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The Psilocybin-Telomere Hypothesis: An empirically falsifiable prediction concerning the beneficial neuropsychopharmacological effects of psilocybin on genetic aging☆

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ABSTRACT

We introduce a novel hypothesis which states that the therapeutic utilisation of psilocybin has beneficial effects on genetic aging. *Ex hypothesi*, we predict *a priori* that controlled psilocybin interventions exert quantifiable positive impact on leucocyte telomere length (telomeres are a robust predictor of mortality and multifarious aging-related diseases). Our hypothesising follows the Popperian logic of scientific discovery, viz., bold (and refutable) conjectures form the very foundation of scientific progress. The 'psilocybin-telomere hypothesis' is formalised as a logically valid deductive (syllogistic) argument and we provide substantial evidence to support the underlying premises. Impetus for our theorising derives from a plurality of converging empirical sources indicating that psilocybin has persistent beneficial effects on various aspects of mental health (e.g., in the context of depression, anxiety, PTSD, OCD, addiction, etc.). Additional support is based on a large corpus of studies that establish reliable correlations between mental health and telomere attrition (improved mental health is generally correlated with longer telomeres). Another pertinent component of our argument is based on recent studies which demonstrate that "meditative states of consciousness" provide beneficial effects on genetic aging. Similarly, psilocybin can induce states of consciousness that are neurophysiologically and phenomenologically significantly congruent with meditative states. Furthermore, prior research has demonstrated that a single dose of psilocybin can occasion life-changing transformative experiences (≈ 70% of healthy volunteers rate their experience with psilocybin amongst the five personally most meaningful lifetime events, viz., ranked next to giving birth to a child or losing a loved one). We postulate that these profound psychological events leave quantifiable marks at the molecular genetic/epigenetic level. Given the ubiquitous availability and cost effectiveness of telomere length assays, we suggest that quantitative telomere analysis should be regularly included in future psilocybin studies as an adjunctive biological marker (i.e., to facilitate scientific consilience via methodological triangulation). In order to substantiate the 'psilocybin-telomere hypothesis' potential neuropsychopharmacological, endocrinological, and genetic mechanisms of action are discussed (e.g., HPA-axis reactivity, hippocampal neurogenesis, neurotropic growth factors such as BDNF, 5-HT_{2A} receptor agonism, neuroplasticity/synaptoplasticity, brain-wide alterations in neuronal functional connectivity density, involvement of the SLC6A4 serotonin transporter gene, *inter alia*). The proposed research agenda is thus intrinsically highly interdisciplinary, and it has deep ramifications from a philosophy of science perspective as it connects the epistemic level (qualitative experiential phenomenology) with the ontic level (quantitative molecular genetics) of analysis. In the long term, multidisciplinary and innovative investigations of the 'psilocybin-telomere hypothesis' could contribute to the improvement of senotherapeutic psychological interventions and the identification of novel geroprotective and neuroprotective/restorative pharmaceutical targets to decelerate genetic aging and improve well-being and quality of life during the aging process.

Introduction

A plethora of genetic and geroscience studies indicate that telomere length is a reliable biomarker of cellular aging [1,2], i.e., telomeres are regarded as a robust indicator of mitotic cell and possibly organismal longevity [3]. Attrition/uncapping of telomeres is associated with the

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degeneration of multiple systems such as various organ failures, depletion of the totipotent stem cell répertoire, tissue atrophy, impairments in injury responses and various (neuro)restorative processes, *inter alia* [4]. Furthermore, it has been proposed that telomeres function as a "psychobiomarker" as they are partially regulated by psychological factors [5,6]. *In sensu lato*, a healthy lifestyle and a positive outlook on life are generally associated with longer telomeres while, *vice versa*, an unhealthy lifestyle and a negative/pessimistic mindset are associated with shorter telomeres [7,8]. There are numerous factors that influence telomere attrition, for instance, maternal genetic predispositions [9], *in utero* stress-levels, quality of diet [10,11] and availability of $\omega - 3$ fatty acids [12], alcohol consumption [13], tobacco smoking [14], sleep patterns [15], a variety of social/interpersonal variables [16–18], fitness and physical exercise [19,20], exposure to environmental toxins such as traffic pollution [21] and various chemical compounds found in plastics [22], etc. pp. (for a comprehensive review see, [23]). Furthermore, converging evidence indicates that telomeres are affected by psychological conditions such as chronic stress, depression, and repetitive negative thought patterns, viz., chronic rumination [3,24–27] and self-referential mind wandering[1] [28]. The pertinent literature delineates the following dichotomous pattern: Positive psychological states are correlated with longer telomeres, whereas depression, chronic stress, and anxiety display a negative correlation [29].

In line with this empirical background, our primary hypothesis is based on the major premise that psychological conditions affect telomeres. In addition, our hypothesis rests on the minor premise that the therapeutic utilisation of psilocybin exhibits significant beneficial effects on various aspects of psychological health.[2] Rapidly accumulation converging empirical evidence supports this claim [30–34]. Specifically, a substantial corpus of studies demonstrated that the therapeutic utilisation of psilocybin reduces depression in various populations [35–37] and, for the sake of focus and parsimony, the present discussion will be primarily concerned with this factor. However, similar arguments could be articulated with respect to PTSD, various anxiety[3] disorders, behavioural and substance addictions, etc. (e.g., [38]). Given the well-established comorbidity between these "psychopathologies" [39], it is logically cogent to assume that the underlying cognitive, emotional, and biochemical mechanisms are significantly congruent in numerous respects, e.g., in terms of characteristic neurotransmitter dynamics and brain-wide network dynamics.

Hypothesis as a deductive syllogistic argument

Our hypothesis is based on the empirically grounded assumption that neuropsychological factors influence aging at the genetic level. We postulate that beneficial psychological conditions are associated with telomeric health (i.e., longer telomeres via activation of the enzyme telomerase reverse transcriptase which adds nucleotide sequences to the ends of DNA). Consequently, we predict *a priori* that therapeutic psychological and neurobiological changes induced by psilocybin are quantifiable by telomere analysis (but also via alternative biomarkers of aging, as discussed subsequently). The primary hypothesis can be stated as a deductive argument in form of a valid Aristotelian categorical syllogism.

Syllogism #1

Major premise:	Depression is associated with shorter telomeres.
Minor premise:	Psilocybin reduces depression.
Conclusion:	∴ Ergo, psilocybin positively effects telomere length.

N.B.: According to syllogistic logic, each of the three distinct terms represents a category, i.e.: [Depression] — [Telomeres] — [Psilocybin].

In Syllogism #1 the category [Telomeres] constitutes the major term and [Psilocybin] represents the minor term. Crucially, the premises have a single term in common (the middle term)[4] that appears as the subject or predicate of the categorical proposition, *in casu*, [Depression].

According to the principles of propositional logic, the conclusion follows deductively[5] *if* the major and minor premise are accepted as veridical. In the following sections we will thus provide empirical evidence in order to substantiate the major and minor premise, i.e., 1) that depression is associated with shorter telomeres and 2) that psilocybin reduces depression. Note that our hypothesis could also be remodelled in the framework of Bayesian epistemology. In this case the subsequently presented information can be utilised to calibrate/parametrise "informed priors" which severe as a conditional probabilistic basis for Bayesian prediction, viz., *degrees of belief* or credence.

Auxiliary hypothesis

We posit that negative psilocybin phenomenologies may not reliably produce the *a priori* predicted genetic effects. Thus, our hypothesis is directional (one-tailed) in the case of a positively valenced psilocybin phenomenology, but bidirectional without any additional specification as we assume that negatively valanced phenomenologies can cause acute stress and anxiety. In the worst-case scenario such experiences (colloquially referred to as "bad trips") can induce lasting psychological traumata.[6] *Ex hypothesi*, negative psychological conditions facilitate telomere attrition [40]. However, from a longitudinal perspective, a *prima vista* seemingly negative psilocybin experience can exert beneficial longitudinal psychotherapeutic/cathartic effects which may take substantial time to unfold (*per analogiam* to the occurrence of various negative side-effects that frequently accompany physiological detoxification which can cause the release of deposited toxins that trigger various seemingly negative side-effects which are in actuality conducive to long-term healing—similarly, psilocybin can render problematic unconscious contents more accessible which may be acutely problematic but conducive to longitudinal improvements of mental health and quality of life). Negatively valenced phenomenologies should therefore be investigated in a nuanced and diachronic fashion to evaluate the psychotherapeutic developmental time course (e.g., by

[1] Mind wandering has been associated with consistently shorter telomeres across different immune cell types, i.e., granulocytes and lymphocytes [28]. The authors concluded that "a present attentional state may promote a healthy biochemical milieu and, in turn, cell longevity."

[2] Contrary to wide spread public *doxa* [109], epidemiological data indicate that psychedelics are not linked to psychopathology or suicidal behaviour [[110], cf. [115]. The mass-media utilized propagandistic/PR methods à la Bernays [117,113] in order justify the governmental "War on Drugs" (initiated by the Nixon administration) which was clearly politically motivated, for instance, in order to target Vietnam war opponents and racial minorities and to serve the "prison-industrial complex" [119,115]. This juridically enforced interregnum interupted the very promising psychedelic research agenda abruptly. One can only speculate how much progress psychedelic science could have achieved in the interim if research would not have been systematically inhibited by irrational polictical factors.

[3] Recently, an anxiolytic function of endogenous tryptamines (i.e., N,N-Dimethyltryptamine) has been hypothesised [see [116]] which may be pertinent for the hypothesis at hand (for instance, persistent stress reduction via activation of the parasympathetic branch of the CNS).

[4] The absence of the middle term in both premises leads to a syllogistic fallacy, i.e., the logical fallacy of the undistributed middle (lat.: *non distributio medii*).

[5] D.M.: From a philological vantage point, the term "deduction" is etymologically derived from the Latin *deducere* "to lead, to derive". Thus, the premises (automatically) *lead* to the conclusion, i.e., the conclusion is logically derived. This methodological approach exemplifies the basis of the deductive-nomological model (Popper–Hempel model) of scientific explanation [117].

[6] The DSM-5® diagnosis "Hallucinogen persisting perception disorder" (HPPD) has been applied in extreme cases (low incidence rate).

employing a longitudinal research design and appropriate analytic procedures such as statistical time-series analysis).

In a generic presentment, the 'psilocybin-telomere hypothesis' can be reformulated in a more relaxed/flexible semantic format as illustrated in Syllogism #2. However, for the sake of specificity (i.e., experimental operationalism/falsifiability) we will focus the subsequent discussion on the more concrete formalisation which focuses exclusively on depression. Moreover, it is hitherto unclear whether psilocybin *per se* is sufficient to induce beneficial neuropsychological effects or if it is generally advisable to combine it with psychotherapy to harness its full psychological potential. The open question is thus: Is psilocybin intrinsically therapeutic (as various indigenous cultures would purport)[7] or is additional psychotherapy indicated to "guide" the process and to facilitate *post festum* integration in order to improve the psychological and medical effectiveness of the intervention? This is an empirical question which should be investigated in a controlled manner. Future research should also elucidate the synergistic effectiveness of psilocybin (cf. [41]) when combined with different psychotherapeutic treatment modalities, e.g., cognitive behavioural therapy, somatic therapy, transpersonal therapy, psychoanalysis, music therapy, meditation, mindfullness training, *inter alia*. We maintain that the transcendental/spiritual phenomenological aspects are pivotal to the therapeutic effects of psilocybin (cf. the etymological meaning of the composite lexeme "psychology"; i.e., derived from the Greek ψυχή *psyche*, hence, in its original root meaning psychology refers to the study of the soul/spirit/breath). However, a genuine appreciation of this reconceptualisation requires a Kuhnian paradigm shift in mainstream scientific thought (viz., a holistic/integral perspective which supersedes dogmatic material reductionism and epiphenomenalism).

Syllogism #2

Major premise:	Beneficial neuropsychological changes positively effect telomere length.
Minor premise:	Psilocybin has quantifiable beneficial neuropsychological effects.
Conclusion:	∴ Ergo, psilocybin positively effects telomere length.

It should be emphasised that we selected depression as a *representative exemplar* to demonstrate a much broader line of thought. Psilocybin has multi-layered effects on psychological health and the predicted genetic/epigenetic effects are thus likely complex and multifactorial and not exclusively restricted to telomeres. However, telomeres are a convenient biomarker which is readily quantifiable with modern laboratory methods (e.g., PCR-based assays). Ergo, the 'psilocybin-telomere hypothesis' allows for the straightforward construction of an *experimentum crusis* (a decisive experiment which allows for direct falsification), i.e., a controlled experiment based on the *ceteris paribus* principle (viz., an experimental design in which all *known* potential confounding variables are rigorously controlled across experimental conditions in an attempt to isolate a cause = > effect relationship between psilocybin and telomeres). For a more synoptic test of the 'psilocybin-telomere hypothesis' enzymatic telomerase activity should be measured and alternative methods to quantify the aging process should be employed. Other "biological clocks" are, for example, transcriptomic predictors, proteomic predictors, metabolomics-based predictors, and composite biomarker predictors [42]. Data indicates that different biomarkers measure different (unrelated) aspects of biological aging [43].

For instance, in addition to telomere analysis, epigenetic clock analysis based on DNA methylation data could be utilised as a complementary measure [44]. Telomere length and the epigenetic clock are independently associated with chronological age and mortality [45] and could therefore be utilised in a cross-validating manner.[8] It has been proposed that DNA methylation age quantifies the "cumulative effect of an epigenetic maintenance system" and that "this novel epigenetic clock can be used to address a host of questions in developmental biology, cancer and aging research" [46] and also questions related to "epigenetic reprogramming and rejuvenation" [47]. Like telomere analysis, epigenetic clock analysis shows correlations with diet, exercise, education, and lifestyle factors.

Evidence in the support of the major premise: Depression is associated with telomere attrition

Numerous studies indicate that depression has quantifiable effects on telomeres [48–50] and animal models support this finding [51].[9] A recent meta-analysis of 83 studies confirmed a significant correlation between depression and telomere length [149]. The pertinent literature indicates a general pattern: Positive mental psychological states have beneficial effects on telomere length while the opposite holds true for negative states such as stress, depression, and anxiety [40,52]. Accumulating evidence thus indicates that depression accelerates genetic aging (i.c., telomere attrition/senescence) and it has been hypothesised that the link between depression and genetic aging is, *inter alia*, mediated by the hypothalamic–pituitary–adrenal axis (HPA axis) [53]. The HPA axis is crucial for the elicitation of stress responses in reaction to a given stressor, e.g., release of the stress hormones cortisol, epinephrine/adrenalin, and norepinephrine. Inflammation is another important interrelated factor in the context of stress, depression, and genetic aging [54]. The exact psychoneuroendocrinological mechanisms are a matter of ongoing scientific debate (for an evolutionary account see [55]). Another important factor associated with depression is oxidative stress [56]. Again, it has been demonstrated that oxidative stress contributes to genetic aging, i.e., it accelerates telomere attrition [57,58]. In fact, inflammatory and oxidative stress biomarkers can be regarded as "peripheral biomarkers" in major depression (for a review see [56]). The role of psilocybin and structurally related tryptamines as anti-inflammatory agents is a topic which recently gained attention [59] and particularly the role of the σ1 receptor in neuroinflammation and neurodegeneration is of interest in the present context.

Alterations in concentrations of various brain growth factors have been associated with stress and depression. Specifically, BDNF (brain-derived neurotrophic factor) has been thoroughly investigated in this

[7] Indeed, indigenous shamanic healers (alias *doctores*) refer to psychoactive plants as immensely intelligent "plant teachers" or "plant healers" [118], a piece of evidence from anthropological linguistics that corroborates the notion that specific plants/fungi possess an inherent therapeutic potential because they are *living* organisms endowed with a *soul* (not merely complementary Watson-Crick base pairs to be manipulated by an omniscient "LaPlacian" scientist). This much older and much more nature-bound "primitive" animistic *Weltanschauung* is fundamentally incompatible with the almost ubiquitously adopted doxastic philosophical axioms of mainstream reductive materialism and its unique myopic perspective on the very question of what constitutes knowledge [119]. For example, attempts to reduce neurochemically induced transformative transcendental experiences to specific synaptic and dendritic molecular processes (e.g., 5-HT_{2A} agonism) may turn out to be a naïve reductionist fallacy—a "*Zeitgeist* bias" that influenced much of 20th century neuroscience in an irrational and prejudiced manner towards a view that (unsuccessfully) attempts to reduce psychology to physics, i.e., it is believed that material processes form the causative foundation of psychology in its entirety (due to a misapplication of the covering law model of explanation). However, the assumption that psychology (and consciousness) can be *in toto* reduced to physics has *de facto* become increasingly more implausible.

[8] The Pearson correlation coefficient with chronological age is $r \approx 0.96$; for telomeres length it is $r \approx -0.53$.

[9] N.B.: For various quasi-Kantian ethical and moral reasons we are categorically opposed to studies which harm or kill animals. Further, such studies are specifically problematic with respect to chemical compounds that alter consciousness as animals presumably lack the complexity of consciousness human beings possess (i.e., a lack of generalisability/external validity).

regard [60] and it appears to be decreased in clinically depressed populations [61–63]. Lower BDNF-levels may be responsible for neuroanatomical changes that accompany depression. Particularly relevant for the hypothesis at hand, it has been suggested that telomerase mediates the cell survival-promoting actions of BDNF [64]. Consequently, it would be of great interest to examine the effects of psilocybin on BDNF concentrations [65] as this might provide basic insights into intermediary biochemical mechanisms that mediate between psilocybin and its postulated effects on genetic aging.[10]

Research indicates that various forms of stress (including chronic rumination as a symptom of depression) set in motion a psychoneurochemical cascade of detrimental effects which negatively affect telomeres [66–68]. Stress magnifies various endogenous inflammatory responses which in turn inhibit telomerase activity (see also [69]). Again, the exact mechanisms are currently a topic of active research (see [6]). It has been hypothesised that exposure to stress activates a broad and complex array of interacting biological mediators which results in the shortening of telomeres [70]. To recapitulate: Stress arousal increases stress hormones, neuroinflammation, and oxidative stress. Thesefactors have been reliably associated with telomere attrition [67,71,72].

There are several protective factors which modulate the detrimental impact of chronic stress. For instance, certain neurosteroid hormones counteract the negative effects of excessively high levels of cortisol. For example, the endogenous steroid hormone dehydroepiandrosterone (DHEA) has been shown to possess antiglucocorticoid properties which offer protection against the deleterious effects of cortisol [73], thereby reducing neurocognitive deficits in depression. Likewise, BDNF induced hippocampal neurogenesis has positive protective effects on chronic stress levels [74–77] and reduces social avoidance [78,79]. Important for the present hypothesis is the empirical finding that psilocybin induces neurogenesis in the dentate gyrus of the hippocampus and that it facilitates fear extinction in animal models [80]. Studies have demonstrated that stress and depression are associated with a reduction of hippocampal volume due to atrophy and loss of neurons [75]. Several studies indicate that hippocampal neurogenesis may be required for some of the cognitive-behavioural effects of antidepressants [81].

Current evidence indicates that plasma BDNF levels are decreased in unmedicated depressed patients and that antidepressant treatment (e.g., SSRIs)[11] can increase BDNF to normal concentrations [82]. In addition to these mediators, there are several moderators which influence the effects of depression and stress on telomeres. Numerous studies have investigated the moderating role of genetic predispositions that are responsible for a heightened vulnerability to various life stressors. Given that personality traits have a strong heritability component (as indicated by twin studies [83]) it is not surprising that some individuals are much more resilient when exposed to stress, compared to others who are hypersensitive and show negative reactions even to minor life-stressors. For instance, meta-analytic research indicates that a specific polymorphism of the serotonin transporter promoter (5-HTTLPR) moderates the correlation between stress and depression [84]. In addition to genetic differences, epigenetic changes are thought to play a moderating role (e.g., via DNA methylation which alters gene expression by inhibiting the binding of transcription factors; see [85]). In contrast to genetic changes, epigenetic changes alter the expression of genes (but, by definition, not the genetic code itself). Epigenetic changes can be reversible and non-reversible depending on specific conditions (also see [86]). We propound that that the psychologically profound “transformative transcendental experiences" that can be occasioned by psilocybin are accompanied by specific/characteristical epigenetic changes. That is, we predict that the qualitative phenomenological aspects of psilocybin are reflected at the epigenetic level, viz., we hypothesise a correspondence between phenomenology[12] and epigenetics.

A landmark study [144] experimentally demonstrated that a single high dose of psilocybin is capable to induce long-lasting personality changes in the basic personality trait “Openness to Experience” (as measured by the widely used NEO Personality Inventory). This finding is very intriguing because there is broad scientific consensus that basic personality traits are relatively stable over time (i.e., a genetic basis is assumed; [145]) and that they can only be altered by major life events (e.g., [146]). Ergo, it is logically cogent to predict that the personality changes induced by psilocybin are paralleled by epigenetic changes. This line of thought connects neatly with the previously presented empirical results. A genetic pilot study [87] found that OTE is related to SERT polymorphism (5-HTTLPR which is associated with SLC6A4, the serotonin transporter gene discussed previously in the context of depression and PTSD). Based on this empirical background it is thus logically sound to assume that psilocybin has epigenetic effects on genes related to serotonin dynamics. Specifically, 5-HTTLPR is a plausible candidate gene given its association with depression, anxiety-related personality traits, and addiction (for a meta-analysis of the moderating role of 5-HTTLPR in stress and depression see [84]). Given that psilocybin has been utilised psychotherapeutically to treat all of these disorders [88] a common genetic mechanism is thus predictable on an *a priori* basis. To recapitulate: We provided evidence which substantiates the major premise of Syllogism #1 (the predicate of the conclusion): Telomere length is a reliable indicator of genetic aging and it has been repeatedly demonstrated that telomeres are affected by psychological conditions such as chronic stress, anxiety, and depression, *inter alia*. In

[10] Given that ≈ 95% of 5-HT in the human body are found in the gut, and given that the functioning of the gut-brain axis has been associated with depressive states, it would be interesting to investigate if psilocybin alters the gut microbiome (which is crucial for the maintenance of physiological homeostasis and brain functioning). Further, it would be of interest to see if this hypothetical correlation stands in any relation with endogeneous neurothrophic brain growth factors (e.g., BDNF/NFG/CNTF/GDNF) and telomeres/telomerase activity. Indeed, the possibility of a peripheral regulatory role for DMT and/or 5-HO-DMT in gastrointestinal function has recently been suggested [120].

[11] N.B.: There are numerous detrimental neuropsychological “side-effects” associated with SSRIs which deserve constant emphasis, specifically given the highly biased lobbyism of “Big Pharma” [126–123].

[12] This line of thought is also revealing from a neurophenomenological vantage point which connects the 17/18th century Husserlian school of thought (defined as German transcendental-idealist philosophy) with the methods and technologies of modern neuroscience [129,125]. This approach emphasises that phenomenology is subject to scientific inquiry and it further highlights the importance of embodiment. Future psilocybin research should attempt to integrate principles derived from the embodied cognition framework into its modelling efforts as current research on psychoactive compounds is almost exclusively brain-centred (i.e., at the level of specific classes of neurons or particular neuronal circuits). This “brain-bias” limits the scope of psilocybin research in an irrational manner. To put it another way, it has been cogently argued that the processes crucial for consciousness cut across the *prima facie* assumed tripartite brain-body-world division which structures most of contemporary science at the most axiomatic level of analysis [126]. This insight might turn out to be a crucial component in order to reconceptualise the adamantine “hard problem of consciousness”—the most fundamental and hitherto completely unresolved scientific problem which has an intrinsic affinity with research on altered states of consciousness. We suggest that the transdisciplinary cybernetic concept of *autopoiesis* [132–129] is of central pertinence in this respect as psilocybin and related tryptamines can facilitate very productive analytic/contemplative introspection on the relationship between percipient and perceived (i.e., subject and object, mind and matter, *psyche* and *physis*). This introspective phenomenological analysis allows for modifications of the *modus operandi* in which information is processed, e.g., modifications of stimulus appraisal (an important factors in depression and anxiety disorders [see [130]). Subjective time perception (time conscientiousness) is a particularly relevant topic in this regard [136,132]. We argue that “intention” is a variable which interacts with the phenomenology (and hence the physiological effects) of psilocybin. This psycho-physical interaction between intention and psychobiology deserves further investigation.

the next section we will provide a synopsis evidence which indicates that therapeutic utilization of psilocybin exerts beneficial effects on various aspects of mental health. We will specifically focus on its postulated effects on depression.

Evidence in support of the minor premise: Psychotherapeutic utilisation of psilocybin reduces depression

Psilocybin[13] has been reliably associated with numerous mental health benefits (e.g., in the context of anxiety, PTSD, OCD, addiction, etc., for a systematic review see [150]). Rapidly accumulating evidence demonstrates that psilocybin significantly reduces clinical symptoms in depressed populations [89–91,93]. Further, it has been reported that psilocybin improves emotional face recognition in treatment-resistant patients [92]. This quasi-interpersonal improvement was statistically significantly correlated with a reduction in *anhedonia*, viz., deficits in the capacity to experience hedonic pleasure (including reduced intrinsic motivation). From a neuroanatomical point of view, the observed reduction of depressive symptoms reported in [93] was associated with increased resting-state functional connectivity (RSFC) within the default-mode network (DMN; 5 weeks post-treatment as per fMRI data). Furthermore, post-treatment response was associated with increased ventromedial prefrontal cortex RSFC and bilateral inferior lateral parietal cortex RSFC, in addition to decreased RSFC in the parahippocampal-prefrontal cortex. Moreover, brain-wide analysis revealed a post-treatment decrease in cerebral blood flow (CBF) in the temporal cortex and the amygdala. Importantly, reductions in amygdala CBF were statistically significantly correlated with a reduction in depressive symptoms. It should also be noted that the fMRI study (op. cit.) demonstrated that the acute effects of psilocybin differ from the longitudinal effects. In the following paragraphs we will primarily concentrate on the involvement of the DMN and the amygdala in depression.

According to the controversial 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-5®) (but see [147]) published by the American Psychiatric Association, one of thefeatures of depression is obsessive rumination/brooding, i.e., repetitive thought patterns that cause long-term organismic stress on multiple levels. *In abstracto*, "Psychological Rumination" can be regarded as a non-somatic analogon to digestive "Rumination Disorder" which involves the repeated regurgitation of food materials over elongated periods of time. Similarly, rumination in depression involves the chronic mental regurgitation of primarily negative emotionally laden psychological materials, i.e., a chronically distressing inward-directed attentional focus that is not actively solution oriented but rather a passive and counterproductive coping-style that is significantly debilitating for the individual ("locus of control" and self-efficacy are important moderating variables in this respect). Ruminative thought patterns are associated with various subconscious cognitive biases that are based on negative, automatic, recyclic, and self-centred cognitions.

It is of pivotal pertinence for the 'psilocybin-telomere hypothesis' at hand that rumination has been associated with telomere attrition [3]. Rumination, in turn, has been associated with hyperactivity of the default-mode-network[14] [94,95]. Experimental studies have demonstrated that psilocybin significantly downregulates DMN activity [93]. Interestingly, a recent experimental study indicated that psilocybin-assisted mindfulness training modulates DMN connectivity with lasting effects [41]. Ergo, we argue that the downregulation of DMN activity is an important neuroanatomical component of the 'psilocybin-telomere hypothesis'. Rumination is a persistent symptom of depressive disorders. Consequently, a reduction in rumination is likely to positively affect telomere length. We suggest that the reduction of rumination is an aspect which is common to psilocybin interventions, mindfulness training, and mediation, i.e., these *prima facie* different methods predict a similar outcome criterion, viz., a reduction in negative repetitive thought motifs. Rumination is a cause for chronic stress which, in turn, is associated with various inflammatory processes and the down-regulation of the immune system, factors that have been associated with shorter telomeres [71,96,97].

Psilocybin can occasion the most profound transformative experiences known to science. For example, in a longitudinal study ≈ 70% of healthy volunteers rated their experience with psilocybin amongst the five most meaningful and significant experiences of their entire live, i.e., the neurochemically induced experience was on average ranked next to the most formative lifetime events such as giving birth to a child or to losing an intimate loved one [99] cf. [98]. We argue that these experiential peak events have a quantifiable genetic counterpart, i.e., the psilocybin-occasioned phenomenological apogee produces a unique quantifiable epigenetic footprint (epigenetically traceable qualia). The underlying logic is based on the supposition that profound psychological experiences are associated with equally profound genetic changes (i.c., in proportion to the phenomenological valence). This ideas is motivated by recent genetic studies which reintroduce quasi-Lamarckian elements into quantitative genetic biology and thereby challenge the "central *dogma* of molecular biology"[15] [100] which was for a long time unchallengeable axiomatic to genetic research. For instance, it has been shown that acquired olfactory conditioning can be epigenetically inherited by subsequent generations (at least up to F2) [101]. The odorant receptor (*Olfr151*) was used to condition F0 mice and subsequent generations (which were utterly naïve to the olfactory conditioning paradigm) revealed CpG hypomethylation in the *Olfr151* gene. We submit that if a simple Pavlovian olfactory conditioning paradigm can cause quantifiable quasi-Lamarckian epigenetic effects, then it is predictable (with a high likelihood) that a profound and life-changing psilocybin experience (cf. Griffiths et al., 2008) has equally quantifiable effects at the genetic level.[16]

[13] In their native language, *Náhuatl*, the Aztecs referred to the *Psilocybe mexicana* fungi specimen as "*Teonanácatl*", a composite lexeme which is etymologically derived from "*teotl*" meaning "god" and "*nanácatl*" meaning "fungus". In the chemical literature psilocybin was also referred to as a "teonanácatl hallucinogens" [e.g., [133]]. Along the same philological lines, the term entheogen has been introduced into the western scientific literature by Ruck et al. [134]. Per definition, an entheogen is a chemical substance used in a ceremonial, religious, shamanic, and/or spiritual contexts that has the potential to produce profound psycho-spiritual insights and changes. The etymology of the neologism "entheo-gen" is a Greek compound lexeme derived from ἔνθεος (*entheos*) and γενέσθαι (*genesthai*) and translates into "generating the divine within" (cf. the cognate term "enthusiasm"). Indeed, the Greek Dionysian Mysteries may be grounded in the utilisation of entheogenic biomaterial. The ecstatic cult of Dionysus involved the consumption of *Kykeon*, a drinkable concoction which potentially included tryptamine-like compounds. The *Kykeon* possibly contained ergot-parasitized barley. The ergot [135] are a fungal parasite of the barley or rye grain, which contains the alkaloids ergotamine and ergonovine, i.e., precursors of LSD-25. The relation between spirituality and aging has recently gained renewed attention [for a review see [136]].

[14] Specifically, various connectivity density differences have been demonstrated which differentiate healthy individuals from individuals diagnosed with major depressive disorder, i.e., more neural functional connectivity between the posterior-cingulate cortex and the subgenual-cingulate cortex during rest periods, but not during task engagement [but see [93]].

[15] The obvious question is: Should science ever be dogmatic? [cf. [137]].

[16] The pineal indole hormone melatonin (*N*-acetyl-5-methoxy tryptamine) is a tryptaminergic structural relative of psilocybin and it has been suggested that melatonin acts as an antioxidant geroprotector [138,139]. For instance, longitudinal supplementation of melatonin increased longevity in *D. melanogaster*. The interactions between psilocybin and the melatonin system are therefore a topic of great interest, particularly in regard to immunosenescence [140] and neuroinflammation [141], but also from a depth-psychological point of view, given the peculiar properties of the photoreceptive "parietal third eye" [142] and its pivotal role in basic circadian regulation (biochronology) and dream-

We suggest that genes associated with the serotonins system (e.g., SLC6A4 gene associated with sodium-dependent serotonin transporter) are a likely genetic locus for planned comparisons (specifically in the context of depression and anxiety). For instance, it has been reported that individuals with specific serotonin transporter (5-HTT) promoter polymorphism (associated with reduced 5-HTT expression) exhibit greater amygdala activity (fear and anxiety-related behaviours) as assessed by BOLD functional magnetic resonance imaging ([102], cf. [103]). Interestingly, it has been experimentally demonstrated that psilocybin decreases amygdala reactivity and that this limbic downregulation correlates with enhancements in positive mood [103]. These effects of psilocybin on emotional processing are specifically relevant for the hypothesis at hand because the central nuclei of the amygdala are involved in the genesis of various fear responses such as the fight flight response, ANS responses such as changes in heart rate, elevation of blood pressure, and neuroendocrine responses such as cortisol release. A topically related study investigated the spatiotemporal brain dynamics of emotional face processing and reported that psilocybin modulates emotional processing presumably via agonism of the $5HT_{1A/2A}$ serotonin receptor subtypes [104].

Taken together, the idea which connects genetic research to psychological research is that cellular mechanisms (e.g., telomeres/telomerase activity) are intimately coupled with cognitive processes (anxiety, depression, mood, stress, etc.). To use a mnemonic "sticky formulation" provided by Professor Elissa Eppel in a lecture at the University of California in 2011: "*Our cells are listening to our thoughts*". We submit that therapeutic utilisation of psilocybin has significant beneficial effects on various organismic levels and, specifically, that the therapeutic effects of psilocybin on the human mind-body complex are of great interest against this empirical background. From our vantage point, neuromechanistic accounts are complementary to metaphysical perspectives on the effects of psilocybin and we will discuss the therapeutic potential of transcendental experiences in forthcoming publications (e.g., discussing the therapeutic value of ego-dissolution/nonduality; see also [148]).

Conclusion

We provided converging empirical evidence from a plurality of sources in order to substantiate the stipulations entailed in the major and minor premises of Syllogism #1. Based on this evidential background, we argue that the 'psilocybin-telomere hypothesis' warrants systematic experimental testing. Specifically, we argue that the convergence of evidence indicates scientific consilience.[17] According to this pivotal meta-scientific concept, strength of evidence increases when multiple independent sources of evidence are in agreement. The generalisability and robustness of converging evidence for a given logical conclusion is a function of the number of different research approaches in support of the conclusion. Furthermore, if equivalent conclusions are reached from multiple perspectives (e.g., different disciplines/theorectical frameworks) this provides evidence in support of the reliability and validity of the utilised research methodologies themselves. Resilience thus reduces the impact of confounding factors (e.g., method related measurement errors) because these errors do not influence all research methods equally. That is, resilience "balances-out" method specific confounds. Perhaps more importantly, the same principle also applies to logical confounds (e.g., logical fallacies and unconscious cognitive biases). In the philosophy of science, this has been termed "consilience of inductions" [105,106]. Inductive consilience can be described as the accordance of multiple inductions drawn from different classes of phenomena. Or, in somewhat more elaborate terms, the "colligation of facts" through "superinduction of conceptions" [107]. The term has recently been adopted within neuroscience (e.g., [108]) where the converge of evidence from multiple (hierarchically arrangeable) sources (molecular, cellular, neuroanatomical, cognitive, behavioural, social, etc.) plays a crucial role for the development of meta-disciplinary (unifying) theoretical frameworks. Following this line of thought, scientific experiments which investigate the effects of psilocybin across multiple levels of analysis and explanation would be of great value. The 'psilocybin-telomere hypothesis' provides impetus for this endeavour as it connects the epistemic and the ontic level of analysis.

Multiple pathways may be involved in the effects of psilocybin on telomeres (neurogenesis, neuroplasticity, downregulation of the default-mode network, modulation of the rich-club architecture of the brain, enhanced functional interconnectivity between various brain networks, anti-inflammatory activity, changes in microbiota, immunomodulation, changes in cognitive and emotional appraisal, improvements in interpersonal relations, transpersonal/spiritual aspects, etc.). From a neurochemical vantage point, the differential involvement of various 5-HT receptor subtypes is naturally of aprioristic interest as serotonin participates in a multitude of physiological/psychological processes. For instance, in order to systematically test for the involvement of the $5\text{-}HT_{2A}$ receptor in the hypothesised effects of psilocybin on telomeres, the non-selective antagonist Ketanserin could be utilised. Repeated (sub-threshold) microdosing of psilocybin is yet another interesting longitudinal research methodology in the context of the hypothesis at hand. Furthermore, the differential effects on telomeres of various cell types should be systematically examined (specifically given the shortening at varying rates). In addition, phenomenological and neurological similarities between meditation and psilocybin should be systematically mapped in the context of genetic aging. Research suggests that states of consciousness induced by meditation and those occasioned by various tryptamines have significantly congruent neurochemical and neuroanatomical correlates. We conclude that future studies that integrate phenomenological aspects of "higher states of consciousness" with quantitative assessment methods have significant potential to advance and deepen our understanding of the interactions between psychological, neuronal, and (epi)genetic processes.

Conflict of interest

The author declares no conflict of interest.

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(*footnote continued*)
states (note that psychoactive phenethylamines and tryptamines such as mescaline, DMT, and psilocybin induce comparatively similar dream-states [see also [143]]).

[17] From a philological point of view, the etymological root of the term consilience is derived from the Latin *consilient*, from *com* "with, together" and *salire* "to leap, to jump". Hence, it literally means "jumping together" (i.e., of knowledge). Scientific resilience is thus semantically synonymous with the expression "concordance of evidence".

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