300 amplitudes the differential P300 amplitude due to the presence of illusory contour is accentuated by psilocybin.

12.



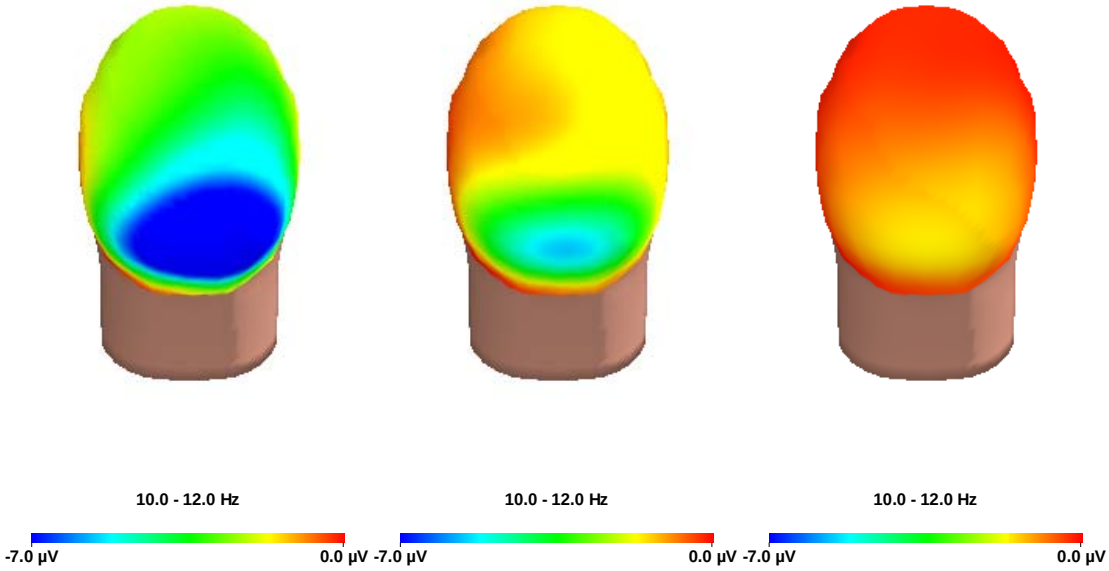
Chapter 4 Figure 12 legend. Psilocybin dose effect on P300 component amplitude. P300 Amplitude + SEM for Kanizsa illusory triangle trials compared to the control figure trials during placebo, low dose psilocybin, and high dose psilocybin. *,**,*** indicate a significant increase in P300 amplitude for the Kanizsa triangle relative to control figure trials at the relevant scalp locations at $p < 0.05$, $p < 0.01$, and $p < 0.001$ levels.

13a. 13b. 13c.



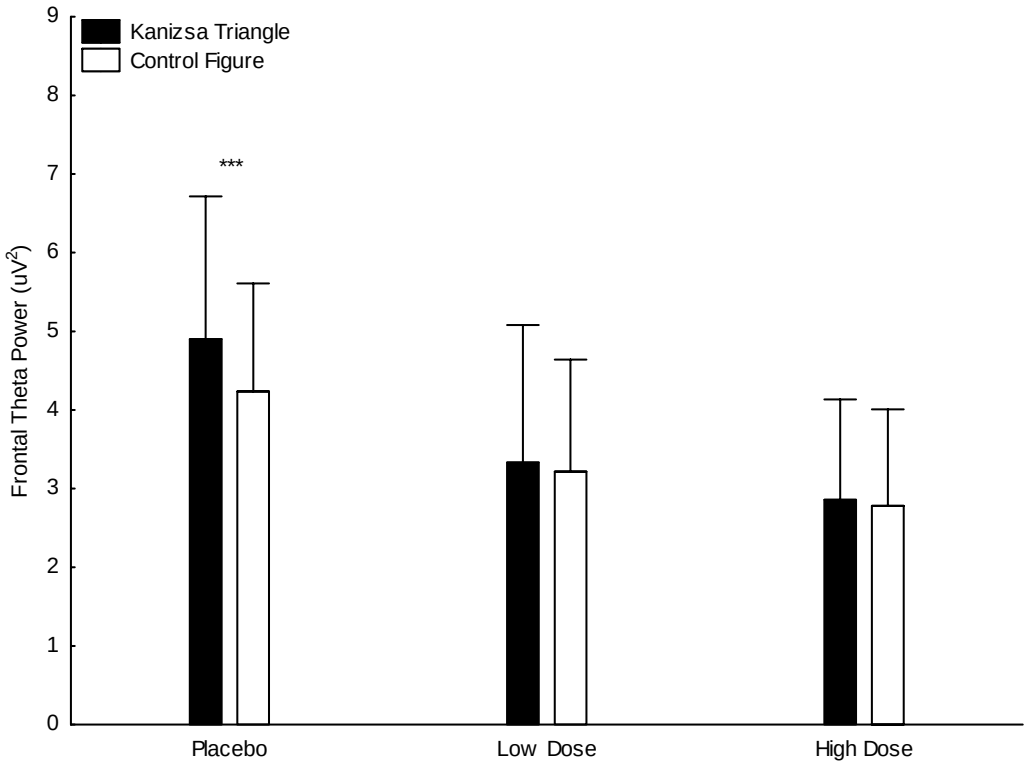
Chapter 4 Figure 13 legend. Difference maps for theta (6-8 Hz) power (13a-c) depicting the difference between pre and post stimulus theta power (poststimulus – prestimulus theta power). 13a Placebo 6-8 Hz power difference map; 13b Low dose 6-8 Hz power difference map; 13c High dose 6-8 Hz power difference map.

14a. 14b. 14c.



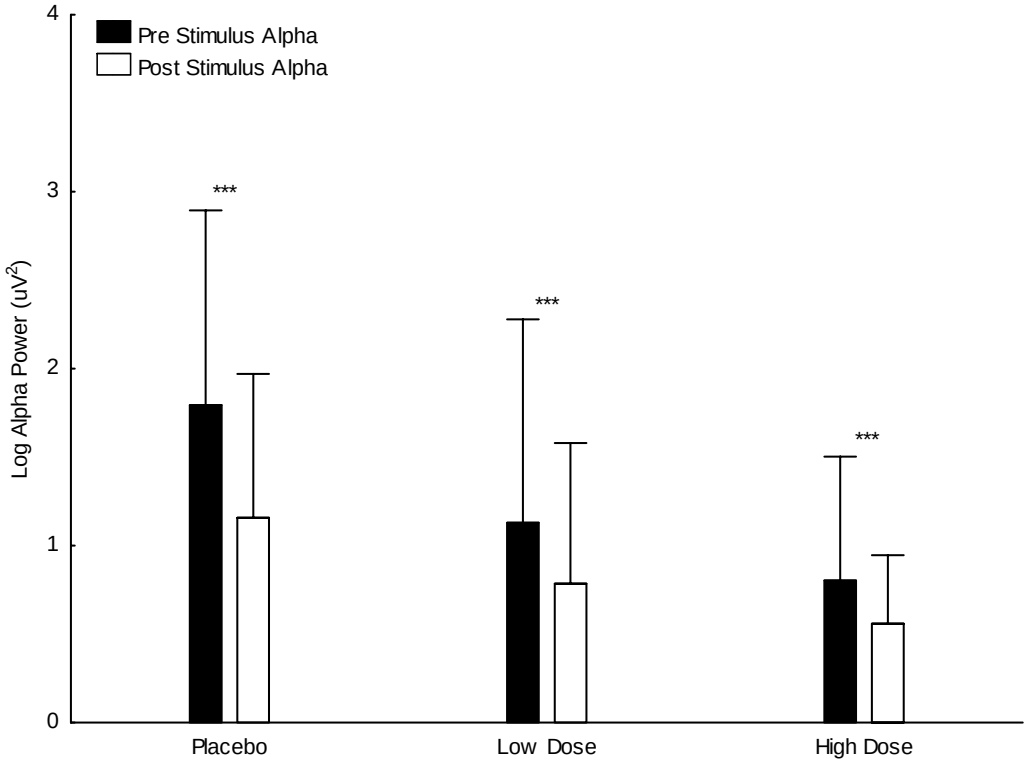
Chapter 4 Figure 14 legend. 10-12 Hz power difference map; poststimulus - prestimulus alpha power. Difference maps for 10-12 Hz power depicting the difference between post and pre stimulus alpha power for placebo (14a), low dose (14b), and high dose (14c) conditions.

15.



Chapter 4 Figure 15 legend. Psilocybin dose effect on illusory contour-induced frontal theta power. Frontal theta power amplitude + SEM for Kanizsa illusory triangle trials compared to the control figure trials during placebo, low dose psilocybin, and high dose psilocybin. *** Indicates a significant increase in theta power amplitude for the Kanizsa triangle relative to control figure trials at $p < 0.001$ levels.

16.



Chapter 4 Figure 16 legend. Psilocybin dose effect on illusory contour-induced alpha power. Alpha power amplitude + SEM for Kanizsa illusory triangle trials compared to the control figure trials during placebo, low dose psilocybin, and high dose psilocybin. *** Indicates a significant increase in theta power amplitude for the Kanizsa triangle relative to control figure trials at $p < 0.001$ levels.

CONCLUSION

Studies on the electrophysiological effects of meditation and psilocybin have been described. These are the first studies of the effects of psilocybin using modern EEG/ERP methodology and provide a number of new findings that may be of significant import in the understanding of the role of serotonergic activity in visual processing and awareness, the understanding of the biological parameters correlated with altered states of consciousness which may be applicable outside the field of drug-induced changes, possibly including endogenous psychoses and schizophrenic states.

The finding that psilocybin tends to increase the early positivity observed in the P1 time range to visual stimuli, specifically at medial areas, is intriguing and deserving of further study. The use of a flash visual evoked potential paradigm would help to sort out whether this effect was mediated by signaling at the first stage of V1 processing in the 40-50 msec time range or due primarily to feedback from accessory cortical areas. What seems clear, however, is that whatever the mechanism of this early enhanced midline positivity, later component amplitudes starting with the N1 tend to be decreased in amplitude. In the work described herein the N1 to stimuli processed in the dorsal stream (Kanizsa triangle, distracter checkerboard) showed greater inhibition than those processed in the ventral stream (standard and target blue circles in the visual oddball paradigm).

The strong reduction in P300 amplitudes and induced theta activity seem related and also sensible given the earlier reduction of N1 amplitudes. Moreover they seem to

indicate a possible marker of the altered state brought about by psilocybin as involving less context-updating and monitoring of the visual surround. It would be of interest to assess other sensory modalities as visual hallucination is one of the hallmarks of psilocybin effects and thus some of these reductions in later processing to the visual stimuli employed herein may not hold for the other sensory systems including somatosensory and auditory modalities.

One similarity observed between the two findings was the decrease in frontal theta power induction to distracting stimuli in both the passive auditory oddball paradigm used to assess the effect of meditation and the visual oddball paradigm used to assess the effects of psilocybin. While the observed effects on theta were quite similar, an important distinction between the visual oddball experiment conducted with psilocybin and the auditory oddball experiment conducted with meditators is that the visual experiment was an active one involving the requirement for behavioral response and the auditory paradigm was passive with specific instructions to ignore the stimuli given to the research participants prior to onset of the stimuli. Thus, the effects of psilocybin on theta power induction to the attended distracting visual stimuli was somewhat similar to the effects of Vipassana meditation on theta power induction to unattended distracting auditory stimuli.

One possible conclusion is that psilocybin invokes a similar disconnection of the attentional networks from the immediate sensory surround as meditation. It is important to note, however, that due to the voluntary nature of the disengagement of attention brought about through meditation, one would not predict that an active task would be

similarly affected by meditation – indeed the few studies that have been conducted on the P300 response to meditation using an active task before and after meditation have shown increases, rather than decreases, in P300 amplitude as a result of meditative practice (Banquet & Lesévre, 1980; Travis & Miskov, 1994). To date the study described herein is the first assessment of stimulus-induced theta activation with meditation so a similar comparison can not be made with this measure. What can be supported is the notion that meditation compared to thinking caused a decrease in theta activation to distracting stimuli in a passive task and that the observed similarity to the effect of psilocybin in the active visual oddball task implies a similar disengagement of the brain's attentional networks from sensory stimuli. It is reasonable to hypothesize that this similarity may underlie some of the similar unusual experiences encountered both under the effects of hallucinogenic drugs and due to meditative practice – experiences as diverse as dramatically altered experience of self, synesthesia-like phenomena, re-experiencing of long forgotten memories and the like. All of these experiences involve a disengagement from the immediate sensory surroundings which the reduced theta reactivity may index.

The correlation between frontal theta power and the degree of altered state experienced under high dose psilocybin was unexpected. A correlation between the degree of reduction in theta power and experienced altered state was a more expected correlation for this variable, but no signs of such correlation were found. Instead there was a strong correlation between the theta power – both at baseline and during the effects of psilocybin – and the experienced altered state. The finding seems to imply that individuals with higher frontal theta power during this cognitive engagement tend to

experience more of the positive aspects of altered state when given high doses of psilocybin and that, moreover, their theta power stays relatively high under the effect of the drug.

Neuroticism has been identified as a predictor of negative experiences during altered states of consciousness (Dittrich, 1994). Thus, the reported association between increased frontal theta power and low anxiety and neurosis scores (Inanaga, 1998) may be related to the finding that high theta power was seen in those individuals experiencing a very positive altered state of consciousness in response to psilocybin. Further, as reviewed in Chapter 1, meditation has been shown to be associated with decreases in anxiety and increases in theta power thus supporting the notion that meditators would be predicted to have especially positive responses to psilocybin. The assessment of this prediction would be a natural extension of the work presented herein, possibly offering further insight into the key commonalities and differences induced by these two very different ways of inducing altered states of consciousness.

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