In press, October 2025, in: J. Grafman and P. McNamara (editors), *Neuroimaging and Psychology of Religion.* Routledge Press.

The God receptor: naturalistic, psychotic and entheogenic neurocognition in the origins and phenomenology of spiritual and religious thought

Bernard Crespi [1], Nancy Yang [1], Sam M Doesburg [2]

[1] Department of Biological Sciences, Simon Fraser University, Burnaby, British Columbia, V5A1S6, Canada**, crespi@sfu.ca** for correspondence.

[2] Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, V5A1S6, Canada

Abstract

The human brain apparently harbors no network or region uniquely dedicated to spiritual or religious thought, or clearly evolved specifically in these contexts. God is thus nowhere in the brain. Could God, instead, be virtually everywhere in the brain? We propose and evaluate the hypothesis that religious and spiritual cognition are derived predominantly from the effects of (virtually ubiquitous) HT2A receptors on perception, cognition and emotion. We evaluate the hypothesis using integration of data from recent fMRI and lesion studies of spiritual and religious neurocognition with data from studies of the HT2A receptor, its distribution, activation, and functions, and its high activation in psychedelic experience, psychiatric conditions, and socioecological and physiological stress. We describe how the God-receptor hypothesis is consistent with diverse, independent lines of evidence. To the extent that the hypothesis is true, further progress in understanding the cognitive neuroscience of spirituality and religion will depend on studies of how adaptive HT2A receptor activation, and supraphysiological hyperactivation associated with stress, psychedelics, or psychotic-affective conditions, is mediated by predictive coding and other functional systems in religion-relevant regions of the brain.

Suddenly my whole being was filled with light and loveliness and with an upsurge of deeply moving feeling from within myself to meet and reciprocate the influence that flowed into me. I was in a state of the most vivid awareness and illumination. What can I say of it? A cloudless, cerulean blue sky of the mind, shot through with shafts of exquisite, warm, dazzling sunlight. In its first and most intense stage it lasted perhaps half an hour. It seemed that some force or impulse from without were acting on me, looking into me; that I was in touch with a reality beyond my own; that I had made direct contact with the secret, ultimate source of life. What I had read of the accounts of others acquired suddenly a new meaning. It flashed across my mind, "This is what the mystics mean by the direct experience of God."

M. Coate, describing psychotic experience.
***Beyond All Reason.* New York: J.B. Lippincott, 1965, page 21.**

Introduction

Spirituality and religion represent central features of human experience and culture. Their existence and forms remain enigmatic, however, on two main fronts. First, under what selective pressures, and through what other genetic and environmental processes, did these uniquely human and culturally ubiquitous traits originate and evolve? Is the conception of God, gods or higher powers an adaptation, a byproduct, a delusion, an accident, or some combination of these options? Second, how are spirituality and religion instantiated in the human brain? Brains are comprised of functional modules and networks - are there regions or networks that evolved to represent gods and spirits, like the fusiform face area evolved to encode human faces? These questions remain especially puzzling because spiritual and religious experiences differ qualitatively from ordinary life, because the causal connections of spirituality and religion to components of reproductive fitness in humans remain largely obscure, and because the existence of gods and spirits is manifestly impossible to verify in any logical or scientific way.

The past ten years have seen substantial progress in addressing these questions, especially through neuroimaging studies of humans engaging in spiritual or religious thought or activities (e.g., Ferguson et al., 2022; McNamara & Grafman, 2024). These studies have demonstrated that activations of specific regions and networks in the brain are positively or negatively associated with such forms of cognition and affect. However, essentially all of the relevant brain architecture implicated in spirituality or religiosity has been functionally spoken for by previous, secular, neuroimaging studies; spiritual and religious forms of cognition recruit regions of the brain that subserve sociality, agency, salience, logic, pleasure, pain, and other basic or advanced human adaptations, among others (e.g., Rim et al., 2019; McNamara & Grafman, 2024). On one hand, such findings should not be surprising, because the human brain has evolved predominantly via expansion, grafting and co-option of pre-existing areas and circuits for new or expanded roles, such as language. On the other hand, the ubiquity, uniqueness, and central importance of religiosity to humans suggest that this cognitive phenotype should have a specific and detectable neural substrate - a god-region, god-network, or god-signature of some form that is beyond a cobbling together of otherwise, elsewhere dedicated parts.

In this article, we evaluate the hypothesis that the core neural bases of spiritual and religious cognition are mediated not by brain regions or networks, but microscopically, by activation of specific receptors, in particular ways, in the context of the aforementioned macroscopic regions and their circuits. By this hypothesis, the novelty of god-cognition in humans derives predominantly from the novelty of supraphysiological activation of HT2A receptors, that subserves the mechanisms of predictive coding centrally regulating human perception, consciousness and learning. Such supraphysiological activation is driven by three human-elaborated or unique mechanisms, two internal (stress-challenge responses and psychosis, that are overlapping with one another) and one external (psychedelic biochemicals), that converge in their effects on cognition via the downstream effects of high HT2A activation - all in the context of the already-highly-social, and thus primed-for-god, human brain. Diverse aspects of this hypothesis have been addressed before, especially in the literature on psychedelic drugs in relation to spirituality and religion, but the relevant threads have yet to be woven fully together.
We first sketch the God-receptor hypothesis, and its components, in broad strokes.

Second, we provide essential background regarding the HT2A receptor, especially with regard to its roles in predictive coding in the contexts of perception and self-perception.

Third, we describe how most psychedelic biochemicals hyperactivate HT2A receptors, and how their effects appear to lead to a suite of novel experiences that overlap broadly with those derived from non-psychedelic causes. We also provide a brief overview of the uses of psychedelic biochemicals in diverse human cultures, especially with regard to how psychedelic experiences often form the bases, or have promoted the origins, of spiritual and religious thought and its cultural instantiations.

Fourth, we discuss the connections of the HT2A receptor hyperactivation with psychosis and schizophrenia, in the framework of cognitive models and predictive coding frameworks for this condition. We also describe relevant overlaps of psychotic and psychedelic experience with one another, as well as with spiritual and religious experience.

Finally, we synthesize these diverse lines of evidence in the context of human evolution, and discuss the predictions and limitations of the God-receptor model with special emphasis on what data are needed for robust tests.

We recognize that each of the academic domains represented by a section of this article is deeper and broader than we can hope to comprehensively address. In this context, our main goal is to outline the God-receptor hypothesis and provide a synopsis and synthesis of the relevant evidence. Most generally, we believe that the hypothesis is consilient with virtually all previous theory regarding the evolution and neural basis of spirituality and religion, and is best conceived in this light.

The God-receptor hypothesis

The God-receptor hypothesis, in the form described here, was motivated by the observations that spiritual and religious cognition are apparently unique to humans, represent an evolutionary novelty, exhibit no apparent adaptive significance in their earliest and simplest forms, and are evidently not instantiated within specific macroscopic brain areas or networks (Ferguson et al., 2022; McNamara & Grafman, 2024). Given these conditions, novel phenotypes must arise by novel or unselected evolutionary mechanisms, not driven by the typical processes of selection for adaptive variants. By the hypothesis proposed and evaluated here, religiosity and spirituality derive primarily from three inter-related mechanisms.

The first such mechanism is adaptive, to a point. Humans are periodically subject to forms of stress or challenge that have selected for means of coping with them. One such means involves challenge-induced activation of the HT2A receptor, that results in a cascade of cognitive effects leading to enhanced associative learning and insight, among a suite of additional adaptive shifts in neural functions (Brouwer & Carhart-Harris 2021; Brouwer et al., 2024). Extreme ecological and social stresses can also lead, however, to *hyper*-activation of the HT2A receptor (defined here in terms of emergent sequelae that are not adaptive in terms of stress coping), that results in novel, extreme-of-adaptation cognitive-affective states that serendipitously engender spiritual and religious mental phenotypes. The cause here is selection for adaptive responses to stressors, where responses sometimes overshoot their neurocognitive goals.

A second such mechanism is internal and pathological, deriving from large mental perturbations that generate maladaptive neuropsychological states. Such internal effects are postulated here to derive mainly from psychosis - reality distortion involving altered perception, hallucinations and delusions - as well as some cases of temporal lobe epilepsy (e.g., Elliott et al., 2009). Psychosis apparently represents a qualitative extreme of human personality-related, psychological states related to the salience (meaning) (Kapur 2003; Corlett & Fraser 2025) and imagination (Nettle, 2001; Crespi et al., 2016) that have been instrumental in making humans what they are in terms of creative cognition (Looijestjn et al., 2015; Acar et al., 2018). It also centrally involves hyperactivation of HT2A receptors, especially in conjunction with alterations to dopaminergic and glutamatergic systems. The cause here is variation in personality and psychology, due proximately to variation in genes and environments.

A third mechanism is effects on the human brain from external, qualitatively novel environmental inputs. In the context of religiosity and spiritual cognition, such effects derive from fungus and plant-derived biochemicals (so-called psychedelics) that happen to hyperactivate human HT2A receptors because they resemble serotonin in their chemical structure (Cameron et al., 2023). The cognitive-affective effects are thus evolutionarily new. The cause here is serendipity.

These mechanisms of spiritual and religious experience recall the 'three visions' theory of Saint Augustine, who considered a trio of sources for visionary events: the natural and physical world, the human imagination, and God. Our present-day, science-based trinity of causes is clearly inter-related in being underlain by a single core neurophysiological structure. Thus, supraphysiological activation of HT2A can result from (1) overshoot of natural, adaptive processes of external, stress-induced learning, (2) psychotic-affective extremes of internal, psychological-personality variation, that are similarly exacerbated by stressors, or (3) the external, artificial mechanism of psychedelics. In this context, and as described in more detail below, religious and spiritual perception, cognition and affect thus emerge as extreme manifestations of the brain-wide suite of changes that drive responses to actual or induced challenges, all in the contexts of the evolution of human sociality, psychological variation, imagination and culture.

Neither the serendipitous external mechanisms of psychedelics, the maladaptive internal mechanisms of psychosis, nor the overlapping but typically-adaptive mechanisms of socioecological or physiological stress, work, of course, on a mental *tabula rasa*. In all three situations, the effects of the novelty channel through neural circuity that evolved in other selective contexts, and that serves especially in the interpretation of perceptual-cognitive-affective experiences driven by HT2A hyperactivation. A primary such framework, fundamental among animals but developed especially-highly in humans, is using the mind to draw inferences and meaning from the world via the neural machinery of Bayesian predictive coding. By this central mechanism of cognitive function, internal, *a priori* hypotheses (as models or predictions) about the world are continually compared to perceptual inputs, with discrepancies between the two ('prediction errors') being resolved through adjustments to beliefs, yielding improved *a posteriori* models of perceived 'reality' (reviews in Smith et al., 2021; Pezzulo et al., 2022). Predictive coding models are of key importance here because mental models about the world instantiate human beliefs, feelings, values, goals, and meaning, all of which are massively modified in spiritual and religious thought. They do so in the specific human context of highly developed social cognition, which involves theory of mind, inference of mental states and intentions of others, social imagination and scenario-building, human social relationships involving important ancestors and leaders, and neurally-based conceptualizations of the self and its existence. Spirituality and religion thus presumably must be built using the scaffold of predictive coding, and the blocks of mental modules and circuits subserving human sociality, imagination, and learning.

The key to the God-receptor hypothesis is that psychedelic biochemicals, psychosis, and overactivated stress responses all show clear evidence of involving high activation of the serotonin receptor HT2A, thus generating novel cognitive-affective states that result in thoughts and feelings that overlap broadly with those typical of spiritual and religious cognition (Barrett & Griffiths, 2018; McNamara, 2022). Most importantly, HT2A also shows evidence of mediating neural mechanisms of predictive coding in such a way that its hyperactivation generates spiritual-religious experiences centred around surprise, awe, consciousness, self, and meaning, thus connecting foundational neural processes with the intersecting phenomenologies of psychedelic experience, psychosis, stress, and spirituality and religion (van Elk & Aleman, 2017; Brouwer & Carhart-Harris, 2021).

In full, the God-receptor hypothesis posits several broad stages in the origins of spirituality and religiosity:

(1) Evolutionarily-novel mental experiences, involving visions and profound perceived insights, caused by some combination of entheogenic, psychotic-affective spectrum, and stress-related effects;

(2) Imaginative interpretation of such visions and insights as indicative of supernatural gods and spirits, that are culturally instantiated into stories, narrative arcs, and institutions that serve to explain the otherwise-inexplicable vagaries of past, current and expected-future life and events, and that motivate forms of within-group unity deriving from shared, powerful beliefs and entities, including actual or perceived ancestors;

(3) Fitness-related benefits from belief in such stories, entities, and participation in such institutions, due primarily to enhanced cooperation among individuals within families and groups, as well as loss of benefits or punishment for non-cooperators.

Health and fitness benefits of spirituality and religiosity have been described in detail elsewhere (e.g., Borges et al., 2021; Lynch et al., 2022). We focus predominantly on the first and second stages, especially as regards the neural bases of spiritual and religious experiences and their interpretations. The God receptor hypothesis makes extraordinary claims; what is the evidence?

The God receptor

HT2A is a G-protein coupled receptor that is widely expressed in the central nervous system (Guiard & Giovanni, 2018). Its activation mediates the effects of psychedelics drugs, which serve as agonists of the receptor due to the structural similarities of serotonin to LSD, psilocin, and their chemical relatives (Cameron et al., 2023). By contrast, antagonism of HT2A underlies many of the effects of most atypical antipsychotic drugs, in addition to the effects of these drugs in downregulating hyperdopaminergic states via effects on DRD2 (Kantrowitz, 2020).

How might HT2A agonism trigger the profound cognitive-affective effects of psychedelics? A suite of convergent evidence supports the hypothesis that HT2A activation mediates the neural instantiation of prediction errors, the mismatches of predicted with actual sensory inputs used by the brain to continually update internal, top-down models for extracting meaning from interactions with the world (Smith et al., 2021; De Filippo & Schmitz, 2024). Such mismatches can be conceptualized, in typical cognition, as *surprise*, that specifically compels updating of information in the brain, especially for beliefs. By acting as HT2A agonists, psychedelics may thus generate 'synthetic' and enhanced surprise, with increased prediction errors that mediate increased top-down updating of beliefs (De Filippo & Schmitz 2024). In turn, hyper-updating of top-down predictions guides and shapes the processing of bottom-up inputs, leading to the novel landscape of sensations and feelings that characterize psychedelic experience. This model represents an extension and update of the REBUS (Relaxed Beliefs Under Psychedelics) model for predictive coding in psychedelic experience (Carhart-Harris & Friston, 2019), and it was developed to alleviate some of its shortcomings and better account for the subjective experiences involved.

The synthetic surprise model for understanding the neural and psychological effects of HT2A agonism, in relation to spiritual, religious and mystical experiences, and models based on relaxed belief effects from psychedelics more generally, are underpinned by several lines of information:

(1) Psychedelics show evidence of activating HTR2A receptors on SST interneurons, providing an apparent neural mechanism for enhanced prediction error effects (De Fillipo et al., 2021);

(2) Serotoninergic neurotransmission encodes novelty in the brain, and activation of HT2A receptors underlies reversal learning, which is driven by prediction error signalling (Kanen et al., 2021);

(3) The physiological effects of surprise include enlarged pupil diameter, which is driven by serotoninergic neurotransmission (Cazettes et al., 2021), and which characterizes effects from psychedelics (Aday et al., 2021) as well as problem-solving via sudden insight (Salvi et al., 2020);

(4) Psychedelics, and surprise, exert similar effects on cortical alpha-wave oscillations (De Filippo & Schmidt, 2024), which have also been implicated in mechanisms of predictive coding (Alamia & Van Rullen 2019);

(5) N170 event-related potentials have been shown to reflect perceptual surprise (Robinson et al., 2020), and activation of HT2A receptors underpins the effects of psilocybin on alpha-wave oscillations and N170 potentials, in the context of hallucinations (Kometer et al., 2013);

(6) Psychedelic experience is uniquely characterized by high levels of 'imaginative suggestibility', the ability to become immersed in novel, externally-generated scenarios, which implicates enhanced openness to new top-down models, and which may help to explain its therapeutic effects (Carhart-Harris et al., 2015);

(7) Greatly-increased levels of surprise can accurately and usefully be described as *awe*, an emotion that is fundamental to the effects of psychedelics (Hendricks, 2018; De Filippo & Schmitz 2024). Awe, in turn, can be designated as a feeling derived from vastness, power, and mystery, that challenges existing systems of belief, and requires foundational adjustments to mental ideas and structures in order to assimilate the meaning of the new experience (Keltner & Haidt, 2003; Ihm et al., 2019).

The contexts of awe in non-psychedelic experience centrally include spirituality and religion; indeed, Ihm et al. (2019) suggest that "precursors to modern religions were conceived and developed during awe-like states in our hominid ancestors". These considerations provide notable links of the synthetic surprise model with the trappings of spirituality, mysticism and religion, from the magnificence of beauty in the natural world, to the vastness of cathedrals and the grandeur of religious art and music, and to emotional subjugation to fearsome highly-powerful individuals and beings - all in the context of novel systems of generation of meaning from the otherwise-inscrutable vagaries and apparent meaninglessness of existence (Keltner & Haidt 2003; Haidt, 2012; Vaillant, 2013; Ihm et al., 2019). Increases in the accessibility of different models of the world, that derive from synthetic surprise, may also help to explain the overlaps of psychedelic with spiritual experiences in terms of enhanced openness, discovery of novel connections and perspectives, feelings of insight and revelation, ego dissolution via cognition less bounded by prior entrenched models of the self, and beliefs that 'everything is connected', with additional links to 'insight experiences' among individuals experiencing the schizophrenia prodrome or psychosis itself (Stoliker et al., 2022; Harding et al., 2024).

These considerations suggest central roles of the HT2A receptor in the surprise component of predictive coding of brain function, with mechanistic linkages to spirituality, religion, and psychosis that derive from receptor agonism, and from the role of serotonin in encoding the value of surprising rewards (Harkin Grossman 2025). The primary empirical and theoretical shortcomings of this hypothesis derive from inadequate understanding of how prediction-error signalling and belief instantiation actually work in relevant areas of the brain, especially with regard to the roles of prediction-error precision (as opposed to magnitude) in cognitive states related to HT2A hyperactivation, since precision is believed to influence the levels of confidence ascribed to bottom-up and top-down information. Moreover, religious beliefs, and delusions in psychosis, commonly involve unusually-inflexible top-down belief systems - the antithesis of relaxed beliefs and cognitive flexibility. Apparently, then, there are neural mechanisms that hyper-stabilize newfound, especially-strong beliefs with synthetic, entheogenic or delusional and psychopathological origins (Zeifman et al., 2025), perhaps via temporary down-regulation of HT2A

(Brouwer and Carhart-Harris, 2021) or through dopaminergic effects on delusion formation and stability (Huber Lepping 2022). Belief and meaning systems thus follow an arc from uncertain, to especially-flexible, to remarkably fixed, for reasons that still require explanation in terms of neurophysiological mechanism and cause.

HT2A activation effects in the religious Bayesian brain

In 1748, the philosopher David Hume made an argument, based on probabilities, for the unlikelihood of miracles such as personal observation of the resurrection of Jesus. The Reverend Thomas Bayes proved that Hume's logic was incorrect, and in doing so laid the foundation for conception of the brain as a Bayesian engine for predictive inference (Friston, 2003). Bayes believed that religious miracles, visions and epiphanies were objectively true, but we explore here the argument that they can instead arise from supraphysiological activation of the HT2A receptor in areas of the brain with functions accidentally relevant to religious belief and experience.

How, then, do the HT2A receptor and predictive coding work in different religion-related neural regions and networks, in typical, adaptive cognition and, also in hyper-activation? Many brain regions are involved, but four appear to be especially important.

First, as described above, HT2A receptor activation mediates surprise, considered as the difference between expected and experienced 'actual' events; this function is mediated in large part by the anterior cingulate cortex, part of the salience (meaning) network, although a suite of other regions is involved (e.g., Mousavi et al., 2022). The hyper-activated extreme of surprise, awe, represents a central feature of religious experience, that connects directly with hyper-salient meaning. The ACC also appears to be involved in the acquisition and maintenance of religious beliefs (van Elk & Aleman, 2017), as expected if the hyper-salience of awe inspired these effects.

Second, abundant HT2A receptors in the visual system subserve the balanced top-down, bottom-up dynamics of visual stimuli, whereby the brain generates and maintains predictive models regarding this form of sensory input through mental imagery (Dijkstra et al., 2019). Given the close anatomical and activational overlaps of the visual-perception system with the mental-imagination system (e.g., Dentico et al. 2014; Ganis et al. 2004), hyperactivation of HT2A in these brain regions appears to increase the influence of top-down influences in such a way that imagination can prevail, resulting in visual hallucinations (Kometer et al., 2013), sometimes in the context of religious visions depending upon cultural context, setting, and expectations.

Third, different dimensions of the self are instantiated in several brain regions with high densities of HT2A receptors and links to religiosity, the default mode network (the narrative self), the insula (the interoceptive self), and the claustrum (apparently, the integrative, conscious self) (Craig 2019; Yeshurun et al., 2021; Mantas et al., 2024; Tisserand et al., 2023; Anderson et al., 2024). These brain areas mediate the self in the context of self-other boundaries, which subserve emotional empathy and mentalistic perspective-taking, with boundaries being broader and more permeable among individuals with more psychotic-affective patterns of cognition (Minas et al. 1994; Bakhshaie et al. 2011; Crespi & Dinsdale, 2019; Lee et al., 2021). The DMN is also involved in inward attention, and the dominance of self-narrative over attention to external tasks (Simony et al., 2016), consistent with a shift toward imposition of top-down constraints over sensory input. Hyper-activation of HT2A receptors in these brain areas appears responsible for the forms of ego-dissolution that characterizes psychedelic use, psychosis, and religious and mystical experiences, such that it apparently involves hyper-extension of self-other and self-nonself boundaries to the point of fusion and unity, via some combination of top-down and bottom-up effects on neural self-system and embodiment functions (e.g., Vollenweider et al. 1998; Kometer et al., 2012; Quednow et al., 2012; Stoliker et al., 2022). Mechanistically, such ego-dissolution and loss of self-nonself boundaries are associated with desynchronization of neural oscillations with relevant brain regions (Muthukumaraswamy et. al., 2013) which are associated with connectivity widespread connectivity changes (Carhart-Harris et al., 2016). Neural oscillations and their coordination among brain areas, particularly in the alpha band where HT2A desynchronization effects are most pronounced (Carhart-Harris et al., 2016) are understood to regulate information inhibition and selection together with information flow among regions (Palva & Palva 2007), consistent with the view that these psychedelic compounds may be disrupting normal predictive coding across brain networks. Consistent with this view LSD was found to cause a decrease in directed connectivity in MEG, indicating a breakdown of typical inter-regional communication (Barnett et al., 2020). Importantly, combined EEG-PET investigation of HT2A psychedelics show that entropy reductions, a measure of complexity or uncertainly closely linked to neural oscillations and connectivity, were concentrated in areas with high HT2A receptor density (Singleton et al., 2025). HT2A drugs are also associate with decreases in connectivity involving the default and salience networks (Lebedev et al., 2015). Showing some convergence with HT2A-mediated psychedelic effects, yogic practice has also been shown to be associated with such broadband desynchronization of EEG rhythms (Niazi et al., 2022), and the perceived efficacy of religious ritual is likewise associated with reductions in alpha and beta band power (Cho et al., 2018).

Finally, spirituality has recently been associated with the periaqueductal gray (PAG) (Ferguson & Grafman, 2024), a brain region rich in HT2A receptors that subserves periconsciousness (non-reflexive, automatic neural processes that underlie complex conscious experience), involving aspects of basic emotion and experience such as pain modulation, anxiety, and attachment (the psychological basis of social bonding and love)(Nelson & Panksepp, 1998), with additional links to Von Economo neurons that subserve complex sociality and self-awareness (Saleh et al. 2017). Increased HT2A activation shows evidence of reducing pain and anxiety through its downstream effects on release of enkephalins, endorphins, serotonin, dopamine and oxytocin (Nelson & Panksepp, 1998; Silva & McNaughton, 2019; McPherson & Ingram, 2022). Given that production of such endogenous agents not only reduces pain, but can also, at higher levels, induce pleasure, hyperactivation of HT2A receptors in the PAG may, in part, be responsible for the hedonic, ecstatic, and love-imbued (as well as antidepressant more generally) nature of many mystical and religious experiences (Sierra et al., 2022; Salinsky et al., 2023). This hypothesis is consistent with the anti-nociceptive effects, for example, of LSD, and with the anti-depressive and anti-nociception therapeutic effects of some psychedelics (Castellanos et al., 2020; Ramaekers et al., 2021; Ko et al., 2023; Kooijman et al., 2023). The PAG is also known to play key roles in the encoding of prediction errors regarding aversive stimuli (Grahl et al., 2018), and descending modulation of pain especially through stimulating release of endorphins and enkephalins.

The four brain regions evaluated here in the context of the God receptor hypothesis provide only preliminary evidence regarding the roles of HT2A receptor activation, and hyperactivation, in religious, spiritual and mystical experiences (Figure 1), but they suggest an empirical way forward to better understand their neural bases, with clear predictions. These predictions are motivated by the observation that HT2A agonist psychedelic drugs can reliably produce such experiences, but, given that high activation of HT2A can and does also result from natural, endogenous, and socioecological causes (s discussed in more detail below), psychedelics are by no means implicated as necessary or sufficient in the origins of spiritual and religious thought and experience.

What is important for empirical work, under this hypothesis, is the prediction that the brain areas and systems linked with spirituality and religion should harbor notable densities of HT2A receptors that have region-specific normal and adaptive functions that, when hyper-activated, regularly produce elements of spirituality and religion experiences, that are explicable in terms of amplification (or other hyper-activational effects) of predictive coding mechanisms. This prediction provides for specific tests of the idea that HT2A activation represents a 'master key' to the doors of religious and spiritual perception and thought. What is not explicable by this framework is why this should all be so, in terms of the adaptive significance of HT2A receptor functions. What, then, could it be about these functions that, when hyperactivated, result in such a remarkable set of religious and spiritual cognitive-affective phenotypes?

The evolved, adaptive significance of HT2A activation

The life of any organisms can be represented as a series of opportunities and threats. To the extent that these potentially affect fitness, they can be considered as stressors or challenges. In turn, organisms have evolved means of dealing with such stresses, many of which are cognitive, affective, and behavioral. The HT2A receptor in particular has been shown to be activated and upregulated in response to stressors, be they social, ecological, or physiological (Leonard, 2005; Murnane, 2019). Brouwer and Carhart-Harris (2021) provide a comprehensive review of evidence linking HT2A to acute or chronic stresses, and suggest an adaptive reason for these responses: that HT2A activation causes a suite of neural changes that facilitate increased neural plasticity and enhanced associative learning (e.g., Kanen et al., 2023; Vargas et al., 2023), thereby generating 'pivotal' mental states that are better-suited for alleviating or overcoming the challenge, especially via active coping (Brouwer & Carhart-Harris, 2021). The clearest and simplest evidence for this hypothesis comes from experimental studies whereby administration of HT2A agonists notably facilitate associative learning, for example in rabbits (Harvey et al. 1983) and humans (Hensman et al., 1991) given LSD. More generally, activation of HT2A receptors in response to stresses can be seen as an adaptive system for learning through associative-imaginative insight (Brouwer & Carhart-Harris 2021; Tulver et al., 2023; McGovern et al., 2024) in situations where it is especially important, for fitness, to do so.

Under typical conditions, enhanced learning in response to HT2A activation is expected to involve surprise, insight, recognition of salience (meaning) in some association, process or pattern, and the emergence of novel beliefs about the world that help in dealing with the relevant task. Successfully overcoming a stress through these mechanisms should also result in pleasure, the body's reward for a job done well. Learning should be facilitated by increased mental exploration of possible responses to challenges (e.g., divergent thinking, strong imagination, and mental imagery), and by thinking that reaches outside of the self to better encompass the dimensions of the external social or ecological threats. Stresses also commonly engender conditional suppression of pain, such as hungry mice feeling less pain (Alhadeff et al., 2018), or humans suppressing pain during fight-flight events (Melzack, 2014), as enabled via descending anti-nociceptive pathways. The full arc from initial stress or challenge to resolution involves a well-orchestrated suite of changes, with learning insight and HT2A activation, at the core (Figure 2).

Relatively-extreme stresses are expected to commonly involve increased, hyper-activation of HT2A receptors, that can lead to cognitive-affective extremes that should include awe, novel insights and beliefs, hyper-salience (meaning), hallucinations or visions, ego-dissolution, and euphoria. To the extent that hallucinations or visions require logical 'explanation' by the brain, to maintain a coherent reality, they should also engender delusions: imagined, self-generated narratives that can make sense, in cultural perspectives, of the extraordinary and otherwise-inexplicable experience (Graseman et al., 2009; Mishara & Corlett, 2009). Delusions of the supernatural, and all-powerful 'gods', would be most effective at explaining to ones-self, and to others, otherwise ineffable and awe-inspiring experiences, and these can then be enmeshed in culture-specific narratives.

Of course, all of these hypothesized manifestation of HT2A hyperactivation are hallmarks of religious, spiritual, and mystical experience, whether they derive from psychedelics, forms of psychosis, 'spirit quests' that involve fasting, social isolation and other self-induced stress (e.g., forty days in wilderness), or related causes (Friesen, 2013; Taves, 2020; Demmrich et al., 2023). In principle, this hypothesis can link HT2A activation, and its hyper-activation due to many causes, to diverse religious, spiritual and mystical experiences. Such experiences thus become emergent properties of an adaptive evolved system that centrally involves perhaps the most human of cognitive-affective traits: imagination, narrative, mentalistic explanation, and social bonding. Hyper-development of these properties, in turn, motivates genesis of the major features of gods: awesomeness, omnipresence, omnipotence, provision of meaning in the world, and love.

A fourth arena for phenomenological overlap between psychedelic, psychotic, and stress-related events is dreaming, that often similarly involves vivid visions, bizarre narrative content, mystical experiences, out of body experiences, and high levels of anxiety and fear (Carhart-Harris, 2007; Carhart Harris & Friston, 2010; Kraehenmann, 2017; Jalal, 2018). Dreaming has been considered by some authors as a possible source for human spiritual and religious thought, due to the magical nature of some dream content, the presence in dreams of 'spirits' who include known but deceased individuals, and, most generally, the anthropological links of dreams with aspects of religiosity in small-scale societies (Tylor, 1871; Nordin & Bjälkebring, 2021). Is dreaming mediated by HT2A receptor effects, and does it have adaptive significance in this context? Activation of this receptor in the medial temporal lobe has been linked with synaptic plasticity and memory consolidation (Zhang & Stackman, 2015), and with bursts of medial temporal lobe activity that characterizes dreaming in the context of ponto-geniculo-occipital waves that are instrumental in the visual, hallucinatory aspects of dreams (Carhart-Harris 2007; Gao et al., 2023). These findings, diverse links of HT2A with sleep and dreaming (Luppi et al., 2017; Narikiyo et al., 2020; Renouard et al., 2015; Timofeev & Chauvette, 2020; Monti et al., 2018), and studies showing that administration of LSD to humans before or during sleep increases dreaming (see Carhart Harris and Friston 2010), suggest that dream states are mediated by HT2A activation, although the neural mechanisms remain unclear. The adaptive significance of dreaming may likewise be associated with medial temporal lobe activation, in that it appears from observational and experimental studies to involve enhancements to creative problem solving abilities that derive, in part, from processing of memory content in contexts independent of conscious control (e.g., Schredl & Erlacher, 2007; Barrett, 2017; Klepel et al., 2019). If this hypothesis is correct, then the adaptive significance of HT2A activation in conscious, stress-related cognition will be similar to that in dream states, in that they both provide fitness benefits from plasticity-related, imaginative thought directed at fitness-salient challenges. As for the effects of psychedelics, psychosis, and HT2A hyperactivation due to stress, religious and spiritual thought then arise from attempts to provide coherent narrative, cultural context and 'explanation' for the extraordinary aspects of the otherwise incomprehensible experience.

HT2A, psychedelics and the origins of human spirituality and religion

The God-receptor hypothesis posits that the *de novo* origins of spiritualistic bodies of thought, and religions, should involve some combination of entheogenic, adaptive stress-related, and psychological psychotic-affective influences. The idea of entheogenic (psychoactive drug mediated) origins for human spirituality and religions has been evidenced by a large body of anthropological and historical studies that draw links between (1) use of various naturally-occurring psychedelic substances, (2) spiritual and religious experiences that involve visions, ego-dissolution, and interactions with godlike entities, and (3) scriptures and histories of large-scale religions, and current practices in small-scale groups (e.g., Rush, 2013; Brown & Lupu, 2014; Hoffman, 2019; Nemu, 2019; Samorini, 2019; Winkelman, 2019; Spiers et al., 2024). As regards neurological and psychological considerations, perhaps the most telling evidence for entheogenic origins of religions is the remarkable similarities of spiritual and religious insight or revelation experiences with the more-general cognitive and affective experiences caused by psychedelic drugs (Buckley, 1981; Carhart-Harris et al., 2013; Lebedev et al., 2015; Griffiths et al., 2019; Friesen, 2022; Brouwer et al., 2024).

Despite such compelling cross-cultural and historical evidence, and the apparent lack of comprehensive alternative scientific explanations for convergent visionary and hallucinatory religious inspiration experiences across thousands of years and diverse cultures, the entheogenic-origins hypothesis for human spirituality and religions remains challenging to evaluate in a robust scientific manner. Such limitations involve several factors:

(1) In even the most otherwise-persuasive cases, the specific psychoactive compounds and their sources usually remain unclear, apparently due in part to the highly secretive treatment of 'sacred' agents on one hand, and the usual later suppression of such agents by self-interested parties in established religious institutions that are sustained through their administrations;

(2) Many cases are known of dramatic spiritual and religious experiences, even among founders of particular religious groups or subgroups, that clearly do not involve use of entheogens (though they may involve stress-induced visions). Examples include the visions of Francis of Assisi and Ignatius Loyola, each of which led to successful religious movements.

(3) Entheogenic theories for the geneses of human religions beg the question of the actual origins of the concept of gods or God in human societies, which would appear to represent more an explanation for psychedelic experiences than a necessary or likely sequel to visions, perceived insights, and hallucinations. Indeed, at the actual origin of psychoactive drugs use in humans, there would presumably be no established cultural context (or a god-being or equivalent) within which to interpret the experiences, other than long-dead, memorable, powerful human ancestors, who may indeed have represented the first gods (Crespi, 2021). As such, the question of the psychological and neural context for the initial psychological creation of gods and spirits remains unresolved.

(4) In any given human group, only a small number or proportion individuals would likely ingest, or have ingested, entheogenic substances in the context of spirituality and religion. Some such individuals would have had large influences in their society and beyond, as prophets, saints, shamans or seers with

personal experience of the supernatural, but the growth and maintenance of religions would still depend upon the psycho-cultural assimilation of others (O'Grady, 2012).

Taken together, these considerations suggest that, while entheogens may have been instrumental in the origins and early evolution of human spirituality and religion, in generating a direct route to supernatural experiences through HR2A hyperactivation, they are clearly only one of multiple contributory neural and psychological factors. What other causes are involved?

HT2A and psychosis

Psychedelic drugs represent external and evolutionarily-novel causes of spiritual and religious experiences. Such experiences can also be mediated by the two forms of internal causes that are not evolutionarily new: high levels of stress, and psychosis. As described above, stress can apparently induce such experiences through hyper-expression of neurophysiological mechanisms that underly insight through associative learning. By contrast, psychosis represents reality distortion, usually hallucinations and delusions, as seen most prominently in people with schizophrenia or bipolar disorder with mania. Whereas the diagnoses of schizophrenia and bipolar disorder are dichotomous, their psychological features and personality-related underpinnings grade into typical cognition (e.g., Kwapil & Barrantes-Vidal, 2015; Yamada et al., 2020). Psychosis-related experiences are thus by no means uncommon, and many are enjoyable, such as hypomania (mild forms of mania that involve elation, high energy levels), positive delusions about one's abilities or self-importance (a mild form of delusions of grandeur), or auditory hallucinations that are positively-valanced, such as kind hallucinated words from a beloved, deceased aunt or uncle (e.g., Corentin et al., 2023). Typically, forms of psychosis are brought to the attention of psychiatrists only when they are disturbing to ones-self or to others, as in schizophrenia with delusions of persecution.

A striking proportion, around 20-60% depending upon the population and study, of hallucinations and delusions are religious or spiritual in nature (Grover et al., 2014). Most of these experiences and beliefs are positive, raising the obvious questions of whether a line can be drawn, and where to draw it, between religiosity or spirituality and psychosis, since both involve ideation that is hallucinatory or delusional in its inability to be verified in any objective way. Here, the current criteria are generally twofold: if the delusion is shared by members of some culturally-identified group, and if it is emotionally agreeable, it is deemed mentally 'healthy' (Pierre, 2001). These criteria, however, do not apply to nonwesternized and ancestral cultures, for whom 'natural' and 'supernatural' need not be distinguished from one another, although members of such cultures presumably vary in how much they attribute events in the world to divine versus observable causes. More broadly, the high rates of religious and spiritual content in psychoses, and the positive associations of schizotypy with religiosity and spirituality, contrast sharply with the low levels of religiosity and spirituality among individuals on the autism spectrum (Crespi et al., 2019), which may, in turn, be linked with reduced activation of the HT2A receptor in autism as evidenced by imaging studies that show reduced serotonin binding to this receptor (Muller et al., 2016). As such, questionnaire-based and imaging-based studies of religiosity and spirituality provide support for the hypothesis that autism and schizophrenia represent diametric (opposite) disorders (Crespi and Badcock, 2008).

Are the broad overlaps of psychosis with religiosity and spirituality underlain by shared effects of HT2A receptor activation? Diverse, independent lines of evidence link psychoses, as expressed in schizophrenia or bipolar disorder, with this receptor, all in the broader context of psychosis being mediated by shifts in integrated serotoninergic-glutamatergic-dopaminergic activity (e.g., Stahl, 2018):

First, most antipsychotic drugs exert antagonistic effects on the HT2A receptor (e.g., Casey et al., 2022), and some psychosis-inducing agents, notably ketamine and MK801, act as agonists (e.g., Lin et al., 2018; Nasrallah et al., 2019). By contrast, drugs that block the NMDA receptor, such as ketamine and phencyclidine, induce psychosis as well as activating HT2A (Kapur & Seeman, 2002).

Second, HT2A stimulation increases midbrain dopaminergic activity, which exacerbates psychotic (as well as negative) symptoms of schizophrenia. HT2A also exhibits increased functional activity among individuals with schizophrenia compared to controls (Diez-Alarcia et al., 2021). Increased midbrain dopamine also mediates learning via enhanced prediction errors (Gibbs et al., 2007), such that the hyper-salience of psychosis can also engender forms of delusional 'hyper-learning' to make sense and meaning of the experience (Graseman et al., 2009), thus linking conceptually to learning under stress in typical, adaptive conditions (Brouwer & Carhart-Harris, 2021).

Third, the schizophrenia 'prodrome', a period of some months or years before frank psychosis, is characterized by a suite of psychological changes that include heightened sensitivity to stressors and enhanced attribution of significance and meaning to 'ordinary' or 'irrelevant' stimuli (e.g., Kim, 2021; Buckley, 1981; Roiser et al., 2013). Such exaggerated perception of salience or meaning, which is often imbued with mystery, may be followed by moments of sudden, deep insight as psychosis develops, such that the trajectories of psychotic experience can closely parallel those of psychedelics, in ways that implicate HT2A effects in both. More broadly, schizophrenia itself has been usefully described as 'salience dysregulation syndrome' (van Os, 2009), whereby assignment of meaning or importance to stimuli is altered, and frequently exaggerated, in cognitive or affective (mood-related) ways. As such, psychosis involves the same sort of anxiogenic, aversive initial stage as do psychedelics and genetic stressors (Figure 3).

Fourth, as noted above, individuals with schizophrenia or high in positive schizotypy exhibit reductions in the sharpness of self-other boundaries compared to controls, such that their sense of self tends to merge more readily and broadly into the external worlds of people and non-human features of the environment (Bleuler, 1950; Lee et al., 2021; Green & Jimenez, 2022). Such lessening of self-nonself borders expresses itself in various ways, from embodiment as indexed by the rubber hand illusion (Crespi & Dinsdale, 2019), to increases in empathy as evidenced by genetic correlations (Warrier et al., 2018), and to broader reduction in ego boundaries, and loss of sense of ownership of thoughts and actions, as originally described by Bleuler over 100 years ago. These phenomena on the psychotic spectrum closely resemble losses of ego boundaries, and more-general losses of the unitary, perceived, agentic self, under psychedelics, which can be attributed to agonism of HT2A.

A key limitation on comparisons of spiritual and religious experiences under psychedelics with idiopathic psychotic-affective disorders such as schizophrenia is that the same data-collection or experimental paradigms have seldom been used for both sets of conditions. However, the broad phenomenological similarities between psychotic, psychedelic, and religious-spiritual experience, and the links of each to HT2A activation, implicate this receptor in the perception of meaning in the world, and Gods as their imaginative instantiation (Buckley, 1981; Carhart-Harris et al., 2013; Lebedev et al., 2015; Griffiths et al., 2019; Friesen, 2022; Brouwer et al., 2024). A further commonality appears to be psychosocial and other forms of stress: it represents a crucial environmental trigger for the development of psychosis (van Winkel et al., 2008), and drives HT2A activation itself in the context of adaptation-related challenges more generally as described above; moreover, the early stages of psychedelic experience commonly involve acute stress responses and anxiety (Brouwer & Carhart-Harris, 2021; Brouwer et al., 2024)(Figure 3). Determining the extent to which these three contexts overlap and recapitulate one another, mediated by trajectories of HT2A-activation in different brain regions with downstream effects on cognition and mood, should represent one of the major goals for the cognitive neuroscience of religion and spirituality.

The similarities described above are striking. What, then, of the differences in experience, and its causes, between psychotic-affective disorders, spirituality and religion, and psychedelics? One of the main distinctions, that is crucial as regards mental health and well-being, is valence, with spirituality, religion, psychedelics, mania, and megalomania typically manifesting as positive, but other psychotic symptoms such as hostile hallucinatory voices, paranoia, other intense aversive delusions, and severe depression as extremely negative. Positive emotion in mania appears to be mediated by high dopamine that enhances pleasure-seeking and reward, with dopaminergic system activation also leading, in some circumstances, to release of oxytocin (mediating feelings of bonding and love)(Carter, 2022) and endorphins (mediating feelings of euphoria and overall well-being)(Corder et al., 2018). Aversive psychotic and depressive states, as seen in schizophrenia and schizoaffective disorder, may be related to deleterious exaggerations of social defeat effects (Selten et al., 2013), high social threat sensitivity (Reininghaus et al., 2016), and dysregulated negative feedbacks in mood regulation, but the neurophysiological bases of these specific phenotypes remain unclear. The clear therapeutic benefits of psychedelics in the specific contexts of depression and PTSD may, in this context, stem from their ability to reorganize the structure and valence of meaning-related cognition and affect in relevant brain systems, apparently through HT2A-mediated recapitulation of evolved mechanisms for successful problem-solving through insight.

DISCUSSION

In this article we have proposed and evaluated the 'God-receptor' hypothesis for the neural bases of human spirituality and religion. The hypothesis was motivated and evaluated through integration of information from: (1) studies of psychedelic drug effects in the brain, (2) evidence regarding the entheogenic origins and forms of human spirituality and religions; (3) analyses of how psychoactive drugs and HT2A hyperactivation affect predictive coding of cognition and affect; (4) studies of what specific brain regions are most involved in spiritual and religious thought and experience, and the adaptive and hyper-activational effects of HT2A stimulation and predictive coding systems in these areas; and (5) research on how the causes and effects of psychosis and its subclinical forms overlap with spiritual-religious cognition, in the specific context of HT2A typical and hyper-active functions.

By the God-receptor model, the concept of God is most-parsimoniously represented, mechanistically, by the serendipitous cognitive-affective results of supraphysiological activation of the HT2A receptor. Such activation, which can be due to either external, entheogenic or internal, psychophysiological causes, results in a suite of HT2A-mediated alterations to predictive-coding systems that orchestrate central brain functions, most notably: (a) belief in profound, novel insights, driven by lowered thresholds for inferences of meaning, (b) awe, the extreme of prediction-error surprise, that enhances the strength of these beliefs; and (c) ego-dissolution and feelings of oneness with the world as a manifestation of God, apparently due to relaxation of priors regarding self-instantiation and self-other boundaries at different hierarchical levels in the brain including the periaqueductal gray, default mode network, and claustrum. These feelings of insight, awe, and oneness are interpreted, via instantiations of culture-specific imagination, in terms of supernatural and preternatural presences, powers, minds, agents, events, and narrative arcs, that take on unique roles in human cognitive-affective and cultural landscapes through the provision of meaning, purpose, and explanation for existence. As such, hyper-stimulation of HT2A can elucidate the origins of god-perception and god-experiences, which come to form the core inspirations and shared delusionary beliefs upon which a supernatural-based religion is initially built.

Ultimately, the God-receptor model is based on the physiological and psychological connections between the evolved, adaptive, usual functions of the HT2A receptor and the effects of receptor hyperactivation, that are supraphysiological and novel but mechanistically and experientially connected to normal function. The adaptive functions of HT2A (and its interacting ligand-receptor systems such as those involving DRD2 and NMDA) in the typically-functioning brain depend, in turn, on the specific brain region, network, or operation concerned, but they can, at least in some instances, be linked with supraphysiological effects, including imagination with hallucination, surprise with awe, dissociation with universal oneness, and momentary pleasure with ecstasy and euphoria.

Given that the origins of religiosity and spirituality are indeed mediated by HT2A hyperactivation, the key question becomes just what factors contribute to the hyperactivation process, and how they do so. The first factor is intrinsic susceptibility to high levels of activation, which results from genetic, personality-related, psychiatric and neurological influences related to psychotic-affective spectrum phenotypes and their subclinical manifestations. Intrinsic susceptibility would thus be enhanced by an associated suite of traits including positive schizotypal personality, openness to experience, absorption, tendency to dissociation, and strong imagination (Lifshitz et al., 2019). At the extreme, frank psychosis (or salient forms of epilepsy) can occur more or less spontaneously, resulting in hallucinations and delusions that are interpreted in spiritual and religious frameworks often involving sudden insights leading to novel and deeply-held beliefs.

Second, among individuals less intrinsically prone to psychosis, hyperactivation effects from HT2A would be driven more by forms of physiological and neurological stress and challenge, that mediates associative, prediction-error based learning commonly manifesting as imaginative insight moments. Such moments would usually be useful and adaptive, but would sometimes gravitate to novel beliefs that were false and delusional, though they may have adaptive elements in helping to cope with unusual perceptions. This mechanism is part and parcel of the cognitive changes that have made us human, and that underlie the functions of the expanded transmodal association neocortical regions whose development, function and neurological plasticity are orchestrated in notable part by HT2A effects (Luppi et al. 2024). Most importantly, it is the adaptive trajectory of stress, associative cognitive exploration, insight, learning, and belief that apparently generates potential for the remarkable constellation of supraphysiological effects in different brain regions (especially awe, universal oneness, and love) that make up transformative spiritual and religious experiences. In essence, such experiences represent extremes of adaptive mental states.

The third mechanism for HT2A activation is, of course, psychedelic biochemicals, whose cognitive-affective effects on HT2A in humans are entirely accidental but, once discovered, can be regulated as to time, person and place, thus laying the groundwork for organization and control of spiritual and religious experience and institutions among nascent groups. As evidenced by a host of anthropological and historical studies, many religions indeed derive in part or whole from such entheogenic events or rituals, that lend them supernatural legitimacy through miracles and compelling narratives directly connecting humans with gods (Brown & Lupu, 2014; Beckstead et al., 2019; Hoffman, 2019; Nemu, 2019; Samorini, 2019; Winkelman, 2019; Spiers et al., 2024).

Because they are all mediated by HT2A, these three mechanisms are essentially one and the same, explaining the deep and broad similarities between psychedelic, spiritual-religious, and positively-valenced psychotic experiences (Buckley, 1981; Brouwer et al., 2024)(Figure 3).

The God-receptor hypothesis has several important implications for study of the cognitive neuroscience of religion. Perhaps the most noteworthy is that it shifts focus of the field towards analysis of the neurophysiology and adaptive functions of the HT2A receptor, and the neurotransmitter-receptor systems directly associated with it, in different regions of the brain. Here, we have concentrated on the visual system, brain areas mediating surprise, self-instantiation, and the periaqueductal gray, as four regions whose connections to the phenomenology of HT2A hyperactivation effects appear most obvious and relevant to spirituality and religion. Many other brain areas and systems must also be intimately involved, together representing a network of god-related activation and receptor effects (e.g., Gobbi, 2024). Predictive coding theory provides the key cognitive-science instrument for understanding how the network components work separately and together, and it will need to be elaborated in concert with studies of HT2A's adaptive and hyper-activated functions.

Finally, studies of the neurocognitive physiological basis of spirituality and religion should generate novel insights into the mechanisms of psychedelic-based therapies, that are beginning to revolutionize treatments for depression and trauma (Velit-Salazar et al., 2024). Do psychedelic therapies work because they amplify the evolved, adaptive, plasticity-inducing process of challenge, exploration, and discovery that is typically imbued with fitness-related pleasure and love? Can this process be optimized, personalized, or recapitulated through psychophysiological rather than just biochemical means? Finding God throughout the human brain may be only the origin of this field, and its many profound applications to human health and well-being.

ACKNOWLEDGEMENTS

We are grateful to Ari Brouwer, Patrick McNamara, and Jordan Grafman for insightful comments, and the Templeton Foundation and NSERC for financial support.

REFERENCES

Acar, S., Chen, X., & Cayirdag, N. (2018). Schizophrenia and creativity: A meta-analytic review. *Schizophrenia Research, 195*, 23–31. https://doi.org/10.1016/j.schres.2017.08.036

Aday, J., Wood, J., Bloesch, E. & Davoli, C. (2021). Psychedelic drugs and perception: a narrative review of the first era of research. *Reviews in the Neurosciences*, *32*(5), 559-571. https://doi.org/10.1515/revneuro-2020-0094

Alamia, A., & VanRullen, R. (2019). Alpha oscillations and traveling waves: Signatures of predictive coding? *PLoS Biology, 17*(10), e3000487. https://doi.org/10.1371/journal.pbio.3000487

Alhadeff, A. L., Su, Z., Hernandez, E., Klima, M. L., Phillips, S. Z., Holland, R. A., Guo, C., Hantman, A. W., De Jonghe, B. C., & Betley, J. N. (2018). A neural circuit for the suppression of pain by a competing need state. *Cell, 173*(1), 140–152. https://doi.org/10.1016/j.cell.2018.02.057

Anderson, T. L., Keady, J. V., Songrady, J., Tavakoli, N. S., Asadipooya, A., Neeley, R. E., Turner, J. R., & Ortinski, P. I. (2024). Distinct 5-HT receptor subtypes regulate claustrum excitability by serotonin and the psychedelic, DOI. *Progress in Neurobiology, 240*, 102660. https://doi.org/10.1016/j.pneurobio.2024.102660

Bakhshaie, J., Sharifi, V., & Amini, J. (2011). Exploratory factor analysis of SCL-90-R symptoms relevant to psychosis. *Iranian Journal of Psychiatry, 6*(4), 128.

Barnett, L., Muthukumaraswamy, S. D., Carhart-Harris, R. L., & Seth, A. K. (2020). Decreased directed functional connectivity in the psychedelic state. *NeuroImage, 209*, 116462. https://doi.org/10.1016/j.neuroimage.2019.116462

Barrett, F. S., & Griffiths, R. R. (2018). Classic hallucinogens and mystical experiences: Phenomenology and neural correlates. In A. C. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Behavioral Neurobiology of Psychedelic Drugs* (pp. 393–430). Springer. https://doi.org/10.1007/7854_2017_474

Barrett, L. F. (2017). The theory of constructed emotion: an active inference account of interoception and categorization. *Social Cognitive and Affective neuroscience*, *12*(1), 1-23. https://doi.org/10.1093/scan/nsw154

Beckstead, R., Blankenagel, B., Noconi, C., & Winkelman, M. (2019). The entheogenic origins of Mormonism: A working hypothesis. *Journal of Psychedelic Studies, 3*(2), 212–260. https://doi.org/10.1556/2054.2019.020

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias*. International Universities Press.

Borges, C. C., Dos Santos, P. R., Alves, P. M., Borges, R. C. M., Lucchetti, G., Barbosa, M. A., Porto, C. C., & Fernandes, M. R. (2021). Association between spirituality/religiousness and quality of life among healthy adults: A systematic review. *Health and Quality of Life Outcomes, 19*, 1-13. https://doi.org/10.1186/s12955-021-01878-7

Brouwer, A., & Carhart-Harris, R. L. (2021). Pivotal mental states. *Journal of Psychopharmacology*, *35*(4), 319-352. https://doi.org/10.1177/0269881120959637

Brouwer, A., Raison, C. L., & Shults, F. L. (2024). The trajectory of psychedelic, spiritual, and psychotic experiences: implications for cognitive scientific perspectives on religion. *Religion, Brain & Behavior*, 1–17. https://doi.org/10.1080/2153599X.2024.2349151

Brown, J. & Lupu, M. (2014). Sacred Plants and the Gnostic Church: Speculations on Entheogen-Use in Early Christian Ritual. *Journal of Ancient History*, *2*(1), 64-77. https://doi.org/10.1515/jah-2014-0010

Buckley, P. (1981). Mystical experience and schizophrenia. *Schizophrenia Bulletin, 7*(3), 516–521. https://doi.org/10.1093/schbul/7.3.516

Cameron, L. P., Benetatos, J., Lewis, V., Bonniwell, E. M., Jaster, A. M., Moliner, R., Castrén, E., McCorvy, J. D., Palner, M., & Aguilar-Valles, A. (2023). Beyond the 5-HT2A receptor: Classic and nonclassic targets in psychedelic drug action. *Journal of Neuroscience, 43*(45), 7472–7482. https://doi.org/10.1523/JNEUROSCI.1384-23.2023

Carhart-Harris, R. (2007). Waves of the unconscious: the neurophysiology of dreamlike phenomena and its implications for the psychodynamic model of the mind. *Neuropsychoanalysis*, *9*(2), 183-211. https://doi.org/10.1080/15294145.2007.10773557

Carhart-Harris, R. L., & Friston, K. J. (2010). The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. Brain, 133(4), 1265-1283. https://doi.org/10.1093/brain/awq010

Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. *Pharmacological reviews*, *71*(3), 316-344. https://doi.org/10.1124/pr.118.017160

Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., & Nutt, D. J. (2015). LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*, *232*, 785-794. https://doi.org/10.1007/s00213-014-3714-z

Carhart-Harris, R. L., Leech, R., Erritzoe, D., Williams, T. M., Stone, J. M., Evans, J., Sharp, D. J., Feilding, A., Wise, R. G., & Nutt, D. J. (2013). Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis. *Schizophrenia Bulletin, 39*(6), 1343–1351. https://doi.org/10.1093/schbul/sbs117

Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E. E., Nest, T., Orban, C., & Leech, R. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences, 113*(17), 4853–4858. https://doi.org/10.1073/pnas.1518377113

Carter, C. S. (2022). Oxytocin and love: Myths, metaphors and mysteries. *Comprehensive Psychoneuroendocrinology, 9*, 100107. https://doi.org/10.1016/j.cpnec.2021.100107

Casey, A. B., Cui, M., Booth, R. G., & Canal, C. E. (2022). “Selective” serotonin 5-HT2A receptor antagonists. *Biochemical Pharmacology, 200*, 115028. https://doi.org/10.1016/j.bcp.2022.115028

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: a review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, *45*(7), 486-494. https://doi.org/10.1136/rapm-2020-101273

Cazettes, F., Reato, D., Morais, J. P., Renart, A., & Mainen, Z. F. (2021). Phasic activation of dorsal raphe serotonergic neurons increases pupil size. *Current Biology*, *31*(1), 192–197. https://doi.org/10.1016/j.cub.2020.09.090

Cho, P. S., Escoffier, N., Mao, Y., Ching, A., Green, C., Jong, J., & Whitehouse, H. (2018). Groups and emotional arousal mediate neural synchrony and perceived ritual efficacy. *Frontiers in Psychology*, *9*, 2071. https://doi.org/10.3389/fpsyg.2018.02071

Corder, G., Castro, D. C., Bruchas, M. R., & Scherrer, G. (2018). Endogenous and exogenous opioids in pain. *Annual Review of Neuroscience, 41*, 453–473. https://doi.org/10.1146/annurev-neuro-080317-061522

Corentin, C., Fitzgerald, C., & Goodwin, J. (2023). Benefits of hearing voices groups and other self-help groups for voice hearers: A systematic review. *Issues in Mental Health Nursing, 44*(4), 228–244. https://doi.org/10.1080/01612840.2023.2189953

Corlett, P. R., & Fraser, K. M. (2025). 20 Years of Aberrant Salience in Psychosis: What Have We Learned. *American Journal of Psychiatry*, *0*(0). https://doi.org/10.1176/appi.ajp.20240556

Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*(1), 59-70.

Crespi, B. (2021). The kin selection of religion. In J. R. Liddle & T. K. Shackelford (Eds.), *The Oxford handbook of evolutionary psychology and religion* (pp. 135–152). Oxford University Press.

Crespi, B. and Badcock, C. (2008) Psychosis and autism as diametrical disorders of the social brain. *Behavioral and brain sciences*, *31*(3), 241-261.

Crespi, B., & Dinsdale, N. (2019). Autism and psychosis as diametrical disorders of embodiment. *Evolution, Medicine, and Public Health, 2019*(1), 121–138. https://doi.org/10.1093/emph/eoz021

Crespi, B., Dinsdale, N., Read, S. and Hurd, P. (2019) Spirituality, dimensional autism, and schizotypal traits: The search for meaning. *Plos one*, *14*(3), e0213456.

Crespi, B., Leach, E., Dinsdale, N., Mokkonen, M., & Hurd, P. (2016). Imagination in human social cognition, autism, and psychotic-affective conditions. *Cognition*, *150*, 181-199. https://doi.org/10.1016/j.cognition.2016.02.001

De Filippo, R., & Schmitz, D. (2024). Synthetic surprise as the foundation of the psychedelic experience. *Neuroscience & Biobehavioral Reviews*, *157*, 105538. https://doi.org/10.1016/j.neubiorev.2024.105538

De Filippo, R., Rost, B. R., Stumpf, A., Cooper, C., Tukker, J. J., Harms, C., Beed, P., & Schmitz, D. (2021). Somatostatin interneurons activated by 5-HT2A receptors suppress slow oscillations in the medial entorhinal cortex. *eLife, 10*, e66960. https://doi.org/10.7554/eLife.66960

Demmrich, S., Koppold-Liebscher, D., Klatte, C., Steckhan, N., & Ring, R. M. (2023). Effects of religious intermittent dry fasting on religious experience and mindfulness: A longitudinal study among Baha'is. *Psychology of Religion and Spirituality, 15*(4), 459. https://doi.org/10.1037/rel0000423

Dentico, D., Cheung, B. L., Chang, J. Y., Guokas, J., Boly, M., Tononi, G., & Van Veen, B. (2014). Reversal of cortical information flow during visual imagery as compared to visual perception. *Neuroimage*, *100*, 237-243. https://doi.org/10.1016/j.neuroimage.2014.05.081

Diez-Alarcia, R., Muguruza, C., Rivero, G., García-Bea, A., Gómez-Vallejo, V., Callado, L. F., Llop, J., Martín, A., & Meana, J. J. (2021). Opposite alterations of 5-HT2A receptor brain density in subjects with schizophrenia: Relevance of radiotracers' pharmacological profile. *Translational Psychiatry, 11*, 302. https://doi.org/10.1038/s41398-021-01430-7

Dijkstra, N., Hinne, M., Bosch, S. E., & van Gerven, M. A. J. (2019). *Individual differences in the influence of mental imagery on conscious perception* [Preprint]. bioRxiv. https://doi.org/10.1101/607770

Elliott, B., Joyce, E., & Shorvon, S. (2009). Delusions, illusions and hallucinations in epilepsy: 1. Elementary phenomena. *Epilepsy research*, *85*(2-3), 162-171.

Friesen, N. (2013). Vision quest structures in the ethnographic and archaeological record, with examples from Saskatchewan. *Contributions to Northern Plains Archaeology*, 61-84.

Friesen, P. (2022). Psychosis and psychedelics: Historical entanglements and contemporary contrasts. *Transcultural Psychiatry, 59*(5), 592–609. https://doi.org/10.1177/13634615221129116

Friston, K. (2003). Learning and inference in the brain. *Neural Networks*, *16*(9), 1325-1352. https://doi.org/10.1016/j.neunet.2003.06.005

Ganis, G., Thompson, W. L., & Kosslyn, S. M. (2004). Brain areas underlying visual mental imagery and visual perception: an fMRI study. *Cognitive brain research*, *20*(2), 226-241. https://doi.org/10.1016/j.cogbrainres.2004.02.012

Gao, J. X., Yan, G., Li, X. X., Xie, J. F., Spruyt, K., Shao, Y. F., & Hou, Y. P. (2023). The ponto-geniculo-occipital (PGO) waves in dreaming: an overview. *Brain Sciences*, 13(9), 1350. https://doi.org/10.3390/brainsci13091350

Gibbs, A. A., Naudts, K. H., Spencer, E. P., & David, A. S. (2007). The role of dopamine in attentional and memory biases for emotional information. *American Journal of Psychiatry, 164*(10), 1603–1609. https://doi.org/10.1176/appi.ajp.2007.06081241

Gobbi, G. (2024). The psychopharmacology of psychedelics: Where the brain meets spirituality (CCNP Innovations in Neuropsychopharmacology Award). *Journal of Psychiatry and Neuroscience, 49*(5), E301–E318. https://doi.org/10.1503/jpn.240037

Grahl, A., Onat, S., & Büchel, C. (2018). The periaqueductal gray and Bayesian integration in placebo analgesia. *Elife*, *7*, e32930. https://doi.org/10.7554/eLife.32930

Grasemann, U., Hoffman, R., & Miikkulainen, R. (2009). Hyperlearning: A connectionist model of psychosis in schizophrenia. In *Proceedings of the Annual Meeting of the Cognitive Science Society* (Vol. 31, No. 31). https://escholarship.org/uc/item/31d5h9qq

Green, M. F., & Jimenez, A. M. (2022). Clinical observations and neuroscientific evidence tell a similar story: Schizophrenia is a disorder of the self-other boundary. *Schizophrenia Research, 242,* 45–48. https://doi.org/10.1016/j.schres.2021.12.032

Griffiths, R. R., Hurwitz, E. S., Davis, A. K., Johnson, M. W., & Jesse, R. (2019). Survey of subjective "God encounter experiences": Comparisons among naturally occurring experiences and those occasioned by the classic psychedelics psilocybin, LSD, ayahuasca, or DMT. *PLOS ONE, 14*(4), e0214377. https://doi.org/10.1371/journal.pone.0214377

Grover, S., Davuluri, T., & Chakrabarti, S. (2014). Religion, spirituality, and schizophrenia: A review. *Indian Journal of Psychological Medicine, 36*(2), 119–124. https://doi.org/10.4103/0253-7176.130962

Guiard, B. P., & Di Giovanni, G. (Eds.). (2018). *5-HT2A receptors in the central nervous system*. Springer International Publishing.

Haidt, J. (2012). *The righteous mind: Why good people are divided by politics and religion*. Vintage Books.

Harding, J. N., Wolpe, N., Brugger, S. P., Navarro, V., Teufel, C., & Fletcher, P. C. (2024). A new predictive coding model for a more comprehensive account of delusions. *The Lancet Psychiatry*, *11*(4), 295-302. https://doi.org/10.1016/S2215-0366(23)00411-X

Harkin, E. F., Grossman, C. D., Cohen, J. Y., Béïque, J. C., & Naud, R. (2025). A prospective code for value in the serotonin system. *Nature*, 1-8.

Harvey, J. A., Gormezano, I., & Cool-Hauser, V. A. (1983). Effects of scopolamine and methylscopolamine on classical conditioning of the rabbit nictitating membrane response. *The Journal of Pharmacology and Experimental Therapeutics, 225*(1), 42–49. https://doi.org/10.1016/S0022-3565(25)33549-4

Hendricks, P. S. (2018). Awe: a putative mechanism underlying the effects of classic psychedelic-assisted psychotherapy. *International Review of Psychiatry*, *30*(4), 331-342. https://doi.org/10.1080/09540261.2018.1474185

Hensman, R., Guimarães, F. S., Wang, M., & Deakin, J. F. W. (1991). Effects of ritanserin on aversive classical conditioning in humans. *Psychopharmacology*, *104*, 220-224. https://doi.org/10.1007/BF02244182

Hoffman, M. A. (2019). Entheogens (psychedelic drugs) and the ancient mystery religions. In P. Wexler (Ed.), *Toxicology in antiquity* (2nd ed., pp. 353–362). Academic Press. https://doi.org/10.1016/B978-0-12-815339-0.00025-1

Huber, M. K., Schwitzer, J., Kirchler, E., & Lepping, P. (2022). Delusion and dopamine: Neuronal insights in psychotropic drug therapy. In G. Gründer, M. A. Geyer, & B. R. Gibbons (Eds.), *Neuropsychopharmacotherapy* (pp. 955–974). Springer International Publishing. https://doi.org/10.1007/978-3-030-55786-4_48

Ihm, E. D., Paloutzian, R. F., van Elk, M., & Schooler, J. W. (2019). Awe as a meaning-making emotion: On the evolution of awe and the origin of religions. In S. M. McNamara & C. E. R. Webb (Eds.), *The evolution of religion, religiosity, and theology* (pp. 138-153). Routledge.

Jalal, B. (2018). The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. *Psychopharmacology*, *235*(11), 3083-3091. https://doi.org/10.1007/s00213-018-5042-1

Kanen, J. W., Apergis-Schoute, A. M., Yellowlees, R., et al. (2021). Serotonin depletion impairs both Pavlovian and instrumental reversal learning in healthy humans. *Molecular Psychiatry*, 26(10), 7200–7210. https://doi.org/10.1038/s41380-021-01240-9

Kanen, J. W., Luo, Q., Kandroodi, M. R., Cardinal, R. N., Robbins, T. W., Nutt, D. J., Carhart-Harris, R. L., & den Ouden, H. E. M. (2023). Effect of lysergic acid diethylamide (LSD) on reinforcement learning in humans. *Psychological Medicine, 53*(14), 6434–6445. https://doi.org/10.1017/S0033291722002963

Kantrowitz, J. T. (2020). Targeting serotonin 5-HT2A receptors to better treat schizophrenia: rationale and current approaches. *CNS drugs*, *34*(9), 947-959. https://doi.org/10.1007/s40263-020-00752-2

Kapur, S. (2003). Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia. *American Journal of Psychiatry*, *160*(1), 13–23. https://doi.org/10.1176/appi.ajp.160.1.13

Kapur, S., & Seeman, P. (2002). NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D2 and serotonin 5-HT2 receptors—implications for models of schizophrenia. *Molecular Psychiatry, 7*(8), 837-844. https://doi.org/10.1038/sj.mp.4001093

Keltner, D., & Haidt, J. (2003). Approaching awe, a moral, spiritual, and aesthetic emotion. *Cognition and Emotion*, *17*(2), 297–314. https://doi.org/10.1080/02699930302297

Kim, S. A. (2021). 5-HT1A and 5-HT2A signaling, desensitization, and downregulation: Serotonergic dysfunction and abnormal receptor density in schizophrenia and the prodrome. *Cureus, 13*(6), e15811. https://doi.org/10.7759/cureus.15811

Klepel, F., Schredl, M., & Göritz, A. S. (2019). Dreams stimulate waking-life creativity and problem solving: Effects of personality traits. *International Journal of Dream Research*, 95-102.

Ko, K., Kopra, E. I., Cleare, A. J., & Rucker, J. J. (2023). Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *322*, 194-204. https://doi.org/10.1016/j.jad.2022.09.168

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. X. (2012). Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biological Psychiatry, 72*(11), 898–906. https://doi.org/10.1016/j.biopsych.2012.04.005

Kometer, M., Schmidt, A., Jäncke, L., & Vollenweider, F. X. (2013). Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. *Journal of Neuroscience*, *33*(25), 10544-10551. https://doi.org/10.1523/JNEUROSCI.3007-12.2013

Kooijman, N. I., Willegers, T., Reuser, A., Mulleners, W. M., Kramers, C., Vissers, K. C., & van Der Wal, S. E. (2023). Are psychedelics the answer to chronic pain: A review of current literature. *Pain Practice*, *23*(4), 447-458. https://doi.org/10.1111/papr.13203

Kraehenmann, R. (2017). Dreams and psychedelics: neurophenomenological comparison and therapeutic implications. *Current neuropharmacology*, *15*(7), 1032-1042. https://doi.org/10.2174/1573413713666170619092629

Kwapil, T. R., & Barrantes-Vidal, N. (2015). Schizotypy: Looking back and moving forward. *Schizophrenia Bulletin, 41*, S366–S373. https://doi.org/10.1093/schbul/sbu186

Lebedev, A. V., Lövdén, M., Rosenthal, G., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2015). Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human Brain Mapping, 36*(8), 3137–3153. https://doi.org/10.1002/hbm.22833

Lee, H.-S., Hong, S.-J. J., Baxter, T., Scott, J., Shenoy, S., Buck, L., Bodenheimer, B., & Park, S. (2021). Altered peripersonal space and the bodily self in schizophrenia: A virtual reality study. *Schizophrenia Bulletin, 47*(4), 927–937. https://doi.org/10.1093/schbul/sbab024

Leonard, B. E. (2005). The HPA and immune axes in stress: the involvement of the serotonergic system. *European Psychiatry*, *20*(S3), S302-S306. https://doi.org/10.1016/S0924-9338(05)80180-4

Lifshitz, M., Van Elk, M., & Luhrmann, T. M. (2019). Absorption and spiritual experience: A review of evidence and potential mechanisms. *Consciousness and Cognition, 73*, 102760. https://doi.org/10.1016/j.concog.2019.05.008

Lin, H., Kim, J. G., Park, S. W., Noh, H. J., Kim, J. M., Yoon, C. Y., Woo, N. S., Kim, B., Cho, I. S., Choi, B. H., & Sung, D. J. (2018). Enhancement of 5-HT2A receptor function and blockade of Kv1.5 by MK801 and ketamine: Implications for PCP derivative-induced disease models. *Experimental & Molecular Medicine, 50*(4), 1–8. https://doi.org/10.1038/s12276-018-0073-6

Looijestijn, J., Blom, J. D., Aleman, A., Hoek, H. W., & Goekoop, R. (2015). An integrated network model of psychotic symptoms. *Neuroscience & Biobehavioral Reviews*, *59*, 238-250. https://doi.org/10.1016/j.neubiorev.2015.09.016

Luppi, P. H., Billwiller, F., & Fort, P. (2017). Selective activation of a few limbic structures during paradoxical (REM) sleep by the claustrum and the supramammillary nucleus: evidence and function. *Current opinion in neurobiology,* 44, 59-64.

Luppi, A. I., Girn, M., Rosas, F. E., Timmermann, C., Roseman, L., Erritzoe, D., Nutt, D. J., Stamatakis, E. A., Spreng, R. N., Xing, L., Huttner, W. B., & Carhart-Harris, R. L. (2024). A role for the serotonin 2A receptor in the expansion and functioning of human transmodal cortex. *Brain, 147*(1), 56–80. https://doi.org/10.1093/brain/awad311

Lynch, R., Shenk, M. K., Shaver, J. H., & Spake, L. (2022). Fertility and faith: Insights from human behavioral ecology, evolutionary psychology, and life history theory. *Religion, Brain & Behavior, 12*(4), 406-413. https://doi.org/10.1080/2153599X.2021.2023617

Mantas, I., Flais, I., Masarapu, Y., Ionescu, T., Frapard, S., Jung, F., Le Merre, P., Saarinen, M., Tiklova, K., Salmani, B. Y., & Gillberg, L. (2024). Claustrum and dorsal endopiriform cortex complex cell-identity is determined by Nurr1 and regulates hallucinogenic-like states in mice. *Nature Communications, 15*(1), 8176. https://doi.org/10.1038/s41467-024-52429-9

McGovern, H. T., Grimmer, H. J., Doss, M. K., Hutchinson, B. T., Timmermann, C., Lyon, A., Corlett, P. R., & Laukkonen, R. E. (2024). An integrated theory of false insights and beliefs under psychedelics. *Communications Psychology, 2*(1), 69. https://doi.org/10.1038/s44271-024-00120-6

McNamara, P. (2022). *The cognitive neuroscience of religious experience: Decentering and the self*. Cambridge University Press.

McNamara, P., & Grafman, J. (2024). Advances in brain and religion studies: a review and synthesis of recent representative studies. *Frontiers in Human Neuroscience*, *18*, 1495565. https://doi.org/10.3389/fnhum.2024.1495565

McNamara, P., & Grafman, J. (2024). Advances in brain and religion studies: a review and synthesis of recent representative studies. *Frontiers in Human Neuroscience*, *18*, 1495565. https://doi.org/10.3389/fnhum.2024.1495565

McPherson, K. B., & Ingram, S. L. (2022). Cellular and circuit diversity determines the impact of endogenous opioids in the descending pain modulatory pathway. *Frontiers in Systems Neuroscience*, *16*, 963812. https://doi.org/10.3389/fnsys.2022.963812

Melzack, R. (2014). Pain and stress: Clues toward understanding chronic pain. In M. E. Lamb & R. M. Lerner (Eds.), *Advances in psychological science: Vol. 2. Social, personal, and cultural aspects* (pp. 63–85). Psychology Press.

Minas, I. H., Klimidis, S., Stuart, G. W., Copolov, D. L., & Singh, B. S. (1994). Positive and negative symptoms in the psychoses: Principal components analysis of items from the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. *Comprehensive Psychiatry, 35*(2), 135–144. https://doi.org/10.1016/0010-440X(94)90059-Q

Mishara, A. L., & Corlett, P. (2009). Are delusions biologically adaptive? Salvaging the doxastic shear pin. *Behavioral and Brain Sciences*, *32*(6), 530–531. doi:10.1017/S0140525X09991464

Monti, J. M., Pandi Perumal, S. R., Warren Spence, D., & Torterolo, P. (2018). The involvement of 5-HT 2A receptor in the regulation of sleep and wakefulness, and the potential therapeutic use of selective 5-HT 2A receptor antagonists and inverse agonists for the treatment of an insomnia disorder. In 5-HT2A Receptors in the Central Nervous System (pp. 311-337). Humana Press, Cham.

Mousavi, Z., Kiani, M. M., & Aghajan, H. (2022). Spatiotemporal signatures of surprise captured by magnetoencephalography. *Frontiers in Systems Neuroscience*, *16*, 865453. https://doi.org/10.3389/fnsys.2022.865453

Muller, C.L., Anacker, A.M. and Veenstra-VanderWeele, J. (2016) The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience*, *321*, 24-41.

Murnane, K. S. (2019). Serotonin 2A receptors are a stress response system: Implications for post-traumatic stress disorder. *Behavioural Pharmacology, 30*(2–3), 151–162. https://doi.org/10.1097/FBP.0000000000000459

Muthukumaraswamy, S. D., Carhart-Harris, R. L., Moran, R. J., Brookes, M. J., Williams, T. M., Errtizoe, D., Sessa, B., Papadopoulos, A., Bolstridge, M., Singh, K. D., Feilding, A., Friston, K. J., & Nutt, D. J. (2013). Broadband cortical desynchronization underlies the human psychedelic state. *Journal of Neuroscience, 33*(38), 15171–15183. https://doi.org/10.1523/JNEUROSCI.2063-13.2013

Narikiyo, K., Mizuguchi, R., Ajima, A., Shiozaki, M., Hamanaka, H., Johansen, J. P., ... & Yoshihara, Y. (2020). The claustrum coordinates cortical slow-wave activity. Nature neuroscience, 23(6), 741-753.

Nasrallah, H. A., Fedora, R., & Morton, R. (2019). Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophrenia Research, 208*, 217–220. https://doi.org/10.1016/j.schres.2019.02.018

Nelson, E. E., & Panksepp, J. (1998). Brain substrates of infant–mother attachment: contributions of opioids, oxytocin, and norepinephrine. *Neuroscience & Biobehavioral Reviews*, *22*(3), 437-452. https://doi.org/10.1016/S0149-7634(97)00052-3

Nemu, D. (2019). Getting high with the most high: Entheogens in the Old Testament. *Journal of Psychedelic Studies, 3*(2), 117–132. https://doi.org/10.1556/2054.2019.004

Nettle, D. (2001). *Strong imagination: Madness, creativity and human nature* (Online ed., 31 Oct. 2023). Oxford University Press. https://doi.org/10.1093/oso/9780198507062.001.0001

Niazi, I. K., Navid, M. S., Bartley, J., Shepherd, D., Pedersen, M., Burns, G., Taylor, D., & White, D. E. (2022). EEG signatures change during unilateral Yogi nasal breathing. *Scientific Reports, 12*(1), 520. https://doi.org/10.1038/s41598-021-04461-8

Nordin, A., & Bjälkebring, P. (2021). The counterintuitiveness of supernatural dreams and religiosity. *Journal of Cognition and Culture*, *21*(3-4), 309-330. https://doi.org/10.1163/15685373-12340114

O'Grady, S. (2012). *And man created God: Kings, cults, and conquests at the time of Jesus*. Atlantic Books Ltd.

Palva, S. & Palva, J. M. (2007) New vistas for alpha-frequency band oscillations. *Trends in Neuroscience, 30*(4), 150-158. https://doi.org/10.1016/j.tins.2007.02.001

Pezzulo, G., Parr, T., & Friston, K. (2022). The evolution of brain architectures for predictive coding and active inference. *Philosophical Transactions of the Royal Society B*, *377*(1844), 20200531. https://doi.org/10.1098/rstb.2020.0531

Pierre, J. M. (2001). Faith or delusion? At the crossroads of religion and psychosis. *Journal of Psychiatric Practice, 7*(3), 163–172. https://doi.org/10.1097/00131746-200105000-00004

Quednow, B. B., Kometer, M., Geyer, M. A., & Vollenweider, F. X. (2012). Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology, 37*(3), 630–640. https://doi.org/10.1038/npp.2011.228

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., & Kuypers, K. P. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology, 35*(4), 398–405. https://doi.org/10.1177/0269881120940937

Reininghaus, U., Kempton, M. J., Valmaggia, L., Craig, T. K. J., Garety, P., Onyejiaka, A., Gayer-Anderson, C., So, S. H., Hubbard, K., Beards, S., Dazzan, P., Pariante, C., Mondelli, V., Fisher, H. L., Mills, J. G., Viechtbauer, W., McGuire, P., van Os, J., Murray, R. M., Wykes, T., Myin-Germeys, I., & Morgan, C. (2016). Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: An experience sampling study. *Schizophrenia Bulletin, 42*(3), 712–722. https://doi.org/10.1093/schbul/sbv190

Renouard, L., Billwiller, F., Ogawa, K., Clément, O., Camargo, N., Abdelkarim, M., ... & Luppi, P. H. (2015). The supramammillary nucleus and the claustrum activate the cortex during REM sleep. Science Advances, 1(3), e1400177.

Rim, J. I., Ojeda, J. C., Svob, C., Kayser, J., Drews, E., Kim, Y., Tenke, C. E., Skipper, J., & Weissman, M. M. (2019). Current understanding of religion, spirituality, and their neurobiological correlates. *Harvard Review of Psychiatry, 27*(5), 303–316. https://doi.org/10.1097/HRP.0000000000000232

Robinson, J. E., Breakspear, M., Young, A. W., & Johnston, P. J. (2020). Dose-dependent modulation of the visually evoked N1/N170 by perceptual surprise: A clear demonstration of prediction-error signalling. *European Journal of Neuroscience*, *52*(11), 4442-4452. https://doi.org/10.1111/ejn.13920

Roiser, J. P., Howes, O. D., Chaddock, C. A., Joyce, E. M., & McGuire, P. (2013). Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. *Schizophrenia Bulletin, 39*(6), 1328–1336. https://doi.org/10.1093/schbul/sbw025

Rush, J. A. (Ed.). (2013). *Entheogens and the development of culture: The anthropology and neurobiology of ecstatic experience*. North Atlantic Books.

Saleh, T., Logothetis, N., & Evrard, H. (2017). Insular projections to brainstem homeostatic centers in the macaque monkey. *Frontiers in Molecular Neuroscience, 11*, . https://doi.org/10.3389/fnmol.2017.00011

Salinsky, L. M., Merritt, C. R., Zamora, J. C., Giacomini, J. L., Anastasio, N. C., & Cunningham, K. A. (2023). μ-opioid receptor agonists and psychedelics: pharmacological opportunities and challenges. *Frontiers in Pharmacology*, *14*, 1239159. https://doi.org/10.3389/fphar.2023.1239159

Salvi, C., Simoncini, C., Grafman, J., & Beeman, M. (2020). Oculometric signature of switch into awareness? Pupil size predicts sudden insight whereas microsaccades predict problem-solving via analysis. *NeuroImage*, *217*, 116933. https://doi.org/10.1016/j.neuroimage.2020.116933

Samorini, G. (2019). The oldest archeological data evidencing the relationship of Homo sapiens with psychoactive plants: A worldwide overview. *Journal of Psychedelic Studies*, *3*(2), 63-80. https://doi.org/10.1556/2054.2019.008

Schredl, M., & Erlacher, D. (2007). Self-reported effects of dreams on waking-life creativity: an empirical study. *The Journal of Psychology*, *141*(1), 35-46. https://doi.org/10.3200/JRLP.141.1.35-46

Selten, J. P., van der Ven, E., Rutten, B. P. F., & Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: An update. *Schizophrenia Bulletin, 39*(6), 1180–1186. https://doi.org/10.1093/schbul/sbt134

Sierra, S., Muchhala, K. H., Jessup, D. K., Contreras, K. M., Shah, U. H., Stevens, D. L., Jimenez, J., Lavilla, X. K., de la Fuente Revenga, M., Lippold, K. M., & Shen, S. (2022). Sex-specific role for serotonin 5-HT2A receptor in modulation of opioid-induced antinociception and reward in mice. *Neuropharmacology, 209*, 108988. https://doi.org/10.1016/j.neuropharm.2022.108988

Silva, C., & McNaughton, N. (2019). Are periaqueductal gray and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review. *Progress in neurobiology*, *177*, 33-72. https://doi.org/10.1016/j.pneurobio.2019.02.001

Simony, E., Honey, C. J., Chen, J., Lositsky, O., Yeshurun, Y., Wiesel, A., & Hasson, U. (2016) Dynamic reconfiguration of the default mode network during narrative comprehension. *Nature Communication.* 8(1), 630. doi: 10.1038/ncomms12141.

Singleton, S. P., Timmerman, C. Luppi, A. I., Eckernas, E., Roseman, L., Carhardt-Harris, R. L. & Kuceyeski, A. Network control energy reductions under DMT relate to serotonin receptors, signal diversity and subjective experience. (2025) *Communications Biology*. 8(1), 631. doi: 10.1038/s42003-025-08078-9.

Smith, R., Badcock, P., & Friston, K. J. (2021). Recent advances in the application of predictive coding and active inference models within clinical neuroscience. *Psychiatry and Clinical Neurosciences*, *75*(1), 3-13. https://doi.org/10.1111/pcn.13138

Spiers, N., Labate, B. C., Ermakova, A. O., Farrell, P., Romero, O. S. G., Gabriell, I., & Olvera, N. (2024). Indigenous psilocybin mushroom practices: An annotated bibliography. *Journal of Psychedelic Studies*, *8*(1), 3-25. https://doi.org/10.1556/2054.2023.00297

Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: Dopamine, serotonin, and glutamate. *CNS Spectrums, 23*(3), 187–191. https://doi.org/10.1017/S1092852918001013

Stoliker, D., Egan, G. F., Friston, K. J., & Razi, A. (2022). Neural mechanisms and psychology of psychedelic ego dissolution. *Pharmacological Reviews*, *74*(4), 876-917. https://doi.org/10.1124/pharmrev.121.000508

Taves, A. (2020). Mystical and other alterations in sense of self: An expanded framework for studying nonordinary experiences. *Perspectives on Psychological Science, 15*(3), 669-690. https://doi.org/10.1177/1745691619895047

Timmermann, C., Kettner, H., Letheby, C., Roseman, L., Rosas, F. E., & Carhart-Harris, R. L. (2021). Psychedelics alter metaphysical beliefs. *Scientific Reports, 11*(1), 22166. https://doi.org/10.1038/s41598-021-01209-2

Timofeev, I., & Chauvette, S. (2020). Global control of sleep slow wave activity. *Nature Neuroscience*, *23*(6), 693-695.

Tisserand, A., Philippi, N., Botzung, A., & Blanc, F. (2023). Me, Myself and My Insula: An Oasis in the Forefront of Self-Consciousness. *Biology*, *12*(4), 599. https://doi.org/10.3390/biology12040599

Tulver, K., Kaup, K. K., Laukkonen, R., & Aru, J. (2023). Restructuring insight: An integrative review of insight in problem-solving, meditation, psychotherapy, delusions and psychedelics. *Consciousness and Cognition, 110*, 103494. https://doi.org/10.1016/j.concog.2023.103494

Tylor, E. B. (1871). *Primitive culture: Researches into the development of mythology, philosophy, religion, art, and custom* (Vol. 2). J. Murray.

Vaillant, G. E. (2013). Psychiatry, religion, positive emotions and spirituality. *Asian Journal of Psychiatry, 6*(6), 590–594. https://doi.org/10.1016/j.ajp.2013.08.073

van Elk, M., & Aleman, A. (2017). Brain mechanisms in religion and spirituality: An integrative predictive processing framework. *Neuroscience & Biobehavioral Reviews*, *73*, 359-378. https://doi.org/10.1016/j.neubiorev.2016.12.031

van Os, J. (2009). A salience dysregulation syndrome. *The British Journal of Psychiatry, 194*(2), 101–103. https://doi.org/10.1192/bjp.bp.108.054254

van Winkel, R., Stefanis, N. C., & Myin-Germeys, I. (2008). Psychosocial stress and psychosis: A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophrenia Bulletin, 34*(6), 1095–1105. https://doi.org/10.1093/schbul/sbn101

Vargas, M. V., Dunlap, L. E., Dong, C., Carter, S. J., Tombari, R. J., Jami, S. A., Cameron, L. P., Patel, S. D., Hennessey, J. J., Saeger, H. N., & McCorvy, J. D. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science, 379*(6633), 700–706. https://doi.org/10.1126/science.adf0435

Velit-Salazar, M. R., Shiroma, P. R., & Cherian, E. (2024). A systematic review of the neurocognitive effects of psychedelics in healthy populations: Implications for depressive disorders and post-traumatic stress disorder. *Brain Sciences, 14*(3), 248. https://doi.org/10.3390/brainsci14030248

Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*, *9*(17), 3897-3902.

Warrier, V., Toro, R., Chakrabarti, B., iPSYCH-Broad Autism Group, Børglum, A. D., Grove, J., 23andMe Research Team, Hinds, D. A., Bourgeron, T., & Baron-Cohen, S. (2018). Genome-wide analyses of self-reported empathy: Correlations with autism, schizophrenia, and anorexia nervosa. *Translational Psychiatry, 8*(1), 35. https://doi.org/10.1038/s41398-017-0082-6

Winkelman, M. (2019). Introduction: Evidence for entheogen use in prehistory and world religions. *Journal of Psychedelic Studies*, *3*(2), 43-62. https://doi.org/10.1556/2054.2019.024

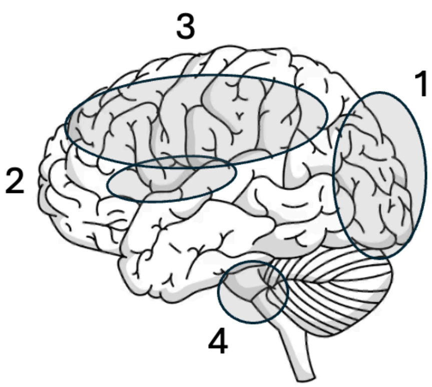
Yamada, Y., Matsumoto, M., Iijima, K., & Sumiyoshi, T. (2020). Specificity and continuity of schizophrenia and bipolar disorder: Relation to biomarkers. *Current Pharmaceutical Design, 26*(2), 191–200. https://doi.org/10.2174/1381612825666191216153508

Yeshurun, Y., Nguyen, M., & Hasson, U. (2021). The default mode network: Where the idiosyncratic self meets the shared social world. *Nature Reviews Neuroscience, 22*(3), 181–192. https://doi.org/10.1038/s41583-020-00420-w

Zeifman, R. J., Spriggs, M. J., Kettner, H., Lyons, T., Rosas, F. E., Mediano, P. A., Erritzoe, D., & Carhart-Harris, R. L. (2025). From relaxed beliefs under psychedelics (REBUS) to revised beliefs after psychedelics (REBAS). *Scientific Reports, 15*(1), 3651. https://doi.org/10.1038/s41598-023-28111-3

Zhang, G., & Stackman Jr, R. W. (2015). The role of serotonin 5-HT2A receptors in memory and cognition. *Frontiers in Pharmacology*, *6*, 225. https://doi.org/10.3389/fphar.2015.00225

Figure 1. Four brain regions show evidence of being centrally involved in the instantiation of neural functions that, under HT2A hyperactivation, generate manifestations of spiritual and religious experiences.



Brain region	Typical function	HT2A hyperactivation
1 Visual cortex	Perception of visual visual stimuli	Visual hallucination, mediated by imagination filtering into perception due to increased top-down predictive coding effects
2 Anterior cingulate cortex	Surprise, registered as prediction errors	Awe, vastness, peak experience, challenge to meaning system
3 Default mode, insula and claustrum	Instantiation of self (narrative, bodily, and multisensory)	Ego-dissolution, due to loss of neural oscillation synchronicity in default mode, and loss of internal bodily and mental state integration; one with others and universe; loss of space, time, self-other boundaries
4 Periaqueductal gray	Pain modulation, basic attachment, basic emotions, periconsciousness	Emotional well-being, bonding, love, connectedness, pleasure

Figure 2. A key evolved function of HT2A activation is the generation of neural plasticity in response to stressors or challenges, leading, if successful, to insight problem-solving, reward, and updated beliefs. Hyperactivation of this system due to high levels of stress, psychotic-affective mental states, or psychedelic drugs can lead to spiritual and religious experiences that involve profound insights and novel supernatural and delusional beliefs.

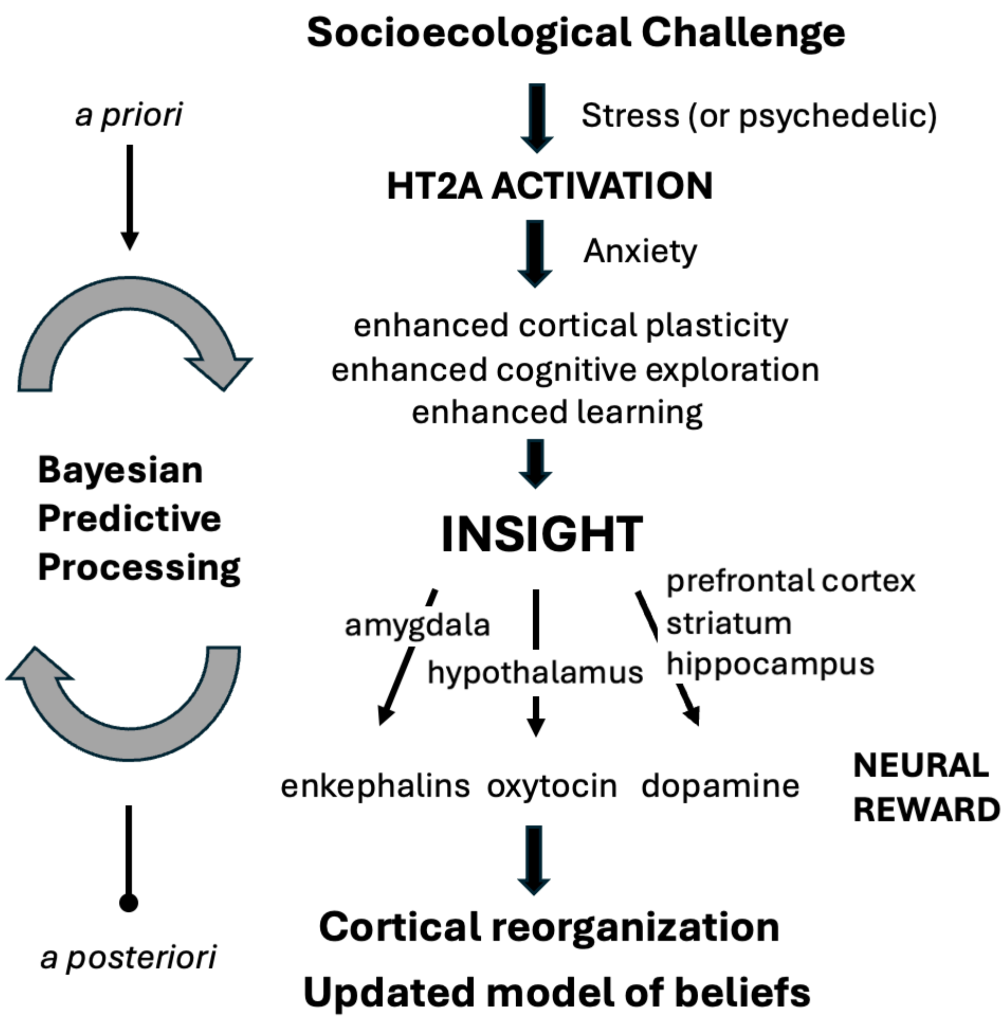


Figure 3. The series of neuropsychological events that leads to insight and belief updating are notably similar under causation by stress, psychosis, and psychedelic drugs, due to common underlying mechanisms instigated and orchestrated by HT2A hyperactivation.