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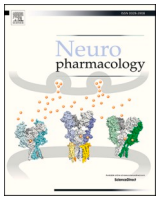

Canalization and plasticity in psychopathology

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ABSTRACT

This theoretical article revives a classical bridging construct, *canalization*, to describe a new model of a general factor of psychopathology. To achieve this, we have distinguished between two types of plasticity, an early one that we call 'TEMP' for 'Temperature or Entropy Mediated Plasticity', and another, we call 'canalization', which is close to Hebbian plasticity. These two forms of plasticity can be most easily distinguished by their relationship to 'precision' or inverse variance; TEMP relates to increased model variance or decreased precision, whereas the opposite is true for canalization. TEMP also subsumes increased learning rate, (Ising) temperature and entropy. Dictionary definitions of 'plasticity' describe it as the property of being easily shaped or molded; TEMP is the better match for this. Importantly, we propose that 'pathological' phenotypes develop via mechanisms of canalization or increased model precision, as a defensive response to adversity and associated distress or dysphoria. Our model states that canalization entrenches in psychopathology, narrowing the phenotypic state-space as the agent develops expertise in their pathology. We suggest that TEMP – combined with gently guiding psychological support – can counter canalization. We address questions of whether and when canalization is adaptive versus maladaptive, furnish our model with references to basic and human neuroscience, and offer concrete experiments and measures to test its main hypotheses and implications.

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1. Introduction

The construct of 'canalization' was introduced in biology in 1942 by British evolutionary scientist, Conrad Hal Waddington, in the context of phenotypic variation in development, where it refers to phenotypic stabilization (Waddington, 1959); see also (Peterson, 2011; Posteraro and Canalization, 2022). Canalization can be used in reference to the development of psychopathology, where it bears relevance to environmental or perturbational sensitivity (Hartman and Belsky, 2016; Belsky and Pluess, 2009), being in this sense, the converse of 'phenotypic plasticity' (Dewitt et al., 1998; Belsky and Pluess, 2013), i.e., increased phenotypic plasticity relates to increased sensitivity, but canalization relates to the opposite of this.

A generalized, standard dictionary definition of 'plasticity' describes it as *the property of being easily shaped or molded*. One definition of neuroplasticity describes it as the brain's 'change capacity': "[neuroplasticity is] the functional and structural reorganization capacity of the brain" (Assaf et al., 2019). If we are true to either, it is apparent that

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canalization is not a good fit. This is because canalization describes how features of the mind, brain, or behavior become less able to change in a non-specific way.

As readers will discover, this distinction is key to the present paper and requires a reconsideration of some popular assumptions regarding plasticity, including a challenge to a traditional, often implicit convention (e.g., in basic neuroscience) of equating plasticity with neuroplasticity – and Hebbian plasticity in particular. Hebbian plasticity can be defined as the principle that neurons or synapses that consistently functionally interact, change their properties in order to facilitate future interactions. To quote psychologist, Donald Hebb, "any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated,' so that activity in one facilitates activity in the other" (Hebb, 1949). This specifically describes the positive i.e., 'potentiation' aspect of what has long been called 'Hebbian plasticity', but we recognize that terms can also be inverted to describe 'long-term depression,' a related mechanism also serving associative plasticity.

1.1. Precision, plasticity, and learning

In a population, for a given 'phenotype' (i.e., a physical, behavioural, or cognitive feature) relevant to psychopathology, we can compute a mean value and a variance around the mean. Such variance can be called 'inverse precision'. An increase in the volatility of a particular phenotype – such as an internalizing style of cognition and behavior (Kotov et al., 2022), over time, or in response to perturbation, would manifest as an increase in phenotypic plasticity and decrease in its 'precision'. In other words, when precision is reduced, the individual is sensitized and able to explore broader regimes of phenotypic state space.

Couched in terms of learning, an increase in phenotypic volatility or plasticity manifests as an increase in *learning-rate* (Iigaya et al., 2018). Trait uniformity or consistency around a mean, despite environmental pressures, would reflect phenotypic canalization, i.e., expressed with high precision, the phenotype is more consistent and resilient. On the role of learning and canalization in evolutionary development - see (Hinton and Nowlan, 1987), and on canalization in habit formation, see (Dickinson, 1985). See also the notion of 'learning traps' and consider how it relates to canalization (Gopnik, 2020).

1.2. A one factor approach to psychopathology

> "*There may be a factor that accounts for meaningful variance across major forms of psychopathology and … research could benefit from probing its origins.*" (Caspi et al., 2014)
>
> Caspi et al. *The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders*?

The aim of the present article is to attempt a new psychological and neurobiological model of a single factor or dimension of mental health or psychopathology (Caspi et al., 2014), inspired by the apparent dialectic between canalization and plasticity. In doing so, we are explicitly treating this 'p factor' as substantive (Levin-Aspenson et al., 2021).

Our general theory states that: cognitive and behavioral phenotypes that are regarded as psychopathological, are canalized features of mind, brain, or behavior that have come to dominate an individual's psychological state space. We propose that the canalized features develop as responses to adversity, distress, and dysphoria, and endure despite, rather than because of, evidence. We also propose that their depth of expression or entrenchment determines, to a large extent, the severity of the psychopathology, including its degree of treatment-resistance and susceptibility to relapse.

1.3. Nosological challenges in psychiatry

For reasons of expediency, measurements in psychiatry have, in the main, been cross-sectional. That is, measurements are rarely longitudinal and neither do they track an individual person's dynamics across extended periods of time e.g., hour-to-hour or day-to-day over periods of months or years. Instead, most major outcome measures, such as patient or clinician rating scales of symptom severity, offer a retrospective and subjective 'snapshot' of the strength of a feature psychopathology in relation to a one-to-four-week period. Accordingly, the ensuing impression is temporally and contextually isolated. It captures the *product* of a process but not how it came to be. This may explain why psychiatry has struggled to explain etiology in terms of a patient's lived trajectory, and as a result, find an effective nosology and accompanying treatments.

1.4. Psychopathologies are acquired but are they adaptive or maladaptive?

We argue that the brain, mind and behavior sometimes develop in putatively 'maladaptive' ways, but still to minimize a variational 'free-energy' (i.e., a quantitative, statistical score of surprise or uncertainty) – which we take to be a universal imperative of all living systems (Friston, 2013) (and see Box 1 regarding 'free-energy'). Thus, psychopathologies remain cognitive and behavioral strategies for minimizing uncertainty; they are not exceptions to this 'free-energy principle' (Friston, 2010). In the sense that they match a universal imperative, we recognize that the styles of thinking and behaving associated with psychopathology may not be intrinsically abnormal or maladaptive.

Thus, we accept that certain cases of psychopathology could be regarded as adaptive (e.g., from the perspective of the individual), given a fuller understanding and appreciation of the adverse contextual conditions out of which the pathology has arisen (Conway et al., 2018; Cleck and Blendy, 2008; Dias-Ferreira et al., 2009; Felitti et al., 2019; Edmiston et al., 2011) – see also (Olthof et al., 2020) and (Sroufe, 1997). Moreover, apparently maladaptive phenotypes may initially have been adaptive for a given context - but critically, have become too entrenched, influential, and insensitive to new or changing conditions, i.e., they become, through canalization, insufficiently adaptive.

In a sense, individuals that develop a psychopathology at any given time are merely obeying a natural imperative to reduce *negatively valanced feeling states*. The colloquial terms 'suffering' and 'pain' are relevant here, as are the more academic constructs of psychological distress and dysphoria. We argue that, while unpleasant, these states are not intrinsically pathological; rather, they are fundamental and universal elements of the human experience.

> "*The First Noble Truth is suffering.*" (Nhât, 1999)
>
> Thich Nhat Hanh. *The Heart of the Buddha's Teaching.*

This universality of states of distress or dysphoria, does not, however, extend to psychopathological *phenotypes*; we argue that these are acquired. Thus, according to our model, pathological phenotypes come secondary to basic feeling states. More specifically, we propose that they are defensive reactions to unpleasant states – featuring e.g., distress or dysphoria. What classifies a psychological or neurobiological phenotype as pathological, is its degree of entrenchment, influence, and resistance to revision e.g., in response to new contexts or evidence.

1.5. Canalization and Hebbian plasticity

Challenging an absolutism regarding the value of Hebbian plasticity for healthy brain development, we propose that pathological cognitive and behavioral strategies for minimizing free-energy can be the product of classical Hebbian learning process that have gone awry. See (Song et al., 2000) and (Sumner et al., 2020a) for a modern account of Hebbian neuroplasticity. Developmental learning - like inter-generational learning (see (Boyd et al., 2011) and (Gopnik, 2020)) - can be generally regarded as a slow process involving the adaptation of the parameters and structure of a person's (generative) world models underwriting

Box 1
Complexity science, free-energy, psychopathology, and psychedelics

This article has taken inspiration from complexity science, dynamical systems theory, and the free-energy principle, but it is not its remit to explain these here. Rather, we refer the interested reader to previous explanations of these frameworks and how they have been applied to psychopathology (Olthof et al., 2020) and psychedelic action (Hipólito et al., 2022; Carhart-Harris and Friston, 2019).

The notion of canalization began with the philosophers Henri-Louis Bergson and Alfred North Whitehead (Peterson, 2011; Posteraro and Canalization, 2022) but was given greater visibility by the evolutionary biologist, Conrad Hal Waddington, who applied it to phenotypic development (Waddington, 1959). In what became known as the 'Waddington Landscape' (Fig. 1), Waddington invites us to imagine a ball rolling down a gradient featuring various valleys of differing depth. Within this metaphorical image, the steepness and depth of the valley or 'canal' walls, is meant to reflect the strength or depth of canalization, encoding phenotypic precision.

Translating this image into a more modern, energy landscape representation, the valleys or canals represent dynamical attractors, whose gravitational pull is also encoded by the steepness of their walls and overall depth. Within a free-energy scheme, the landscape represents a gradient descent, and the steepness and depth of the valleys relates to their precision-weighting, i.e., steep and deep valleys encode precise models. Translating to psychology, we can imagine a valley as representing a cognitive or behavioral phenotype, feature, or 'style', and its depth and steepness is intended to encode its strength of expression, robustness, influence, and resilience to influence and change.

Importantly, these state-space representations are over-simplifications. Moreover, although they depict dynamical phenomena, they remain static images. As is true of living phenomena more generally, the actual reality *is* dynamic, however, and individuals will be able to switch between free-energy minimizing strategies in a context-dependent fashion, as is true of the cycling nature of psychopathology. Dynamical methods will be required to better capture the emergence of different free-energy minimizing processes, in order to better understand their properties and signatures. Fortunately, interesting candidates are already being developed and explored (Eichenbaum et al., 2021), including in the context of psychedelic action (Lord et al, 2019).

perceptual inference and planning as inference, the essence of sentient behavior (Friston, 2022). However, we argue that such developmental mechanisms can go awry in psychopathology, as we shall explain.

Neurobiologically, experience-dependent learning requires synaptic plasticity mediated by experience or activity-dependent changes in neuronal connections strengths (Hebb, 1949). Under the free-energy principle, classical Hebbian plasticity can be cast as Bayesian belief-updating about the parameters of a lived world that correspond to its contingencies and its causal structure. The ensuing parameter updates depend on the precision (inverse variance or volatility) ascribed to sensory transients. The higher the learning rate, the greater potential for the modulation of precision. In a complex, unpredictable world, it may serve an organism's adaptability if learning rate is sufficiently high such that 'mind, brain and behavior' can be appropriately plastic and adaptable (Potts et al., 2020). Indeed, it has been argued before that adaptability is our specie's defining trait – ascribable to our disproportionately expanded transmodal cortex (Fjell et al., 2015; Changeux et al., 2021; Sneve et al., 2019; Buckner and Krienen, 2013; Luppi et al., 2022).

Cast in Bayesian terms, the pathology we have chosen to highlight in this paper pertains to when the precision (or confidence) of prior beliefs (a prediction or model) becomes inappropriately high, leading to a failure of adaptability and the perpetuation of cognitive or behavioural entrenchment. From a purely theoretical and technical perspective, inference and learning can be thought of as a gradient descent (a mathematical optimization algorithm for finding a local minimum i.e., the nearest lowest value, of a differential function) on a variational free-energy landscape. This landscape representation implies that, for every belief state, there is an accompanying free-energy that scores the confidence or certainty of that belief state. As new experiential evidence is garnered, inference and learning typically move belief states in a direction that reduces free-energy (or uncertainty). This developmental direction is encoded by experience-dependent plasticity and learning – and in most cases, it underlies healthy – or even 'wise' development (Moran et al., 2014). However, in certain cases and contexts, the process can 'overshoot' – creating extreme phenotypes that are (too) resistant to change.

Perhaps the most important component of our model is 'precision', which corresponds to the curvature of the free-energy landscape. This is an appealing conceptualization that speaks directly to canalization. In this view, canalization is like a river, carving its own riverbed, where the depth of the eroded valley corresponds to precision and curvature. This means that to be over-canalized in one's sentient behavior is to hold overly-precise beliefs in a specific state-space.

As stated above, canalization is conceptually close to Hebbian learning and plasticity; we appreciate it may be unusual for some to see Hebbian mechanisms equated with pathology, but this is not the first time it has been done (Torregrossa et al., 2011; Ungless et al., 2001; Chistiakova et al., 2014; Luscher and Malenka, 2011; Luscher, 2013; Pascoli et al., 2018). Like normal Hebbian learning, canalization can be regarded as an experience-dependent process that reinforces specific associations. However, our model states that such classical learning mechanisms are recruited in a problematic way in psychopathology. We propose that while the initial learning could be seen as an adaptive response to adversity, distress or dysphoria, the product is maladaptive if it becomes too dominating of a person's future cognitive and behavioural state-space.

1.6. Non-Hebbian (neuro)plasticity

Basic neuroscience has identified and defined types of neuroplasticity other than classical Hebbian-plasticity; examples include: *synaptic scaling* and *homeostatic plasticity* (Turrigiano and Nelson, 2004), *metaplasticity* (Jedlicka et al., 2022; Abraham, 2008), *heterosynaptic plasticity* (Chistiakova et al., 2014), and *critical-period plasticity* (Lepow et al., 2021). All of the above could, and have been, related to the therapeutic action of novel treatments for psychopathology e.g., (Lepow et al., 2021; Kavalali and Monteggia, 2022; Fattore et al., 2018; Nardou et al., 2019), and they are relevant to the mechanisms that we are concerned with here.

However, with the possible exception of heterosynaptic (Olson, 2018) and critical period-like plasticity, mere increases in these types of plasticity may not be sufficient for a therapeutic action and outcome. For example, certain pro-plasticity drugs have been shown to augment stimulus-induced Hebbian plasticity (Sumner et al., 2020b) – which is an example of a metaplastic action i.e., increasing the ease or rate of Hebbian plasticity. Synaptic scaling is generally thought to preserve synapse-specific weighting (Kavalali and Monteggia, 2022) – and thus, the products of Hebbian learning. Reactivated critical period plasticity (or increased learning rate) combined with adverse or trauma-related conditions, could drive aberrant learning mechanisms enroute to

iatrogenic outcomes (Brouwer and Carhart-Harris, 2021). Indeed, given that acute stress has been found to increase neuroplasticity markers in the cortex and aid learning (Brivio et al., 2020) (see also (McEwen, 2019) and (Epel, 2020)), one can conceive how an initial increase in a nonspecific type of plasticity (such as heterosynaptic or critical period plasticity) could be hijacked by Hebbian mechanisms to canalize cognition or behavior in a particular way. See (Brouwer and Carhart-Harris, 2021; Timmermann et al., 2022) for a relevant discussion.

1.7. TEMP and neural annealing

At this point, we are compelled to add an essential qualifier to a potentially fallacious assumption that increases in (an undefined) plasticity are intrinsically health-promoting, salutogenic or therapeutic (see also (Dewitt et al., 1998) and (Brouwer and Carhart-Harris, 2021)). The computational construct we wish to invoke here is that of 'simulated annealing' (Kirkpatrick et al., 1983), see also (Gómez-Emilsson, 2021). Our model states that an effective intervention for psychopathology should, through an acute action analogous to an increase in system temperature or entropy – as per the Ising model (Suzuki et al., 2007; Ruffini et al., 2022) (see also (Singleton et al., 2022a)), trigger a downstream sub or post-acute effect that is analogous to a rebalancing or recalibration of synaptic weights, i.e., a counteraction to canalization.

To aid the construction of this model and its subsequent testing, we have felt it necessary to introduce a new construct that we call 'Temperature of Entropy Mediated Plasticity' or 'TEMP'. To be more concrete, we propose that increases in the complexity or entropy of on-going neural ensemble activity indexes a key early phase of TEMP (Schartner et al., 2017; Carhart-Harris, 2018; Mediano et al., 2022) (see also (Ruffini et al., 2022)). Moreover, we have also created a novel measure to index the psychological counterparts of TEMP – i.e., in this case, decreased confidence in prior assumptions or beliefs (Zeifman et al., 2022). Indeed, this measure could be used to index the degree of precision (confidence) of strongly held beliefs relevant to a person's particular pathological presentation. Critically, this measure will also allow us to quantify intervention-induced changes in belief precision or confidence. The schematic shown in Fig. 2 offers a general (neuroimaging-centric) experimental approach for assessing the effect and consequences of an increase in TEMP.

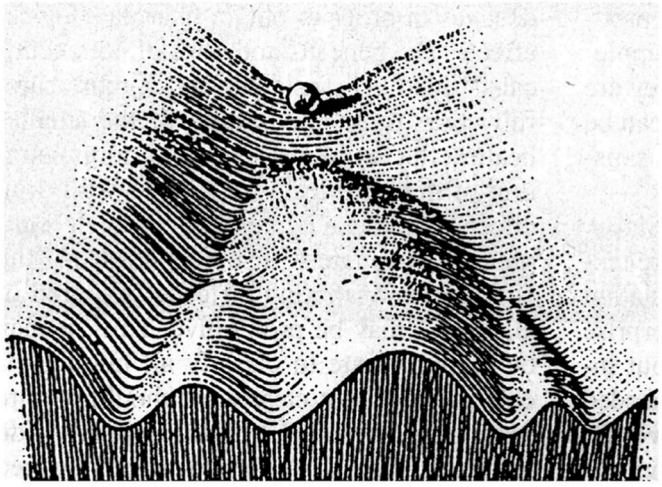

Fig. 1. The 'Waddington Landscape' – first introduced in 1957 (Waddington, 2014). In our scheme, the depth and steepness of valleys encodes the precision of beliefs. The implied gradient descent of the ball symbolizes the implied trajectory toward canalization. This image can guide our conceptualizing of development on multiple scales and in multiple domains, speaking to the value of canalization as a powerful bridging construct e.g., for translating between psychology and biology. In a similar way, computational (Corlett and Fletcher, 2014) and complexity science approaches (Hipólito et al., 2022) offer appealing methods for translating between disciplines within psychiatry, including psychology and biology.

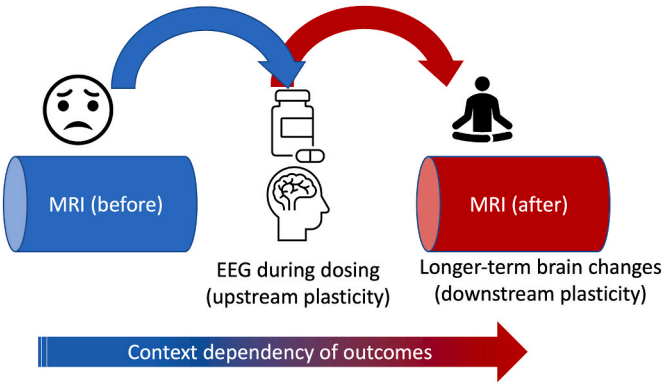

Fig. 2. A simple neuroimaging protocol for assessing the hypothesized action of interventions capable of triggering measurable plasticity processes. EEG is a powerful modality due to its affordability, tolerability, temporal resolution, usability and translatability across populations and species. See (Schartner et al., 2017; Zeifman et al., 2022) and (Mediano et al., 2022) for some strong candidate markers of early, upstream plastic effects – which we refer to as 'TEMP'. EEG could be replaced by other indices of population level activity such as local-field potentials, in non-human animal experiments. MRI approaches are well-suited to pre versus post intervention scanning, where they can be used to detect both functional and anatomical brain changes e.g., (Lyons et al., 2022).

We are intrigued to speculate that heterosynaptic plasticity (Chistiakova et al., 2014) – seemingly the type of plasticity induced by the synaptogenic effect of psychedelics (Ly et al., 2018; Shao et al., 2021) – occurs downstream of an initial increase in the entropy of on-going (e.g., cortical) neuronal ensembles. Indeed, if this link was to be empirically established, it would contribute to validating the construct of 'Temperature or Entropy Mediated Plasticity' or 'TEMP'.

Returning to the model of annealing, transient increase in TEMP can be conceived of as enabling neuronal representations of belief states to escape entrenched minima or 'canals' that constitute the free-energy landscape such that they can explore other free-energy minima or phenotypic possibilities. Note, precision is often associated with an 'inverse temperature' parameter in this setting, see Box 1 – and (Schneider and Sagan, 2005). Importantly, in the annealing model, increased temperature will have an acute and later phase carryover effect, equivalent to rebalancing the landscape by reducing its average skew or curvature, i.e., its precision. In this way, increased temperature would alter not just the energy or exploration rate within a state space, but also the shape of the space itself, i.e., after the system has 'cooled'. Indeed, this two-phase process of heating and cooling to change a system's structure is the essence of annealing.

Thus, according to our model, a transient increase in TEMP within a system should help rebalance its global state-space (Singleton et al., 2022b; Daws et al., 2022). Here, we invoke the analogies of 'wiping the slate clean', 'starting afresh' or 'rebirth'. The idea is that by 'heating' the system, its corresponding free-energy landscape, underwriting neuronal dynamics and accompanying belief precision, will be effectively flattened (e.g., see (Singleton et al., 2022b; Girn et al., 2022)). Moreover, if we translate this to psychopathology, the existence of a skew, deformation, or bias in the system state-space - i.e., reflecting excessive precision on a specific domain within it, will imply that it is sensitive to the flattening effect of an increase in TEMP (e.g., see (Zeifman et al., 2022)).

This process may depend on how the acute entropic action relates to increased post-synaptic gain in deep-layer pyramidal neurons translating into an enhanced sensitivity to bottom-up signaling or prediction error (Carhart-Harris and Friston, 2019) - i.e., the essence of belief-updating and a major component of psychological 'insight' (Peill

et al., 2022) and gains in learning (Friston, 2010).

Consistent with conventional wisdom for psychedelic psychotherapy (Richards, 2015), allowing such a process to play out in a supportive (e.g., 'gently guiding' (Timmermann et al., 2022; Murphy et al., 2021)) environment, both acutely and post acutely, may be most conducive to positive therapeutic outcomes (Murphy et al., 2021; Carhart-Harris et al., 2018a; Melanson et al., 2022). Post-acutely, Socratic questioning (Braun et al., 2015) and inquiry (Hook et al., 2021) may aid patient realizations by challenging canalized beliefs.

1.8. Is canalization intrinsically 'bad', and plasticity, intrinsically 'good'?

The answer here is, of course, "no". In the same way that Hebbian plasticity is essential for healthy learning and development, so is canalization and consolidation of "well-trodden paths" – see also (Moran et al., 2014). Thus, we must address *why* and *when* canalization can become maladaptive. To provide a meaningful answer to this, information is needed on: 1) the nature of the phenotype that is canalized; 2) the extent to which it is canalized; 3) the context in which processes of canalization first occurred; and 4) whether that current context has changed.

1.9. Some specific examples of pathological canalization

Let us consider the example of negatively biased cognition, a common aspect of the 'internalizing' phenotypic style (Kotov et al., 2022), and a hallmark of major depressive disorder (Beck, 1971) – one of the most prevalent psychiatric disorders (Sansone and Sansone, 2010). Here, our formulation states that negatively biased cognition is a canalized phenotype, i.e., it is a cognitive style that a person can develop after a psychological 'injury' (or non-distinct injuries), and that can reinforce over time, with (implicit) practice, such that it is progressively easier to enter.

Figuratively speaking, for the 'internalizer', belief-updating has 'fallen into a rut' (Holtzheimer and Mayberg, 2011); this person's thinking and/or behavior has become entrenched in overly precise beliefs; they 'go there', likely because, given their experiences and circumstances (Maté, 2010), it once made sense – or still makes sense (at least implicitly) - for them to do so. However, if deeply ingrained or allowed to reinforce over time, this canalized style will dominate the individual's phenotypic state-space and be difficult to escape or undo – and when it is left, it will be easy to return to (Holtzheimer and Mayberg, 2011). Indeed, technically, the regimes of belief space that become canalized constitute an 'attracting' set, i.e., they attract or 'pull-in' (confirming) evidence.

Sufficient contextual information would be required to understand whether and why canalization of a given phenotype once provided, or continues to provide, an adaptive function - even if only implicitly (e.g., see (Fisher et al., 2017)). The prevalence of internalizing traits and their apparently high loading onto 'p' (Kim and Eaton, 2015) could be interpreted as implying that 'dark rooming' (Friston et al., 2012a) is a particularly common strategy for minimizing free-energy in response to adversity and distress. In a sense, the individual may (implicitly) 'dark room' because it is intolerable 'out there', and an alternative to harmful (e.g., aggressive) acts, such as suicide.

This internalizing type of canalization is particularly pernicious because reshaping the phenotypic landscape requires an updating of prior beliefs with new sensory evidence. However, avoidant phenotypic styles will preclude exposure to new experiences that could guide the process of narrative revision. Such a picture is familiar one for cognitive behavioral therapy that aims (e.g., through cognitive restructuring and exposures) to challenge prior beliefs by providing contrary evidence to certain prior convictions: e.g., "if I do this or that — or forget to do this or that — some awful thing will happen".

1.10. Generalizing the model to other examples of pathological canalization

One could easily translate the above formulation into another major spectrum of psychopathology – the externalizing dimension (Kotov et al., 2022). Various styles of cognitive and behavioral addictions, such as cravings and compulsions, can be conceived of as involving Hebbian learning 'gone wrong' (Ungless et al., 2001; Ostroumov and Dani, 2018). In a purely psychological sense, the external objects of 'relief' or 'escape' in addiction, come to entice and enslave thought and behavior (Maté, 2010).

"*When I was using, I had tunnel vision.*" (Maté, 2010)

Gabor Mate. *In the Realm of Hungry Ghosts.*

As with 'depressive dark rooming', the 'addictive strategy' could be seen as adaptive, if it works to effectively minimize free-energy in a psychosocial milieu that engenders intolerable suffering (Maté, 2010). This free-energy minimization might be most effective within a brief time horizon, e.g., by inducing a transient emotional escape (Fernandez-Rodriguez et al., 2018), but such relief may still represent a logical option for a person not otherwise able to tolerate their experiences (Maté, 2010). Again, the pathological style could be seen as adaptive for the individual – at least in the short-term, yet dissonant with, and potentially threatening to, community norms and values. In other word, the psychopathology may be Bayes-optimal for a person with a particular history; however, their emergent prior beliefs may nevertheless dissonate with new contexts or diverge from community norms and values in a way that is harmful for the individual or the community (Wakefield, 1992) – yet they 'cannot help it'.

Several other cognitive and behavioral strategies for minimizing free-energy across psychiatric diagnostic categories can be identified (Ainley et al., 2012, 2016; Limanowski et al., 2017; Parr et al., 2018; Limanowski, 2022; Fotopoulou and Tsakiris, 2017; Duquette, 2017). For example, in body-image and eating disorders, image becomes canalized in a distorted way (Riva and Gaudio, 2012) and there is excessive cognitive and behavioral control – typified by caloric control in anorexia. Obsessions and compulsions in obsessive compulsive disorder (OCD) are characteristically repetitive and canalizing. Context-specific triggers in anxiety and stress or trauma-related disorders, including post-traumatic disorder (PTSD), also speak to runaway Hebbian mechanisms (Chistiakova et al., 2014). Again, it's easy to appreciate how certain cognitive and behavioural manifestations may seem appropriate for extreme environments such as military combat, but clash with the norms and values of civilian or post-military life.

Although rarer by prevalence (Sansone and Sansone, 2010), in addition to the internalizing and externalizing dimensions, the spectrum of 'thought disorder', which includes psychotic disorders, is not excepted from our formulation. Entrenched delusional complexes fit the principle of free-energy minimization (Lyndon and Corlett, 2020), again via a strategy that could be felt (by the individual) to be functional (if not essential) for them – but nevertheless remains intensely dissonant with, and potentially threatening to, community norms and values (Leader, 2011). A somatoform category, incorporating functional neurological syndromes such as fibromyalgia and chronic fatigue syndrome, as well as hypochondriasis, is also captured by our formulation. This category encompasses cases in which organic causes of physical symptoms are difficult to identify and isolate, yet come to consume thought and behavior, and can, like so many 'disorders', become inculcated into self-schemas (Edwards et al., 2012).

Some more challenging cases for our canalization model of psychopathology include symptoms of a disinhibition – such as in attention deficit hyperactivity disorder (ADHD) and psychotic disorders. Bipolar disorder is a particularly interesting case, as it straddles internalizing, thought disorder and externalizing dimensions (Kotov et al., 2022).

Returning to an earlier point regarding the cross-sectional nature of

psychiatric diagnosis, the symptoms associated with diagnostic categories may be more accurately regarded as dynamic, phenotypic products of (arguably easier to measure) state-specific phenomena, which clinicians usually do not have sufficient information about due to an absence of individual patient-level longitudinal information – but see (Fisher et al., 2017) and (Fortuna et al., 2022; Bos et al., 2022; Yerushalmi et al., 2021; Jones et al., 2021). A category like bipolar disorder features highly distinct states that are typically cycling, thus more state-sensitive measures are required to capture its mechanisms (Fortuna et al., 2022; Bos et al., 2022; Yerushalmi et al., 2021; Jones et al., 2021).

Regardless, we adopt the position that all of the relevant cognitive and behavioral presentation within a categorical palette or dimensional spectra of psychopathology are consistent with the free-energy minimizing imperative of all living systems (Ramstead et al., 2018). For example, in bipolar disorder, the agent oscillates between a depressive 'dark room', and a frenzied high-energy search; all done for same 'purpose' of minimizing distress or uncertainty. Indeed, notions of 'manic defense' (Baruch, 1997) can extend to other transient states of psychological instability – such as intense emotionality in certain personality disorders, where the individual seeks to suspend distress or uncertainty e.g., via projective or splitting defense mechanisms aimed at simplifying a psychosocial milieu that is experienced as overwhelming, ambiguous, or threatening – e.g., see (Herzog et al., 2022) for a relevant discussion.

It is tempting to speculate that high arousal 'hot states' interact with Hebbian mechanisms to canalize defensive responses, making them easier to find in the future; a process akin to kindling (Young and Dulcis, 2015). Such a process would be consistent with a metaplastic development of pathological habits, whereby endogenous processes involving elevated stress (Brouwer and Carhart-Harris, 2021; Brivio et al., 2020) and increase system TEMP are hijacked by Hebbian mechanisms. In such cases as acute psychoses in psychotic disorders, the 'hot states' may paradoxically represent endogenous efforts to escape local minima 'carved' by canalization – as has been discussed here (Brouwer and Carhart-Harris, 2021); however, because extreme stress and distress typically accompany extreme adversity, it is more likely that the surrounding context is traumatogenic than therapeutic.

Thus, to summarize, according to our model, symptoms of psychopathology are canalized phenotypes, i.e., over-potentiated styles of thinking or behaving that develop as defensive responses to unpleasant states featuring distress or dysphoria. They come to dominate an individual's global psychological state space; they are compelling, difficult to give-up, easy to fall into and resistant to revision.

1.11. When is canalization not pathological?

What of the devoted expert, religious person, political activist, obsessional academic, artist or sportsperson? Do these individuals not exhibit canalized thought and/or behavior? Indeed, it would not be difficult to pathologize some cases, but in-and-of themselves, they do not necessarily meet criteria for psychopathology.

According to our model, an accurate determination of pathology requires information on the context in which the phenotype first arose, the contemporaneous context in which it exists now, and whether it could be deemed to be harmful to the individual or the larger community in which the individual resides. For example, within a micro-community of unhoused individuals with drug addictions, the individual's addictive behaviors will not be abnormal, yet they will nevertheless diverge from the norms and values of the wider community and be regarded as generally harmful, both to the individual and the broader community (Wakefield, 1992).

In the case of a resolute expert, their canalized skillset may be valued – if not admired – by the wider culture. Ironically, their expertise, and perceived need to maintain it, may nevertheless draw them away from other precious micro-communities, such as their family. A 'monomaniacal' dedication could easily spillover into pathology if the individual cannot resist its pull in order to be available for 'other things'. Rigid perfectionism, ruminative deliberation and workaholism are all relevant in this regard, which, while naturally dimensional, become pathological by way of degree and context appropriateness – as well as via the potential recruitment of 'comorbid' ancillary symptoms that are more classically recognized as pathological.

Thus, the question of whether or not a canalized phenotype is pathological, relates to the degree to which it endures or enslaves the individual, constricting and dominating their global psychological state space, while clashing with new situations and evidence as well as wider societal norms and values. For example, a devoted religious person or meditator may retain hobbies, interests and inter-personal relationships that are extraneous to their life of practice, whereas an addicted person may become consumed by their object(s) of addiction, such that their capacity to be engaged and rewarded by anything else, is severely depleted.

1.12. Psychedelic therapy for psychopathology

> *"Factors that make treatments effective can give insight into the cause of a condition."* (Andrews and Thomson, 2009)

Andrews & Thomson. *The bright side of being blue: depression as an adaptation for analyzing complex problems.*

One approach for assessing the usefulness of our model is to ask: *how can we most effectively treat a presentation defined by problematic canalization*?

Here, we make special reference to psychedelic therapy. There is growing evidence from controlled (Carhart-Harris et al., 2021), naturalistic observational (Nygart et al., 2022) and population studies (Hendricks et al., 2015) of robust and diverse improvements in mental health outcomes after psychedelic use. By 'psychedelics' we are referring to direct serotonin 2A receptor (5-HT2AR) agonists such as psilocybin/psilocin and related drugs. If we focus on gold-standard criteria for quality evidence, i.e., from randomized controlled trials, there is consistent evidence of rapid and sustained improvements in depression, anxiety and addiction disorder symptoms, typically after just one or two administrations of a psychedelic alongside psychological support – e.g., (Carhart-Harris et al., 2021).

Buoyed by the promising nature of these findings and related industry investment, psychedelic therapy trials are now underway in obsessive compulsive disorder, various addiction disorders, eating and image disorders, functional neurological syndromes, various anxiety disorders and several other conditions. After promising phase 2B results of psilocybin therapy for treatment-resistant depression (Goodwin et al., 2022), phase-3 licensing trials are set to read out and challenge for regulatory approval in coming years. The development of related interventions — e.g., MDMA assisted psychotherapy (Mitchell et al., 2021), and ketamine (Alnefeesi et al., 2022), is even more advanced.

Does this purposeful activity reflect an optimism overshooting evidence? It seems appropriate to acknowledge that media hype surrounding psychedelic medicine has created high expectations (Yaden et al., 2022). Nevertheless, we propose that a compelling rationale underlies the psychedelic therapy paradigm – including the notion that the intervention can be transdiagnostically effective (Kocarova et al., 2021).

Here, as elsewhere (Carhart-Harris and Friston, 2019), we argue that the core therapeutic action of psychedelic therapy is the relaxation of inappropriately precise beliefs underpinning pathological phenotypes, thereby facilitating (re)learning mechanisms that can generate a healthy recalibration of an individual's psychological state-space. However, we extend this model by further invoking the process of simulated annealing (Kirkpatrick et al., 1983), whereby a direct entropic action on spontaneous cortical activity is followed by downstream synaptic reweighting, effectively de-weighting relevant phenotypes – speculatively, by increasing heterosynaptic plasticity (Chistiakova et al., 2014). Some candidate neuroimaging metrics may also be sensitive to the

effects of this process (Ly et al., 2018; Shao et al., 2021; Moda-Sava et al., 2019; Jones et al., 2009).

1.13. Psychedelics and plasticity

There is converging evidence that serotonergic psychedelics, historically referred to as 'classic' psychedelics, elicit their characteristic behavioral effects via agonism of the 5-HT2AR, potentially via biased signaling (Kim et al., 2020; Kaplan et al., 2022). It has been implied that the promotion of (downstream) anatomical markers of plasticity — such as the growth of new synaptic spines — may be necessary and sufficient for achieving therapeutic outcomes via psychedelic therapy (Vargas et al., 2021). Psychedelics, and 5-HT2AR agonism more specifically, have been found to promote the expression of plasticity genes (Desouza et al., 2021), brain derived neurotrophic factor (BDNF) (Vaidya et al., 1997) as well as spine formation in vitro (Ly et al., 2018; Jones et al., 2009) and in vivo (Shao et al., 2021), with especially robust and reliable effects seen in the cortex (Vaidya et al., 1997; Mason et al., 2020) – see (Calder and Hasler, 2022) for a review.

When viewed through a lens of simulated annealing, other neuronal phenomena such as *increased*: asynchronous glutamate release (Aghajanian and Marek, 1999), expression of neural activity markers (Gresch et al., 2002), complexity of spontaneous oscillatory activity (Schartner et al., 2017), entropy of connectivity motifs (Tagliazucchi et al., 2014), high-frequency harmonics (Atasoy et al., 2017), near (Toker et al., 2022), or supercritical dynamics (Ruffini et al., 2022) sensitivity to perturbation (Jobst et al., 2021), and global integration (Tagliazucchi et al., 2016) – can all be linked to either an *early*, upstream temperature or entropy increase (Schartner et al., 2017) or a *later,* downstream synaptic reweighting effect – e.g., as implied by preclinical data (Shao et al., 2021; Daws et al., 2022; Moda-Sava et al., 2019; Raval et al., 2021).

Future research could examine the link between these distinct phases of a hypothesized annealing process. Relevantly, a recent multimodal healthy human imaging study found increased brain entropy under the effects of high-dose psilocybin and decreased prefrontal cortex-to-subcortex white matter diffusivity one-month later (Lyons et al., 2022). The increase in brain entropy was predictive of long-term improvements in psychological well-being.

The classic serotonergic psychedelic, LSD, has been shown to accelerate learning rate in rabbits via a 5-HT2AR-dependent action (Harvey, 2003), and an increase in learning rate was recently observed in humans under LSD (Kanen et al., 2022). See also (Buchborn et al., 2014; De Gregorio et al., 2022). These findings are complemented by other human studies highlighting *acute increases* in: sensitivity to music (Kaelen et al., 2015) and hypnotic suggestion (Carhart-Harris et al., 2015) under serotonergic psychedelics; plus *sub-acute increases* in cognitive flexibility (Murphy-Beiner and Soar, 2020; Doss et al., 2021); and *long-term changes* in: personality structure (Weiss et al., 2021a, 2021b; Erritzoe et al., 2019; Carhart-Harris et al., 2016), political perspective (Nour et al., 2017; Lyons and Carhart-Harris, 2018), and philosophical (Timmermann et al., 2021) and religious belief (Griffiths et al., 2019); as well as *long-term improvements* in nature relatedness or connectedness (Nour et al., 2017; Lyons and Carhart-Harris, 2018; Forstmann and Sagioglou, 2017), psychological flexibility (Agin-Liebes et al., 2022; Davis et al., 2020; Close et al., 2020), and generic and specific mental health outcomes (Nygart et al., 2022; Mans et al., 2021; Carhart-Harris et al., 2018b).

In many cases, these psychological changes could be viewed as consistent with a rebalancing of a skewed psychological state space – i.e., a 'resetting' (Carhart-Harris et al., 2017) type effect. However, this rule is not absolute, and concerns have been raised over the possibility of exploiting early plasticity mechanisms to instill or reinforce certain beliefs (Brouwer and Carhart-Harris, 2021). The latter scenario would be an example of a drug-induced metaplastic action, where increased TEMP is hijacked to serve canalization rather than recalibration. We believe that such deliberate shaping of phenotypic presentations, as opposed to a rebalancing of global dynamics, is more the exception than the rule, however, but nevertheless remains a risk with pro-plasticity interventions (Safron, 2020) – see also (Timmermann et al., 2022).

1.14. REBUS model

The RElaxed Beliefs Under pSychedelics (REBUS) model (Carhart-Harris and Friston, 2019) is inspired by the free-energy principle (Friston, 2013) - and the 'the entropic brain' hypothesis (Carhart-Harris, 2018; Carhart-Harris et al., 2014). The main tenet of REBUS is that psychedelics decrease the precision-weighting (i.e., inverse variance or 'confidence') of internal predictive models (i.e., 'beliefs' or 'priors') encoded in brain activity. More specifically, REBUS proposes that precision-weighting on priors is decreased *under* psychedelics; effectively flattening the free-energy landscape.

Indeed, REBUS maintains that relaxed model precision is the basic *acute* action of psychedelics, which, within the free-energy framework, is implied by their entropic action – and *vice versa*. Supportive evidence for REBUS was outlined in the foundational paper (Carhart-Harris and Friston, 2019) and more evidence has accrued since (Girn et al., 2022; Alamia et al., 2020); including a recent finding of decreased self-rated 'confidence' in negative self-beliefs after an inaugural high-dose psychedelic experience; an effect explained and predicted by increased entropy in EEG recordings of spontaneous scalp potentials (Zeifman et al., 2022) – see also Fig. 2.

The REBUS model relates well to the canalization model of psychopathology (or 'CANAL', for short), presented here. The former is specific to the action of psychedelics, whereas the latter has evolved from this specific application to appeal beyond it, i.e., to the notion of a single dimension of 'psychopathology' (Caspi et al., 2014) and how this might be understood and treated. The two models are consistent, in the sense that REBUS offers a mechanistic explanation for how psychedelic therapy can 'treat' canalized phenotypes, i.e., the model states that via a drug-induced entropic action, psychedelics plasticize reinforced patterns of cognition and behavior.

The combination of REBUS and CANAL can help to explain the putative transdiagnostic efficacy of psychedelic therapy (Kocarova et al., 2021), and it also inspires speculations about psychiatric symptoms that may be *especially* amenable to psychedelic therapy; i.e., those that most compellingly fit the model of pathology by canalization. The examples considered above include reinforced or entrenched cognitive and behavioral styles or biases. More specifically, ruminative, obsessive, controlling, compulsive cognitive and behavioral styles – such as are exhibited in anxiety and mood disorders, OCD, addiction disorders, and eating and image disorders, somatic syndromes, and presentations of delusion. As we search for an underling mechanism for the principal component to psychopathology (Caspi et al., 2014), it should not be lost on the reader that the list just provided is relevant to the most prevalent psychiatric disorders.

Despite meshing well with psychedelic therapy, our model may, however, also invite reflections on cases where psychedelic-use would be risky. For example, we speculate that cases exhibiting high cognitive and behavioral *instability* — or implying special risk for psychological *decompensation* (Kluft, 1996) — may be contraindicated for psychedelic use, if not psychedelic therapy. The reason being that the entropic or TEMP increasing action of psychedelics may precipitate or augment a psychological instability that cannot be sufficiently well tolerated or recovered from, particularly when there are constraints on the quantity and quality of care available for guiding healthy re-learning. Granted, destabilization in the psychotherapeutic process (Olthof et al., 2020) has been found to predict sudden therapeutic gains (Shalom and Aderka, 2020) – but this principle may be precarious in severe psychopathologies, where there is a threat of decompensation.

A speculative list of especially challenging or risky presentations for psychedelic therapy includes: the at-risk mental state, early or acute

psychosis, schizophrenia, certain personality disorders and bipolar 1 disorder. Our unpublished research also suggests that young age may be a risk factor for certain potential side effects that have been linked to psychedelic-use (Zhou et al., 2022). Future research is required to test hypotheses that, e.g., personality and bipolar disorders are contraindications for psychedelics, or whether an adapted version of psychedelic therapy, e.g., using a more customized and prolonged treatment protocol — with more extensive psychological support and sophisticated dosing — could yield a positive cost-to-benefit ratio.

1.15. Testing CANAL

The CANAL model is speculative and must perform well under testing to establish its value. Despite notable initiatives to discover brain biomarkers of specific psychiatric symptoms (i.e., Research Domain Criteria or R-DoC), results have been largely disappointing (Weinberger et al., 2015). There could be several reasons for this, some of which may relate to cross-sectional sampling, questionable nosology and the "ubiquitous non-specificity" problem within psychiatry (Caspi and Moffitt, 2018).

Briefly, we can list some more specific potential explanations for failures in the discovery of biomarkers of psychopathology: high heterogeneity of symptoms within a given (e.g., sum scored) diagnostic category (Fried and Nesse, 2015; Fried et al., 2022), poor psychological measurement of the focal feature of psychopathology (Fried et al., 2022; Fried, 2017), high comorbidity between psychiatric disorders (Newman et al., 1998), unimpressive diagnostic reliability (Chmielewski et al., 2015), high inter-subject variability in brain function (Mueller et al., 2013), high diurnal intra-subject variability in psychological presentation (Shiffman et al., 2008), an inability to capture pathological states due to an absence of regular and longitudinal monitoring (Shiffman et al., 2008), as well as an absence of symptom provocation paradigms (D'Souza et al., 1999) or other emotionally engaging stimuli capable of 'drawing out' relevant phenotypes (Finn and Bandettini, 2021).

To propose one general psychopathological factor ('p') was to do something bold and disruptive (Caspi et al., 2014). The same is true of proposing a unified psychological and neurobiological explanatory model of 'p'. Our model rests, to a large extent, on the legitimacy of 'p' – and thus, we refer the interested reader to the original text that introduced the notion (Caspi et al., 2014) - as well as other appraisals (Levin-Aspenson et al., 2021; Kelley et al., 2019; Lahey et al., 2012; van Bork et al., 2017) and supportive evidence (Selzam et al., 2018; Brainstorm et al., 2018; Goodkind et al., 2015; Sha et al., 2019; Elliott et al., 2018; Barch, 2017; Menon, 2011; Patalay et al., 2015). The CANAL model is intentionally parsimonious. There are natural strengths and weaknesses to parsimonious models (Ruffini and Lopez-Sola, 2022). Put simply, a useful model should explain a lot with few parameters (Ruffini and Lopez-Sola, 2022), and if it can do this, it will be a powerful data assimilation tool. It will not however, explain everything, but that is not its purpose.

To test CANAL, we must move out of the abstract and into the concrete. In what follows, we hypothesize some specific features of both the *process* and *products* of canalization, and we consider experimental manipulations that could up or down-regulate the relevant features. If entrenched canalization is a useful model of psychopathology, then intentionally up-regulating it could be regarded as unethical. Symptom provocation paradigms are relevant in this regard, but naturalistic sampling — e.g., in longitudinal studies — can track disease progression without intervening on it (Bos et al., 2022).

Many animal models of psychopathology do, however, aim to induce 'pathological' presentations. The most classic method for this is the chronic stress paradigm (Duman and Duman, 2015). Drug reinforcement learning is another classic method, in this case for modelling addiction processes (Robbins and Everitt, 2002). With drug-reinforcement, we recognize an important role for dopaminergic modulation in potentiating reward learning and thus, canalization (Ungless et al., 2001; FitzGerald et al., 2015; Dobi et al., 2011), and the potential for serotonergic neuromodulation to counteract this (Walsh et al., 2018; Li et al., 2021; Boureau and Dayan, 2011) – see also (Bogenschutz et al., 2022; Johnson et al., 2014). We regard these pre-clinical paradigms as valid and useful models of the canalization processes that underlie the development of human psychopathologies. Aberrant learning mechanisms are readily apparent in these models (Ruan and Yao, 2017; Seligman et al., 1968). We are, however, also mindful of the limitations of rodent to human translational research in psychiatry, and have highlighted the usefulness of reverse translation and healthy human to clinical population translation (Carhart-Harris, 2022).

1.16. Synaptic atrophy and growth

Moving to more specific neuronal encoding, evidence is compelling that chronic stress causes dendritic atrophy in the prefrontal cortex (Duman and Duman, 2015) and hippocampus (Duman and Duman, 2015; Qiao et al., 2020) – including in a fashion that biases behavior towards habit formation (Dias-Ferreira et al., 2009) (see also (Piazza and Le Moal, 1996)). Stress is a common risk factor for psychopathology (Kessler, 1997). It is relevant that the severity of general psychopathology has been found to correlate with reduced cortical thickness in a large sample of middle-aged individuals (Romer et al., 2021). Moreover, generalized psychopathology was found to relate to accelerated brain ageing, as well as impaired cognitive and sensory functioning (Wertz et al., 2021), and in two independent studies, estimates of past adversity correlated with reduced gray matter volume in various brain regions (Edmiston et al., 2011; Ansell et al., 2012).

The classic serotonergic psychedelic, psilocybin, has been found to promote rapid and enduring increases in cortical dendritic spinogenesis in vivo (Shao et al., 2021), replicating prior findings of increased cortical synaptogenesis with a variety of 5-HT2AR agonist psychedelics (Ly et al., 2018; Jones et al., 2009). This effect appears to be consistent with increased heterosynaptic plasticity (Chistiakova et al., 2014).

1.17. The complex case of brain network modularity

Brain network modularity is a measure of the extent to which the brain's inter-regional functional connectivity structure can be decomposed into distinct modules, wherein each module consists of regions that are more connected to each other than to other regions or modules. Recent human functional neuroimaging work on the therapeutic action of psychedelics found evidence of decreased brain network modularity after psilocybin therapy for depression across two independent samples. Decreases in brain modularity (synonymous with 'increased global brain integrity' or decreased segregation) correlated with improvements in symptom severity in both datasets (Daws et al., 2022).

Elevated brain network modularity or segregation has been seen in depression (Li et al., 2022; Ye et al., 2015), bipolar disorder (Chang et al., 2022) and cocaine addiction (Liang et al., 2015) - suggesting greater whole-brain functional segregation in these populations. In a similar fashion to high baseline symptom severity in antidepressant trials (Henkel et al., 2011), high baseline modularity has been found to predict response to treatment for schizophrenia (Doucet et al., 2020), OCD (Reggente et al., 2018) and cognitive training (Gallen and D'Esposito, 2019). Moreover, as with psilocybin therapy (Daws et al., 2022), brain modularity has been found to decrease after electroconvulsive therapy (ECT) for depression and schizophrenia (Xu et al., 2020; Huang et al., 2018). ECT is another rapid and robustly acting intervention, which, like 5-HT2AR agonist psychedelics (Vaidya et al., 1997), has been found to increase cortical BDNF mRNA expression (Nibuya et al., 1995).

However, extant findings have not unequivocally linked high modularity to psychopathology. For example, see (Sinha et al., 2019) for a contradictory finding of increased brain network modularity after ECT,

as well as another study suggesting that age-related increases in modularity may be delayed in young people with psychopathology (Kaufmann et al., 2017). See also a particularly difficult to reconcile finding of low brain network modularity in a large sample of patients with depression, bipolar disorder of schizophrenia (Ma et al., 2020).

Neurodevelopmentally, brain modularity increases (i.e., modules become more differentiated from each other) throughout development into adulthood (Baum et al., 2017; Cui et al., 2020), but after reaching adulthood, brain modularity decreases (Chan et al., 2014) -perhaps suggesting a parallel relationship between developments in brain modularity and goal-directed cognition or cognitive aptitude. Indeed, in the case of early brain development or recovery from stroke, observed changes in global network modularity may be dominated by the (re) emergence of patterns of canalization e.g., related to the differentiation of high-level association networks, and healthy brain and cognitive functioning (Baum et al., 2017; Cui et al., 2020; Siegel et al., 2018). Delayed large-scale network differentiation may reflect immature brain network development (Kaufmann et al., 2017; Vanes and Dolan, 2021), but this does not imply that problematic canalization is absent in these cases or a special risk. Indeed, it interesting to reflect whether immature brain development may relate to elevated environmental sensitivity or susceptibility (Greven et al., 2019) – a hypothetical primer for canalization.

It is important to highlight that the typical method for computing brain network modularity estimates the relative amount of functional segregation in the brain as a whole and computes modularity for a set of so-called 'canonical resting-state networks' or RSNs (Newman, 2006). As such, a similar modularity score may be underpinned by distinct patterns of inter-regional or inter-modular connectivity, which would, in turn, have different neuropsychological consequences. Moreover, it is important to state that there is no compelling reason to believe that the canonical RSNs (e.g., identified through independent components analyses on fMRI data) should be especially relevant to entrenched canalization in psychopathology. We speculate that stress, reward, or frontal-subcortical circuitry or networks (Pascoli et al., 2018; Pizzagalli and Roberts, 2022) may be more relevant to psychopathology – and yet are often not focused on in standard network analyses. See (Beam et al., 2021) for just one alternative method for defining brain networks.

Thus, a better justified identification and examination of candidate brain circuitry for assessing markers of canalization in psychopathology could help advance discovery, not just in non-human animal research – where progress has been made (Dias-Ferreira et al., 2009) – but critically, in human neuroimaging (though see (Pizzagalli and Roberts, 2022)). Once compelling candidate systems or circuitry have been identified, it will be easier to use human functional neuroimaging (and fMRI in particular) to test hypotheses inspired by CANAL, including its predictions regarding treatment targets and mechanisms.

1.18. Synaptic replenishment

The picture is arguably clearer and more compelling at the synaptic level. For example, the psychedelic-related dissociative anesthetic, ketamine, was recently found to recover dendritic spines atrophied by chronic stress in an animal model of psychopathology (Moda-Sava et al., 2019). Moreover, recovery of the atrophied spines was selective and related to behaviors reflective of improved functioning (Moda-Sava et al., 2019). See also (Holmes et al., 2022) for relevant findings in humans, using a synaptic density positron emission tomography radiotracer measured prior to and 1-day after a single dose of ketamine.

Given these and related synaptic 'replenishing' findings with classic serotonergic psychedelics (Shao et al., 2021; De Gregorio et al., 2022) — combined with the compelling literature on synaptic atrophy with chronic stress (Duman and Duman, 2015), reduced gray matter in humans reporting histories of adversity (Edmiston et al., 2011; Ansell et al., 2012), and reduced cortical thickness in humans related to psychopathology (Romer et al., 2021) — we can see the emergence of a model of the transdiagnostic therapeutic action of psychedelic therapy that relates to the counteraction of over-potentiated canalization. We speculate that the canalization could occur via (at least) three mechanisms: 1) an atrophy-related reduction in abundant synaptic connections, selectively sparing well-reinforced synapses and associated circuits, 2) top-down inhibition or neglect of specific circuitry (e.g., linked to traumatic memories), or 3) strong potentiation of selective synapses and circuits (Bliss, 1990). All scenarios should reduce freedom within the global system by biasing certain circuits or sub-states.

Finally, we speculate that psychedelic therapy can work to counteract over-potentiated canalization via drug-induced increases in TEMP, replenishing abundant connections i.e., heterosynaptic plasticity (Moda-Sava et al., 2019), to free dynamics within the global system. It matches clinical reports and observations (Carhart-Harris et al., 2018c; Watts et al., 2017) to assume that this effect will be best mediated via gently guiding psychotherapy (Timmermann et al., 2022).

Saying more about the brain mechanisms, we speculate that through a 5-HT2AR agonism-induced modulation of synaptic efficacy and population-level activity — that can be recorded electrophysiologically across species (Schartner et al., 2017; Pascovich et al., 2022) — psychedelics trigger an early phase of plasticity – detectable via EEG as increased signal entropy (Schartner et al., 2017) — that translates downstream into a heterosynaptic plasticity and corresponding rebalancing of synaptic weights. This hypothesized sequence could be detectable at multiple scales and phases e.g., via human (Daws et al., 2022) and non-human animals (Shao et al., 2021; Moda-Sava et al., 2019) imaging techniques.

More work is required to test a hypothesized link between cortical atrophy and canalization (though see (Dias-Ferreira et al., 2009)) as well as the hypotheses that TEMP relates not just to psychological plasticity (Zeifman et al., 2022) but downstream anatomical neuroplasticity, with heterosynaptic plasticity being a compelling candidate in this regard (Shao et al., 2021).

1.19. Stress and canalization

Conceptually, we speculate that there at least two ways in which stress may contribute to canalization in brain circuits and synaptic connections, one would entail chronic stress-induced cortical atrophy (Dias-Ferreira et al., 2009; Duman and Duman, 2015) and another would entail a Hebbian 'hijacking' of stress-induced increases in TEMP (Brivio et al., 2020), see also (Parr et al., 2020; Friston et al., 2012b, 2021) – and (Dias-Ferreira et al., 2009; Moda-Sava et al., 2019). Thus, canalization could narrow the psychological state-space either via removing or inhibiting association non-specific synapses (Moda-Sava et al., 2019) or strengthening association specific ones (Dias-Ferreira et al., 2009). Preclinical examples of Hebbian plasticity serving stimulant addiction can be seen here (Ungless et al., 2001; Dobi et al., 2011) and a separate example of stress-induced circuit reorganization biasing behavior toward habit - can be seen here (Dias-Ferreira et al., 2009).

1.20. Positive psychology and environmental enrichment

While we have focused on the pathology end the mental health spectrum, a speculative marker of psychological health and/or positively valanced mood states may be self-organized criticality (SOC) (Friston et al., 2012b, 2021) – across scales - within and between brain and body (Carhart-Harris et al., 2014). Stated simply, we speculate that *freer* dynamics and information transfer across systems and scales, generally correspond to healthier and happier states of being (Carhart-Harris et al., 2014).

Separately, we are intrigued by evidence that environmental enrichment aids neuroplasticity (Baroncelli et al., 2010; Lee and Soya, 2017; Cancedda et al., 2004; Jha et al., 2016; Grech et al., 2018; Huang et al., 1999; Kazlauckas et al., 2011) and that individuals with above-average phenotypic plasticity or environmental-sensitivity

flourish in enriched environments – i.e., so-called 'vantage sensitivity' (Jolicoeur-Martineau et al., 2020).

1.21. Limitations

Due to empirical gaps between the inter-species and inter-modality findings, we acknowledge that our model is extrapolative and speculative. However, we have been explicit about candidate biomarkers of key measures (Schartner et al., 2017; Mediano et al., 2022) and processes (e.g. (Zeifman et al., 2022),) and can envisage the types of experiments needed to test and potentially validate our hypotheses and constructs. We can be even more explicit: we predict that psychedelic-induced acute increases in spontaneous brain 'temperature' (Ruffini et al., 2022) or 'entropy' (Carhart-Harris, 2018; Carhart-Harris et al., 2014)— as scored through Lempel-Ziv complexity (Schartner et al., 2017) or a recently improved version of it - known as 'Complexity of State-Space Entropy Rate' or 'CSER' (Mediano et al., 2022) applied to electrophysiological data recorded from the neocortex of mammalian species - including humans — should predict increases in downstream markers of neuroplasticity, such as heterosynaptic plasticity in rodents (Shao et al., 2021), plus other anatomical and molecular markers (Raval et al., 2021) across species.

Separately, we hope to see others test whether decreased brain network modularity -as recently observed post psychedelic therapy for depression (Daws et al., 2022) –replicates across trials, including those in other psychiatric populations e.g., (Spriggs et al., 2021). We also recognize that behavioural measures are required to operationalize canalization, but refer the interested reader to one relevant measure in development (Zeifman et al., 2022). Cognitive flexibility and associative learning paradigms may be relevant and useful also, given their translatability across species (Harvey, 2003; Murphy-Beiner and Soar, 2020; Doss et al., 2021; Lu et al., 2021; Kanen et al., 2021).

1.22. Near neighbors

Finally, we believe that our model of psychopathology as canalization occurring in response to adversity-related distress or dysphoria, is novel, but we also recognize that we may have inadvertently overlooked prior models that share similarities with it. In this regard, we recognize the constructs of 'capture' (Kessler, 2016) and 'branching' (Sroufe, 1997), and see also (Klaus, 2002). We also recognize literature on genetic contributions to differential susceptibility or sensitivity (Jolicoeur-Martineau et al., 2020; Belsky et al., 2019). Speculatively, there may be a polygenic contribution to inter-subject variability in TEMP and associated phenotypic plasticity (Greven et al., 2019; Pluess, 2015) – which could prime for canalization, in a context-dependent fashion (Brouwer and Carhart-Harris, 2021) -see also (Hopwood et al., 2022; Musci et al., 2019). Future research could assess individual differences in susceptibility to canalization, where individual differences in propensity for TEMP may be an early but insufficient component of this. In this regard, the question of *why* early increases in TEMP become transformed into canalization in some people (e.g., rather than system freedom or flexibility), seems important. The relevance of individual differences in tolerance of uncertainty (Einstein, 2014), psychological flexibility (Hayes, 2019) or experiential acceptance, may be relevant to examine in this regard. Thankfully, learnable behaviors for countering canalization have been proposed (Hayes, 2019).

2. Conclusion

The present work has introduced a new and intentionally parsimonious model of mental illness, based on the phenomenon of canalization. The model proposes that entrenched canalization, acquired in response to adversity, distress or dysphoria, is a principal component of psychopathology. The model takes inspiration from the (re)emergence of a putative transdiagnostic treatment for psychopathology; namely, psychedelic therapy. We propose that psychedelics promote an early form of plasticity (TEMP), which, when combined with gently guiding psychological support, can serve to counter entrenched canalization.

"*Return to simplicity … [Do] not carve up*" (Tzu, 1993)

Lao-Tzu. *Tao Te Ching.* Translated by Addis and Lombardo.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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