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Transdiagnostic computations of uncertainty: towards a new lens on intolerance of uncertainty

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ABSTRACT

People radically differ in how they cope with uncertainty. Clinical researchers describe a dispositional characteristic known as "intolerance of uncertainty", a tendency to find uncertainty aversive, reported to be elevated across psychiatric and neurodevelopmental conditions. Concurrently, recent research in computational psychiatry has leveraged theoretical work to characterise individual differences in uncertainty processing. Under this framework, differences in how people estimate different forms of uncertainty can contribute to mental health difficulties. In this review, we briefly outline the concept of intolerance of uncertainty within its clinical context, and we argue that the mechanisms underlying this construct may be further elucidated through modelling how individuals make inferences about uncertainty. We will review the evidence linking psychopathology to different computationally specified forms of uncertainty and consider how these findings might suggest distinct mechanistic routes towards intolerance of uncertainty. We also discuss the implications of this computational approach for behavioural and pharmacological interventions, as well as the importance of different cognitive domains and subjective experiences in studying uncertainty processing.

1. Introduction

Uncertainty is ubiquitous in our interactions with the world. Some individuals tolerate uncertainty well, effectively balancing the reliability of different sources of information to flourish and make adaptive decisions (Behrens et al., 2007; Körding and Wolpert, 2004). Others find uncertainty itself aversive to the point of avoidance (Carleton et al., 2007; Grupe and Nitschke, 2013), resulting in conditions such as anxiety disorders, with detrimental impact on quality life (Mendlowicz and Stein, 2000; Olatunji et al., 2007). However, uncertainty is not a single unitary concept, and different people find different situations to be uncertain. In this narrative review, we will provide a non-technical overview of how computational psychiatry interrogates the finer dimensions of uncertainty in relation to psychiatric and neurodevelopmental conditions. We will first consider the transdiagnostic nature of "intolerance of uncertainty" – this construct is multifaceted, generally defined as the tendency to respond negatively to uncertainty, or to struggle when coping with it (Birrell et al., 2011; Freeston et al., 1994; Ladouceur et al., 1997). After a brief review of the history of intolerance of uncertainty (Section 1.1), we will explain how computational modelling could potentially reframe this construct as individual differences in uncertainty processing (Section 1.2 – Section 1.4), particularly in relation to the "misestimation of uncertainty" (Pulcu and Browning, 2019), and review computational studies examining the role of uncertainty across different clinical conditions (Section 2). We will then further unpack the potential causes of altered uncertainty processing, with emphasis on the clinical and treatment implications (Section 3); finally, we will consider the issues of domains and subjective experience in uncertainty processing, alongside other challenges to computational findings (Section 4). Overall, our goal is not to provide an exhaustive overview of existing research in this area, but to highlight how the computational approach can advance our understanding of the pervasive influence of uncertainty on mental health, by drawing predominantly theoretical links between the misestimation and intolerance of uncertainty.

1.1. Intolerance of uncertainty as a psychological construct

The concept of intolerance of uncertainty emerged from cognitive models of anxiety (Dugas et al., 1998; Krohne, 1989) and research

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showing that anxious individuals appraise uncertain situations negatively (Butler and Mathews, 1983). Carleton and colleagues (2007) noted that uncertainty around the frequency or likelihood of negative events (threats) increases the severity of worrying, and potentiates anxiety. Anxiety can arise in response to unpredictable threats, leading to hypervigilance and avoidance behaviours (Grupe and Nitschke, 2013). Meanwhile, individuals who are high in intolerance of uncertainty find *any* source of uncertainty threatening, even in the absence of objective danger (Dugas et al., 1998). This intimate relationship between uncertainty and anxiety led to the development of an effective psychological intervention for generalised anxiety disorder (GAD), cognitive behavioural therapy for intolerance of uncertainty (CBT-IU; Robichaud, 2013; Wahlund et al., 2020). Treatment within CBT-IU is focussed on directly challenging beliefs about uncertainty, and in contrast to general CBT, particularly targets fear and avoidance of uncertain events, which is thought to contribute to excessive worry (Robichaud, 2013).

In an attempt to capture individual differences in uncertainty tolerance, Freeston and colleagues (1994) created a five-factor questionnaire (Intolerance of Uncertainty Scale, IUS) to probe negative attitudes towards uncertainty. To improve psychometric properties of the IUS (see Buhr and Dugas, 2002), Carleton and colleagues (2007) developed a new version of the IUS, the twelve-question IUS-12, with two key factors: prospective anxiety about future events (i.e., a desire for predictability) and inhibition of action (i.e., freezing or inaction).

As the concept of intolerance of uncertainty gained traction throughout the late twentieth century as a core component of GAD (Carleton, 2012), it became increasingly understood as a transdiagnostic aspect of several other mental health conditions. As measured by the IUS, intolerance of uncertainty accounts for unique variance in symptom scores (over and above anxiety-related constructs) in conditions including social anxiety (Boelen and Reijntjes, 2009; Wake et al., 2021), panic disorder (Carleton, 2016; Carleton et al., 2014), post-traumatic stress disorder (Oglesby et al., 2017; Raines et al., 2019), and depression (McEvoy and Mahoney, 2011; Saulnier et al., 2019). Elevated scores on the IUS have also been reported in participants with obsessive-compulsive disorder (OCD; Tolin et al., 2003) and eating disorders (Frank et al., 2012; Sternheim et al., 2017). Further, in neurodevelopmental conditions, such as autism spectrum disorder (ASD), elevated intolerance of uncertainty is commonly reported (Vasa et al., 2018), and the link between autism and anxiety is mediated by intolerance of uncertainty (Boulter et al., 2014; Hwang et al., 2020; Jenkinson et al., 2020; Stark et al., 2021; Wigham et al., 2015). This has led some to hypothesise that intolerance of uncertainty might underscore the high rates of anxiety disorders in the autistic population (Stark et al., 2021).

1.2. Inferences about uncertainty

Whilst self-reported *attitudes* towards uncertainty are important to consider, the IUS has several limitations (Bervoets et al., 2021): it does not capture how individuals represent uncertainty, or quantify how they behave in specific situations that involve uncertainty; furthermore, it does not capture the different kinds of uncertainty an individual may struggle with, or the specific cognitive domains under which people may be particularly "intolerant" of uncertainty. In the rest of this review, we advocate for an alternative approach that has gained traction in the field of computational psychiatry: using cognitive tasks in which experimenters orthogonalise different forms of uncertainty, and characterise how participants estimate and behave in response to these uncertainties through computational modelling. This approach provides a more granular and holistic quantification of how people process uncertainty, and it may describe different mechanistic routes to its intolerance at an individual level.

To illustrate this idea, we will focus on the forms of uncertainty involved in associative learning paradigms (Fig. 1), which underpin

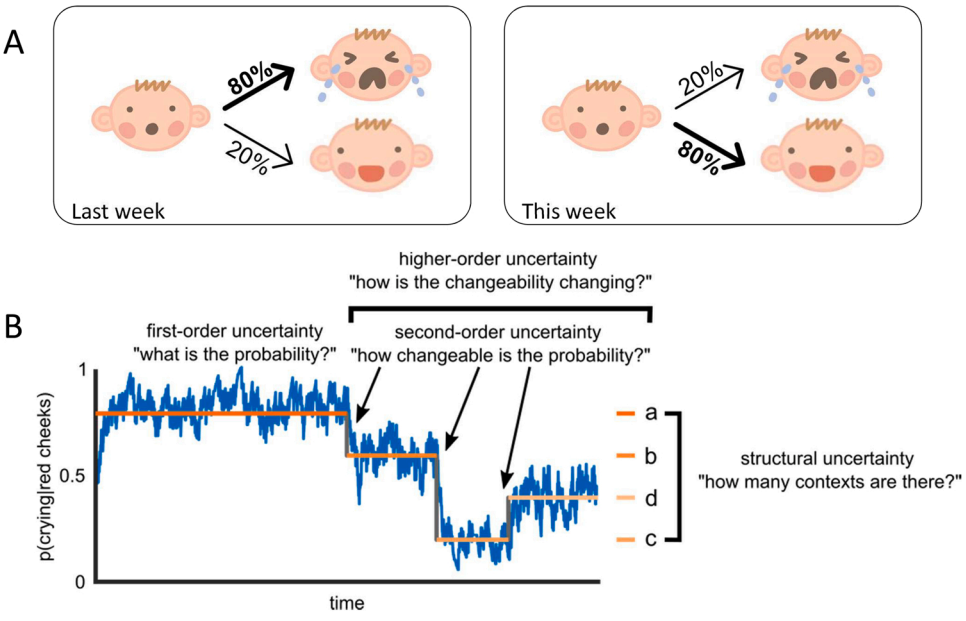


Fig. 1. The challenge of learning under different kinds of uncertainty, in associative learning tasks. A) illustrates Pavlovian conditioning, trying to learn the association between a baby's red cheeks (cue) and hearing them cry (outcome). In a particular week (left hand box), if you see that the baby has red cheeks and cries more often than not, you might infer that they are teething. The next week (right hand box), when the baby has red cheeks but no longer cries as frequently, you might infer that they are just hot. B) The orange trace indicates a changeable probabilistic relationship, while the blue trace represents a person's estimate of this relationship. First-order uncertainty is illustrated as trying to calculate the probability of the baby crying, given that they have red cheeks ("what is the height of the line?"). Note that if the height of the line is at 50%, if the baby has red cheeks, they are crying at random – when contingencies are close to this state, first-order uncertainty is high, and it will be difficult to know whether they are teething or not. Second-order uncertainty (in this context, volatility) is illustrated as estimating the frequency of the changes in this probability ("how often does the height of the line change?"). Volatility would be high when the frequency of the changes is rapid, as in the latter half of the observations, and it would also be difficult to predict whether the baby will cry when you see them with red cheeks. Higher-order uncertainty reflects uncertainty about the changes themselves ("how is the changeability of the line changing?"). Finally, structural uncertainty is illustrated as inferring the number of stable periods of the probability over time ("how many periods are there when the line is stable?"): in context "a", red cheeks are strongly predictive of seeing the baby cry (they are probably teething), while in context "b", red cheeks are weakly predictive of crying (so they might be teething); in comparison, for in context "c", red cheeks are strongly anti-predictive of crying (so they are probably not teething), and context "d" is weakly anti-predictive of crying (so they might not be teething).

much of the computational work on uncertainty processing (see Pulcu and Browning, 2019, for a review). For example, if you notice that your baby cries a lot (outcome) every time they have red cheeks (cue), you might assume they are teething. However, the cue might not predict the outcome with absolute certainty (i.e., they only cry 80% of the time when they have red cheeks), and this probabilistic relationship constitutes a form of **first-order uncertainty**, sometimes referred to as "irreducible uncertainty" or "expected uncertainty" (de Berker et al., 2016; Pulcu and Browning, 2019). Meanwhile, one can be uncertain about the first-order uncertainty itself, which introduces **second-order uncertainty**. When discussing second-order uncertainty, researchers have used "unexpected uncertainty" to refer to the uncertainty about a probabilistic relationship that is introduced by potential changes (Soltani and Izquierdo, 2019; Yu and Dayan, 2005) – with every change, previously accumulated knowledge (i.e., estimates about first-order uncertainty) may no longer provide valid predictions about the world. For example, if your baby still has red cheeks but now only cries 20% of the time, they might not be teething – they could just be too hot. We refer to the changeability of the probabilistic relationships (e.g., how frequently they change) as the volatility of the environment (Behrens et al., 2007; Bland and Schaefer, 2012; Pulcu and Browning, 2019), which is a form of second-order uncertainty. Since changes are typically not signalled, one can be uncertain about changeability itself, introducing **higher-order uncertainty**. There are many aspects to higher-order uncertainty, but, as a simple example, someone who is very certain that they have a volatile baby might expect them to cycle between teething and not teething several times a day, even when teething occurs for a few days every week. Finally, there may be different "contexts" of first-order uncertainty ("probably teething", "maybe teething" etc.), and **structural uncertainty** refers to uncertainty surrounding the *number* of these discrete probabilistic relationships. These distinctions provide a simplified but useful classification of the different forms of uncertainty that can impact behaviour, which we will utilise to draw parallels and distinctions across different studies examining the effect of uncertainty on psychopathology. However, we note that more comprehensive taxonomies have been defined (Bach and Dolan, 2012; Bland and Schaefer, 2012; Soltani and Izquierdo, 2019), and studies can also consider dichotomous distinctions, such as whether or not a specific form of uncertainty can be reduced with new observations (Kobayashi and Hsu, 2017).

Critically, when two people observe the same sequence of cue-outcome combinations, they may still come to form different uncertainty estimates. These estimates may be about the probabilistic cue-outcome relationship, about the changeability of this relationship, about the variability of the changeability, or about the number of possible contexts. These differences may originate from different assumptions about the world: for example, a person who assumes the world to be volatile may infer that a change has happened when there is none. One goal of computational modelling is to reveal these estimates or "beliefs" about uncertainty within each individual. In this process, the model also characterises the style with which people learn under uncertainty, and how people utilise these uncertainty estimates.

1.3. Computational models of uncertainty

In this section, we briefly outline some of the computational modelling approaches which have been commonly used to make inferences about participants' estimates of uncertainty. The development of the models we focus on in this review was brought about by attempts to understand how potential changes (second-order uncertainty) impact associative learning. Associative learning can be quantified with the Rescorla-Wagner model (Rescorla and Wagner, 1972), which describes how the strength of association between a cue (e.g. red cheeks) and an outcome (e.g. the baby crying) changes with repeated pairings. The model is parameterised by the learning rate, which controls the speed of learning, i.e., how much impact new pairings have on the associative strength, with high learning rates resulting in new observations having more influence than past experience. A large body of computational theory has been developed to capture how learning rates can change, including associative learning models with dynamic learning rates (Pearce and Hall, 1980) and the Kalman filter (Dayan et al., 2000; Gershman, 2015); more recent studies have focused on how learning rate should adapt to distinct forms of uncertainty (Behrens et al., 2007; Payzan-LeNestour and Bossaerts, 2011; Piray and Daw, 2021; Yu and Dayan, 2005), which is the focus of this review. In general, the learning rate should be higher in a more volatile environment to keep track of the frequent changes in the probabilistic relationship. To confirm this, Behrens and colleagues (2007) used a Bayesian "ideal observer" approach to consider learning as updating a generative model of the environment (i.e., a model that explains how cue-outcome pairs are generated). The optimal learning rates from this model, obtained with the Rescorla-Wagner rule, were higher when the probabilistic relationship was volatile, and lower when it remained stable. This pattern of learning rates was also found in human participants. Thus, learning rate adaptation can be thought of as a proxy for having inferred a change in the volatility of the environment. Put simply, through modelling how people learn, researchers might probe how people estimate uncertainty.

To better capture individual differences in learning under uncertainty, the Hierarchical Gaussian Filter (HGF) was developed to infer the belief updating processes and learning styles of individual participants (Mathys et al., 2011, 2014). The standard form of the HGF has a similar structure to the model of Behrens and colleagues in that it simultaneously estimates probabilistic relationships (first-order uncertainty) and volatility (second-order uncertainty), based on the outcomes received in an associative learning paradigm. Importantly, beliefs about second-order uncertainty will influence the learning rate for first-order uncertainty. In addition, the HGF can capture the effects of additional sources of uncertainty on behaviour – including low-level sensory noise (i.e. that stimuli are more difficult to resolve when the image is degraded), and uncertainty about uncertainty itself, e.g. "how uncertain are you about your estimate of volatility?" (Lawson et al., 2017; Mathys et al., 2014). It also has "tonic" parameters that reflect a form of long-term or "baseline" uncertainty estimate at each level (Mathys et al., 2014). Most importantly, for any given participant, the HGF can be intuitively thought of as trying to describe what kind of Bayesian learner they are, providing an individualised "computational fingerprint" across these different sources of uncertainty. In other words, this allows each participant to have their own "ground truth" instead of viewing differences in performance as deviations from "the ideal".

In summary, the HGF can provide a comprehensive, modular, and flexible model of how different kinds of uncertainty might be misestimated within individuals and across diagnostic groups. As the HGF has been widely used in associative learning under uncertainty tasks in clinical populations, it forms the focus of our review. However, we note that there are other models for learning and decision-making under uncertainty, such as active inference (Marković et al., 2021), drift diffusion models (Aylward et al., 2020; Pedersen et al., 2017), and signal detection theory (Locke and Robinson, 2021).

1.4. Summary

Self-reported intolerance of uncertainty might be a common feature of many neurodevelopmental and neuropsychiatric conditions, but this dispositional construct is agnostic to *why* someone might find uncertainty aversive. Computational models describe individual differences in the inferences people make about uncertainty, with parameters capturing the "beliefs" about uncertainty that participants bring to a cognitive task (Huys et al., 2021; Moutoussis et al., 2015). Importantly, through distinguishing the different forms of uncertainty (Fig. 1), we may isolate the processes that contribute to alterations in how individuals cope with uncertainty, which will be discussed in the next section.

2. Uncertainty processing across clinical disorders

In this section, we discuss the "misestimation of uncertainty" (Pulcu and Browning, 2019), where estimates of the four forms of uncertainty outlined above differ between diagnosed individuals and controls, or across people with high or low symptom scores. We will also offer links between uncertainty misestimation and the clinical characteristics related to the intolerance of uncertainty.

2.1. "First-order" uncertainty: uncertainty that cannot be reduced

We begin with first-order uncertainty, where we cannot predict the future with 100% accuracy due to the inherent stochasticity in the process (e.g., rolling a die). In decision-making, first-order uncertainty is also termed risk (Payzan-LeNestour and Bossaerts, 2011): when the probability of an outcome is explicitly presented, participants sometimes forgo options with higher net value simply because of the uncertainty associated with it. This phenomenon is described in prospect theory, and is known as risk aversion (Kahneman and Tversky, 1979). Classic paradigms to measure risk aversion do not involve learning, but task behaviour can be described with economic modelling approaches that parameterise how risk averse an individual is. Using these models, participants meeting the criteria for GAD have been found to be more risk averse, over and above the aversion to negative outcomes (Charpentier et al., 2017), indicating that even explicit knowledge of first-order uncertainty is not enough to abate its intolerance.

In many cases, first-order uncertainty must be estimated. Judgment of first-order uncertainty has long been investigated in relation to mental health conditions, with mixed findings: individuals with mood and anxiety disorders may have elevated subjective estimates about the probabilities of negative events (Butler and Mathews, 1983; Dalgleish et al., 1997); meanwhile, another branch of literature suggested that depression might be linked to more "veridical" judgment of contingencies in circumscribed task conditions (Ackermann and DeRubeis, 1991; Alloy and Abramson, 1979). Aside from explicit judgments of uncertainty, researchers have also probed estimates of probabilistic relationships through choice behaviour. Many learning tasks involving probabilistic feedback are "stationary" – that is, the first-order uncertainty itself does not change. One such task is the probabilistic selection task (Frank et al., 2004), where participants chose between stimuli pairs with different combinations of stationary reward probabilities. The reward probabilities can be 80% rewarded on Stimulus A and 20% rewarded on Stimulus B, 70%− 30% for Stimuli C and D, or 60%− 40% for Stimuli E and F, with interleaved presentation of the three stimuli pairs (AB, CD, EF). Altered performance on the training phase of this task has been reported across a range of psychiatric conditions, including depression (Brown et al., 2021), schizophrenia (Waltz et al., 2007), and attention deficit hyperactivity disorder (ADHD; Frank et al., 2007). For instance, patients with schizophrenia made fewer choices of the stimulus with higher reward probability during early phases of the task, especially when choosing between stimulus A and B, when the reward probability is at 80%− 20% (Waltz et al., 2007). Together, these findings from the probabilistic selection task point towards difficulties with learning about first-order uncertainty in reward across a range of different conditions.

In reward learning, participants estimate the uncertainty of a reward from choosing an option. However, in other situations, an action may not result in an outcome, such as choosing to go through one of two doors. Inferring where you will end up upon choosing each door is also plagued by a similar first-order uncertainty. These probabilities are referred to as state transition probabilities (what is the chance that if I do this, I will end up in state X?), and participants' estimates of these state transitions can be inferred from the two-step task (Daw et al., 2005). Recent applications of this task have revealed that individuals high in compulsive traits misestimate these state transition probabilities, showing either reduced expectancy effects in reaction time when transitioning between states (Seow et al., 2021) or poorer performance when tested on their knowledge about transitions between states (Sharp et al., 2021). Misestimating first-order uncertainty in the consequences of one's own action may then constitute a core aspect of compulsivity, and is thought to underlie checking behaviour in obsessive-compulsive disorder (Fradkin et al., 2020). Checking behaviour is thought to be a response to uncertainty (Toffolo et al., 2016), but may arise from a misestimation of state transition uncertainty. Intuitively, if you turn the light off in your living room, by the time you reach the kitchen and cannot see the living room, with high transition uncertainty, you cannot be sure that you turned the light off, and you feel the need to check (Fradkin et al., 2020). Uncertainty about the past reduces reliance on the past, leading to a distrust of memory (van den Hout and Kindt, 2003), which further promotes excessive reliance on future information, manifesting as checking and information gathering.

Overall, multiple psychiatric disorders have been linked to altered performance on tasks involving first-order uncertainty. When reward probabilities are made explicit, anxious people are more averse to risky or uncertain options even if they have a higher net value, consistent with aversion to risk. Misjudging reward probabilities, or the probability of transition from one state to another, will hinder decision-making, representing ineffective problem-solving under uncertainty. Overestimating the probability of negative but not positive events, on the other hand, would reflect pessimistic world views. We stress that these misestimations may not come from the same mechanism, but we wish to highlight the transdiagnostic ubiquity of misestimating first-order uncertainty in the environment.

2.2. "Second-order" uncertainty: inferring changes in a probabilistic world

As knowledge about first-order uncertainty is often incomplete, there are numerous ways in which uncertainty in estimates of first-order uncertainty can be introduced, and we refer to these as second-order uncertainty. For example, in economic paradigms, participants may have to choose between balancing a known first-order uncertainty against an unknown first-order uncertainty. This absence of information is often referred to as ambiguity (Bach and Dolan, 2012), which is a source of second-order uncertainty (Bach et al., 2011). Intolerance of ambiguity is also frequently found in anxiety disorders, which extends the aversion to unpredictability towards incomplete information (Carleton, 2012; Grenier et al., 2005). A recent computational study found that high trait anxious individuals were more influenced by increases in ambiguity (Lawrance et al., 2022). In this study, they used tokens to represent the probability that a cue would lead to an electric shock, and manipulated ambiguity with the number of occluded tokens. They found that ambiguity aversion – captured with model-based and model-agnostic measures – correlated positively with trait anxiety.

In learning paradigms, a key source of second-order uncertainty is the changeability, or volatility, of the environment. As mentioned in Section 1.3, learning should be more rapid in a more volatile world. Thus, if a participant were to employ high learning rates, one might *assume* that they perceive the environment as more volatile (Behrens et al., 2007; Huys et al., 2021). There is a rich literature characterising the (potentially maladaptive) elevation of learning rates across many neuropsychiatric conditions. Increased learning from punishments seems to be characteristic of mood and anxiety disorders (Aylward et al., 2019; Pike and Robinson, 2022), and of trait-level cognitive anxiety (Wise and Dolan, 2020). These findings support the cognitive theories on negative affective bias in anxiety and depression, as they characterise how such a bias manifests in learning (Beck, 1985; Pike and Robinson, 2022; Roiser et al., 2012). Furthermore, a similar learning bias can be induced in non-anxious individuals when punishments are more volatile than rewards, further supporting a mediating role of uncertainty estimation in elevated learning rate from aversive outcomes (Pulcu and Browning, 2017).

Importantly, whether high learning rate is adaptive or maladaptive depends upon the actual level of volatility within the environment (Zhang et al., 2020). Using a common probabilistic reversal learning task, with a single change in reward probabilities, Crawley and colleagues (2020) observed elevated learning rates in children and adults with ASD. The authors then conducted simulations of the 'optimal' learning rates for this task, and they demonstrated that learning rates *higher* than the optimal, as seen in the ASD groups, can lead to *fewer* choices of the more advantageous option, linking learning biases to poorer decision-making. A similar effect has also been reported with non-clinical measures of anxiety, in a reward-based learning task that involves multiple changes in the underlying contingencies for three choice options (Huang et al., 2017). This difference in learning rate is associated with heightened "lose-shift" behaviour, where participants forgo a potentially rewarding option immediately after receiving a negative outcome. This behaviour reflects an oversensitivity to chance events, such that participants benefit less from stable environments, and seems to be common across anxiety and autism, which are themselves highly co-occurring (Buck et al., 2014; Hollocks et al., 2019; Nimmo-Smith et al., 2020).

Another task that addresses second-order uncertainty is the "predictive inference task": here, participants may be asked to indicate the likely location of a helicopter occluded by a cloud, and they do so by learning about where the helicopter drops bags of money; learning rates during this task can be calculated without applying a particular model (McGuire et al., 2014). The position of the helicopter can undergo sudden changes, and the profile of learning rates may reflect expectations about the probability of encountering these "change-points" (Nassar et al., 2016). High learning rates on this task have been reported for adults and adolescents diagnosed with OCD (Marzuki et al., 2022; Vaghi et al., 2017) – the adult sample displayed a general elevation in learning rates across trials (Vaghi et al., 2017), while the adolescent sample was specifically more sensitive to small errors in their position estimates (Marzuki et al., 2022). However, the associations of this effect with continuous measures of psychiatric symptom dimensions are less clear-cut (Seow and Gillan, 2020). Overly high learning rates can hinder the integration of past observations, such that the position estimates provided by individuals with OCD are constantly less exact (Vaghi et al., 2017).

In summary, the role of second-order uncertainty in psychopathology is not only reflected in enhanced ambiguity aversion, but also in the misestimation of volatility – a number of psychiatric and neurodevelopmental conditions have been associated with altered (typically elevated) learning rates across different of probabilistic learning paradigms. These altered learning rates may underscore the "cognitive biases" that are present in these conditions (e.g., a bias to learn more from negative relative to positive feedback), but if elevated learning rates are an adaptive response to volatility, one might also explain these findings with exaggerated expectations about how changeable the world is (e.g., a bias to expect that negative outcomes are more volatile than positive outcomes; Pulcu and Browning, 2017, 2019). Although, to tackle this issue, we require tasks that assess learning under different levels of volatility, or models that parameterise inferences about volatility, as we will discuss in Section 2.3.

2.3. Higher-order uncertainty: inferring the dynamics of volatility

After discussing the impact of volatility on how people estimate (first-order) contingencies, we now discuss differences in how people estimate volatility itself, which is in turn regulated by estimates of higher-order uncertainty. The world can transition between periods of low or high volatility, and there are many different types of volatile environments (for instance, varying the number or frequency of changes). Thus, participants should increase their learning rate flexibly when environmental volatility increases, and this would require participants to update their estimates about volatility. However, this higher-order inference about volatility is difficult to measure with a task with only one change (e.g., a probabilistic reversal learning task; Crawley et al., 2020), or in tasks that do not explicitly manipulate the probability of change (Aylward et al., 2019). One common approach to measure how an individual adapts to volatility is to compare how they learn in a stable environment with no reversal, to a volatile environment with multiple reversals (serial reversal learning, Behrens et al., 2007).

Seminal work from Browning and colleagues (2015) used an aversive instrumental learning task with stable and volatile conditions, where higher trait anxiety was associated with a smaller difference in learning rate between volatile and stable blocks (Fig. 2A, B), which indicates reduced adaptation to volatility. In other words, the learning rates of anxious individuals are comparatively less flexible, and they may differ in how they cope with changes in volatility itself. Similar findings have also been reported by Gagne and colleagues (2020), where the reduced effect of volatility on learning rate was linked to internalising symptoms (a general dimension of mental distress shared across anxiety and depression). Interestingly, neither study reported any association between self-reported symptoms and the baseline learning rate, nor with the learning rate in a specific task condition. To better understand this pattern of learning rates, it may be necessary to apply models where learning rate is allowed to vary across trials (e.g., the HGF). Additionally, the inflexibility in learning rate may reflect the belief that volatility itself is not very changeable. These studies on anxiety contrast with recent findings in the field of eating disorders, where people recovered from anorexia show an elevated adjustment of learning rates (Pike et al., 2022, preprint), which may suggest an oversensitivity to volatility changes. However, the models employed in the above studies cannot directly capture beliefs about the changeability of volatility, nor quantify the volatility that participants ascribe to the two task conditions.

The HGF, on the other hand, allows explicit interrogation of how individual volatility estimates are updated on a trial-by-trial basis (Mathys et al., 2011). The HGF is especially suited for modelling how altered beliefs about higher-order uncertainty impact the estimation of a lower-level uncertainty. For instance, participants with ASD appear to update their estimates of first-order predictive relationships more slowly than controls but update their estimates of volatility more quickly than controls (Lawson et al., 2017). In this study, parameters governing learning about (first-order) probabilistic relationships were similar across groups, while the meta-volatility parameter (a higher-order belief about the instability of volatility) was greater in autistic adults (Fig. 2C). A similar pattern of altered learning has also been reported in borderline personality disorder (BPD), with slower learning about first-order uncertainty and an exaggerated sensitivity to changes in environmental volatility (Fig. 2D; Henco et al., 2020). Not unlike an overestimation of volatility (Section 2.2), overestimating higher-order uncertainty can also render the world a changeable (and potentially aversive) place, where all outcomes are somewhat unexpected due to poorer estimation of probabilistic contingencies (Yon and Frith, 2021).

The HGF has also been employed to assess uncertainty in trial-wise estimates of volatility, which are driven by the meta-volatility parameter, showing higher uncertainty about volatility in high state anxious individuals (Fig. 2E; Hein et al., 2021). It is interesting to compare this result with the findings of reduced learning rate flexibility in *trait* anxiety from Browning et al. (2015) – assuming these findings are generalisable to one another, it might suggest that difficulties in tuning learning in response to volatility arise from greater uncertainty about volatility itself (e.g., when we are unsure of what the volatility level is, we might have higher learning rates when the world is stable, which would manifest as reduced learning rate adaptation). Furthermore, given the high co-occurrence of anxiety in autism spectrum disorders, this result raises the intriguing possibility that the differences in volatility processing reported in ASD (Lawson et al., 2017) might actually reflect features of anxiety, rather than features of autism per se. The interaction between anxiety and autism, as related to the processing of different kinds of uncertainty, warrants further study.

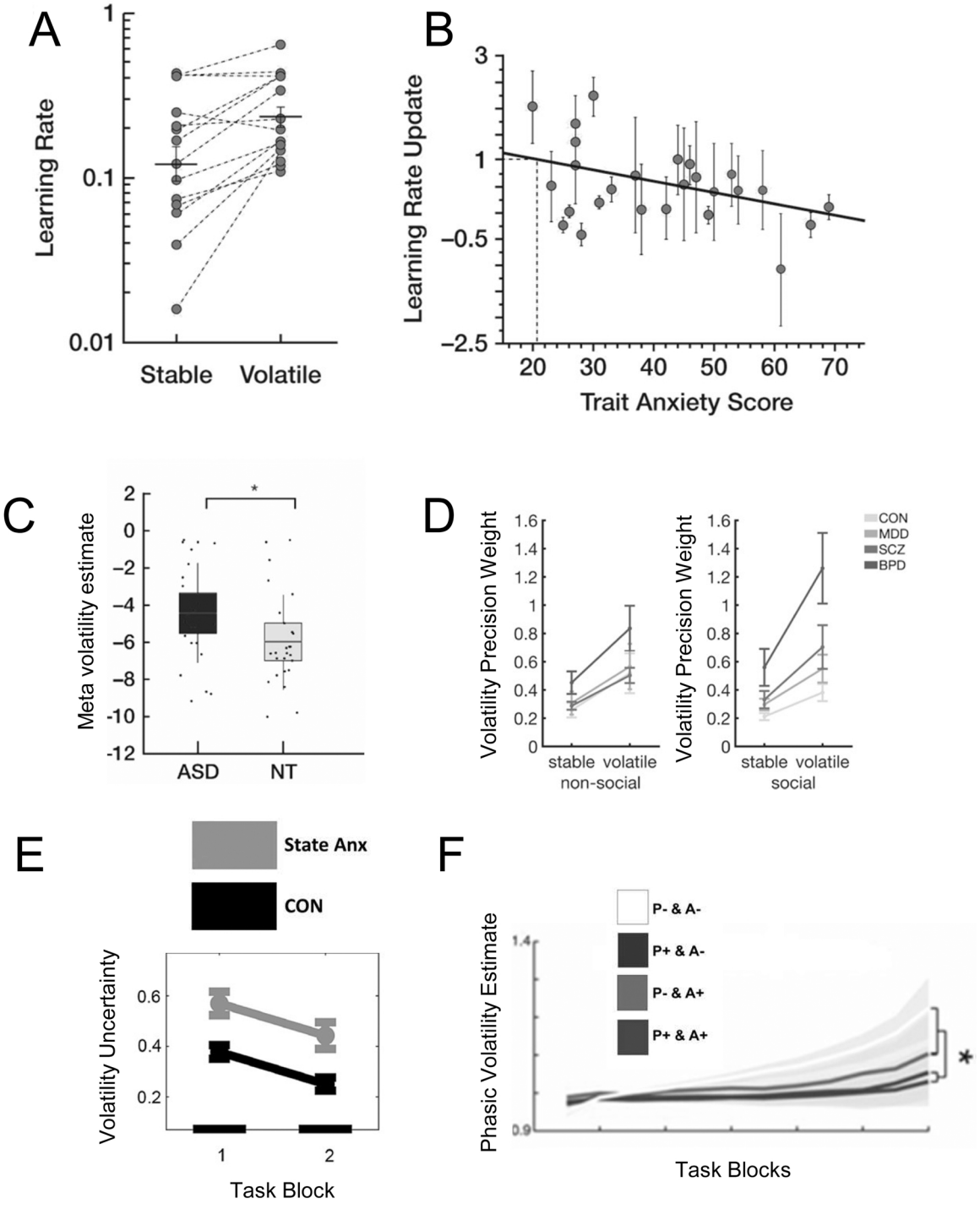


Fig. 2. Difficulties in learning about and estimating volatility seem to be characteristic of several different disorders. A) Adapted from Browning et al. (2015) learning rates estimated from Rescorla-Wagner models fitted to participant choices show elevated learning rates in a volatile environment, compared to when the probabilistic relationship is stable. B) Adapted from Browning et al. (2015) this learning rate flexibility is reduced in high-trait anxious individuals. This task and model speak to learning in response to volatility, but not estimates of volatility itself. In contrast, the three studies on the bottom have all employed the HGF to address individual participant estimates of different aspects of volatility. C) Adapted from Lawson et al. (2017) in autistic adults (dark grey), higher meta-volatility estimates have been reported relative to controls (light grey), indicating a belief that volatility is instable. D) Adapted from Henco et al. (2020) the precision weights for belief updating about volatility – similar to learning rates – show elevated adjustment in response to volatility in borderline personality disorder (BPD), relative to depression (MDD), schizophrenia (SCZ), and controls (CON). This effect is greatest for social relative to non-social learning. E) Adapted from Hein et al. (2021) in all participants, uncertainty about volatility decreases across task blocks, but uncertainty about volatility is higher in state anxious individuals (State Anx, light grey) relative to controls (CT, dark grey). F) Adapted from Powers et al. (2017) in people with psychosis (dark lines), phasic estimates are not sensitive to the increases in volatility across task blocks, relative to people without psychosis (light lines). P+ and P- refers to individuals with or without diagnosis of psychotic illness, while A+ and A- refers to whether the participant experiences auditory verbal hallucinations.

Additionally, the HGF can distinguish between altered initial beliefs about volatility that affect the onset of the task (e.g., Reed et al., 2020; Suthaharan et al., 2021) from differences in the mean volatility estimate that is only evident towards the end of the task (e.g., Cole et al., 2020). These parameters influence how participants estimate volatility, and alterations in these parameters have been reported in multiple studies on psychosis, paranoia, and even pandemic experiences (for review, see Katthagen et al., 2022). These (higher-level) misestimations of uncertainty align with the emerging view that stronger reliance on existing beliefs underlies the phenomenology of psychosis (Adams et al., 2013; Sterzer et al., 2018). In particular, two aspects of psychosis have been highlighted under the framework of misestimating uncertainty: paranoia arises from an unwavering initial certainty that the environment is volatile, resistant to change or persuasion (Reed et al., 2020), and hallucinations arise from strong (aberrantly high certainty in) perceptual expectations (Powers et al., 2017). Finally, psychosis may also reflect a failure to track changes in volatility across time (Fig. 2F; Powers et al., 2017).

Overall, the parameters in the HGF can provide a "fingerprint" for how participants directly estimate different aspects of uncertainty (Marshall et al., 2016). This feature helps with disentangling the heterogeneity amongst participants, and in charting the various paths through which heightened expectations about change can emerge.

2.4. Structural uncertainty: how many contexts are there?

While normative models of volatility estimation build expectations over the timing and frequency of changes, they rarely emphasise inference about the abstract rules which govern the stable periods between changes. These abstract rules reflect the task structure – for instance, in two choice serial reversal learning, it seems plausible that participants infer two stable, distinct rules (or contexts) in alternation (e.g., Behrens et al., 2007, either blue or green is rewarding). These distinct, recurring rules guide decision making during the task, and participants may categorise cue-outcome pairings into clusters which have been generated by the same rule, or within the same "context" (Gershman and Niv, 2012; Lloyd and Leslie, 2013). It is possible that some participants may infer that there are more than two rules, depending on their assumptions about the structure of the task. Latent cause models (Gershman et al., 2010) were developed in order to account for a situation in which participants could infer the presence of (in principle infinitely) many contexts, and hence reveal how individual differences in estimating the number of contexts relate to psychopathology.

Much of the work in this area has been conducted in Pavlovian fear conditioning, in which acquisition of the fear response (presenting stimuli paired with shocks) is followed by extinction (presenting stimuli alone). After extinction, the acquired fear response may reappear with stimuli presentation (i.e., spontaneous recovery). Gershman and Hartley (2015) showed that differences in spontaneous recovery can be attributed to whether the participants have inferred the presence of one latent cause (in which acquisition and extinction are part of the same context), or two latent causes (in which acquisition and extinction are two separate contexts). Participants who inferred two latent causes (contexts) learned not to generalise the "harmful" acquisition context to the "safe" extinction context; as a result, extinction does not update or overwrite the acquired fear response. This predisposes the participant towards spontaneous recovery, triggered by retrieval of the acquisition context. Interestingly, there is an emerging literature on how individual differences in fear conditioning may be explained by differences in the IUS (Morriss et al., 2016, 2021), but in the absence of latent cause modelling, the relationship between the IUS and structural uncertainty is not yet clear.

Preliminary evidence with latent cause modelling suggests that in a cohort of trauma-exposed individuals, symptoms of post-traumatic stress disorder (PTSD) are associated with greater tendency to attribute observations to one cause (Norbury et al., 2021). In this case, since a single context must accommodate a diverse range of observations across trials, this tendency might sometimes impede the discrimination between threatening cues and safety cues, and lead to impoverished extinction. Indeed, overgeneralisation, or a tendency to infer a single non-specific underlying context (Norbury et al., 2021), is related to high levels of intolerance of uncertainty (Morriss et al., 2016), and greater pre-trauma overgeneralisation in fear conditioning may lead to worse symptoms of PTSD (Zuj et al., 2016).

Fear acquisition and extinction can be extended into a serial reversal learning paradigm, in which participants cycle between safe and threat contexts. Zika and colleagues (2022, preprint) investigated how participants learn about the contingency between cues and an electric shock, where participants could provide their prediction about shock probability after seeing each cue. In this case, participants could adopt a strategy of gradual learning (in which inference of any changes in the shock contingency reflect updates to a single context), or state learning (in which changes in shock contingency are thought to reflect switches between contexts). The results from Zika and colleagues suggest that individuals higher in trait anxiety may be more likely to use a state learning strategy than low trait anxious individuals, inferring the presence of distinct contexts.

Taken together, these findings indicate that different estimates of structural uncertainty may underlie conditions such as PTSD and anxiety. It is interesting that these results are in opposite directions, such that individuals with PTSD tend to infer the presence of a single (non-specific) context, and individuals higher in trait anxiety tend to infer multiple distinct contexts.

2.5. Summary

Multiple mental health constructs have been linked to either the misestimation of, or enhanced aversion towards, each of the forms of uncertainty discussed. We have summarised the relevant empirical studies in Table 1. In particular, anxiety is implicated in all forms of uncertainty processing, which may reflect a fundamental role for uncertainty processing in the pathophysiology of anxiety, or a bias in publications, given anxiety was central to the formulation of intolerance of uncertainty. This also raises the question of interactions across the different forms of uncertainty (e.g., if misestimation of the number of contexts may be linked to the misestimation of volatility). However, we note that there are inconsistencies amongst studies linking psychopathology to different forms of uncertainty, with studies reporting null findings (e.g., for learning rate differences, Brolsma et al., 2020), and integration of these findings is difficult due to the heterogeneity of tasks and models (though see Pike and Robinson, 2022, for a possible solution). Another source of discrepancy across studies is the type of information over which participants are uncertain about (e.g., sensory or reward information). For clarity, we have stratified the reviewed studies according to the task domain in Table 1, and we will further discuss the issue of domain-specificity in Section 4.1. Nevertheless, these studies highlight how fractionating different types of uncertainty permit subtle differences on learning and decision-making tasks to be captured and interpreted, and we will proceed to discuss how these findings can be advanced with a more mechanistic view on the role of uncertainty in mental health.

3. Towards more mechanistic views of uncertainty estimation in mental health

What mechanistic insights into mental health might be gained through studying uncertainty estimation? The vast majority of computational studies investigating uncertainty processing are cross-sectional; therefore, it is unclear whether and how altered uncertainty estimates might be involved in the generation and maintenance of psychopathology, and the origins of these estimates also remain unknown. These questions are vital for understanding the role of computational

Table 1
Example studies reporting associations or case-control differences across different forms of uncertainty (left to right: first-order, second-order, higher-order, and structural uncertainty), arranged vertically according to cognitive task domains that have been studied (top to bottom: sensory, reward, punishment, value learning, actions, social). This table is non-exhaustive but is intended to highlight the areas where there are several empirical studies across each domain, as well as the ubiquity of different disorders that seem to show altered uncertainty processing.

	First-order uncertainty: differences in estimates about a stationary probability	Second-order uncertainty: high learning rates *possibly* indicating high volatility estimates	Higher-order uncertainty: differences in inferences about volatility assessed directly	Structural uncertainty: differences in inferring the number of contexts
Sensory			Adults with ASD (Lawson et al., 2017)	
Reward	Depression and anhedonia (Brown et al., 2021); schizophrenia (Waltz et al., 2007); ADHD (Frank et al., 2007)	Non-clinical anxious symptoms (Huang et al., 2017)	Schizophrenia (Katthagen et al., 2022); paranoia (Reed et al., 2020; Suthaharan et al., 2021); state anxiety (Hein et al., 2021)	
Punishment		Mood and anxiety disorders (Aylward et al., 2019; Pike and Robinson, 2022); trait cognitive anxiety (Wise and Dolan, 2020)	Trait anxiety (Browning et al., 2015)	PTSD (Norbury et al., 2021); trait anxiety (Zika et al., 2022, pre-print)
General value-based learning and decision-making	Generalised anxiety disorder (Charpentier et al., 2017)	Children and adults with ASD (Crawley et al., 2020)	Internalising symptom dimension (Gagne et al., 2020); eating disorder (Pike et al., 2022, preprint)	
Actions	Compulsive traits (Seow et al., 2021; Sharp et al., 2021)	OCD (Marzuki et al., 2022; Vaghi et al., 2017)	Adults with ASD (Arthur et al., 2021)	
Social		Borderline personality disorder (Siegel et al., 2020)	Borderline personality disorder (Henco et al., 2020)	

differences in intolerance of uncertainty, with potential utility for triage and treatment in clinical settings.

3.1. Misestimation and intolerance of uncertainty

The misestimation of uncertainty can explain why individuals perform differently on cognitive tasks involving uncertainty, although it is an empirical question as to how these differences map onto the intolerance of uncertainty. Extrapolating from the findings in Section 2, we may tentatively chart out how the misestimation of uncertainty contributes to the anxious and avoidant aspects of the IUS-12: for example, in ASD, a preference for predictability (and hence anxiety when plans change) may arise in a world estimated to be volatile, where one struggles to effectively predict what will happen next. In mood disorders, the inability to ignore decisions that have led to poor outcomes by chance (e.g., Huang et al., 2017; Murphy et al., 2003), or a belief that your actions will be ineffective in preventing negative outcomes (Zorowitz et al., 2020), may result in failure to act in uncertain situations. These examples serve as computationally specified hypotheses about why the amorphous construct of "intolerance of uncertainty" is elevated across these different disorders, even though the mechanisms could be quite distinct.

However, a more direct relationship between misestimation and intolerance of uncertainty can be seen in the mismatch between the objective (or experimentally induced) environment, and the subjective (inferred) environment. In developing the IUS, Freeston and colleagues noted that "intolerance of uncertainty would lead to problems being perceived when none objectively exists and to ineffective problem-solving where problems objectively exist" (Freeston et al., 1994). This crucial distinction is an inherent and fundamental part of the uncertainty estimation framework. On the one hand, cognitive tasks can involve different forms of objective uncertainty that "ought to" impede decision making (e.g. conditions where first-order uncertainty is high, such as when probabilities are close to nonpredictive, or when probabilistic relationships change in 'volatile' blocks), allowing us to address how people cope with these computational challenges. On the other hand, we also consider how participants may detect or perceive an objectively stable period to be changeable or volatile – for instance, anxious individuals who overestimate volatility may perceive a change in the probabilistic relationship, when the observation was in fact due to chance (Huang et al., 2017). This mismatch between a participant's belief and the objective task captures exactly the sentiment of "perceiving problems where none exist". While misestimation of uncertainty does not necessarily equate to intolerance (one can imagine someone who is bad at estimating first-order uncertainties but scores low on the IUS), uncertainty processing biases or difficulties might plausibly lead someone to find uncertainty aversive. By providing a more granular approach to understand how people process different forms of uncertainty, this framework may also reveal the idiosyncratic paths towards its intolerance in different psychopathologies.

3.2. The causal origins and causally altering misestimation of uncertainty

Having discussed what misestimation of uncertainty may cause, we now consider its own causal origins, which may speak to the mechanisms driving psychopathology, and the differential routes to treatment that targets uncertainty processing.

One possibility is that uncertainty estimates reflect the "psychological backstory" of each participant: past experiences with uncertain environments (or risk factors) may lead to altered beliefs about uncertainty (Clark et al., 2018; Huys and Dayan, 2009). For example, early life stress (e.g., neglect, trauma, maltreatment, financial instability) often occurs in volatile, changeable environments where care is inconsistent (Davis et al., 2017), and large population-level studies and meta-analyses have shown that early life stress predicts psychopathology in later life (Carr et al., 2013; McLaughlin, 2020). As highlighted in a recent review, unpredictable environmental or parental signals are a novel and potent stressor that can affect the maturation of brain circuits and lead to vulnerabilities for psychopathology (Short and Baram, 2019). One study in humans showed that adults who self-report high levels of childhood unpredictability perform differently on tasks that involve memory updating under uncertainty, and this effect exists over and above other measures of adversity in childhood (Young et al., 2018). Uncertainty, then, could form a novel aspect of early life adversity that might explain a significant portion of the variance in cognitive outcomes. Early life stress has also been shown to exert profound effects on physiology, both on monoamine signalling in the central nervous system (Gillies et al., 2014), and peripherally, including dysregulation of stress

responses, e.g., the hypothalamic-pituitary-adrenal (HPA) axis (van Bodegom et al., 2017) and inflammatory immune responses (Dutcher et al., 2020). Fig. 3 demonstrates the interplay of these factors. In addition to physiological effects, early adverse experiences might also engender beliefs about uncertainty ("the world is a capricious place") that would be adaptive in a volatile environment, but unhelpful in future life when threats to safety are resolved. If experiences with volatility were indeed "overgeneralised" to outside of the volatile environment itself, they should also influence learning and decision-making tasks (Huys et al., 2015). One piece of evidence for this account comes from a recent study in which participants completed value-based learning and decision-making tasks at three separate timepoints during the COVID-19 pandemic (Suthaharan et al., 2021). They found that, as modelled with the HGF, the initial volatility estimate was influenced by the phase of the pandemic and even local government policies, demonstrating that real-world experience with a highly changeable environment can increase general expectations about volatility.

If previous experience can alter uncertainty estimation, can uncertainty estimation be experimentally altered? Preliminary evidence for the modifiability of beliefs about volatility recently came from Overman and colleagues (Overman, Browning et al., 2021). The authors trained participants with learning tasks where punishments were more volatile than rewards, which was hypothesised to induce a negative learning bias (Pulcu and Browning, 2017). Indeed, this procedure resulted in more loss-driven choices, and increased the punishment learning rates in a separate test block. There were no effects of reward training on learning about uncertain rewards, but the non-clinical sample in this study showed a general ceiling effect for reward learning, consistent with the so-called optimism bias in the general population (Palminteri and Lebreton, 2022; Sharot, 2011). This preliminary work raises the intriguing possibility that through training individuals with depression or anxiety to learn from informative (volatile) positive information, we might modify the commonly reported negative affective biases. It is possible then that CBT and other psychological treatments for mood and anxiety disorders might also challenge these higher-order beliefs about uncertainty (Fig. 3). The same group of researchers also reported that the learning rates for reward can be specifically increased with "antidepressant" transcranial direct current stimulation (tDCS) focussed on the dorsolateral prefrontal cortex (DLPFC; Overman, Sarrazin et al., 2021, preprint). Together, this line of evidence suggests new avenues to alter biases in learning under uncertainty, paving the way for interventions that target the pathological misestimation of uncertainty.

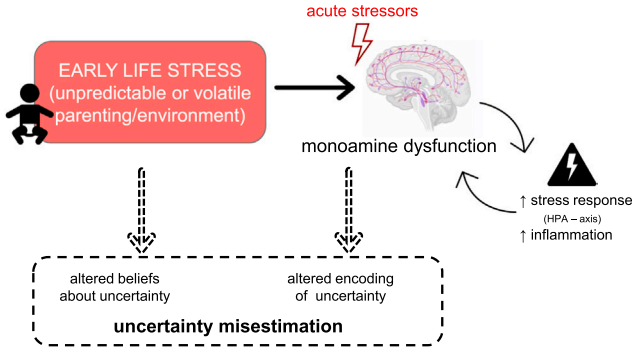


Fig. 3. A schematic to illustrate the possibility that uncertainty-related early life stress (unpredictable or inconsistent care/parenting, trauma, neglect, financial instability) causes a series of profound effects on human physiology, which cascade towards central monoamine dysregulation – especially in the presence of later acute stressors in life – see Short and Baram (2019) and Pagliaccio and Barch (2016) for reviews. Here we speculate (dashed lines and arrows) that this pathway could lead to two forms of uncertainty misestimation. First, early life stress might engender altered higher-order beliefs about volatility that are carried forward into adulthood and cause difficulties coping with uncertainty. These beliefs may be challenged by core aspects of CBT, such as threat-reappraisal. Second, the psychopharmacology of uncertainty processing would suggest that the monoamines (specifically noradrenaline and serotonin) critically encode or represent moment-to-moment estimates of different forms of uncertainty – which could be altered by SSRIs/SNRIs. It is possible then that different treatments (psychological and pharmacological) for neuropsychiatric disorders might target different aspects or levels of a common mechanism: uncertainty processing. We stress that this hypothesis is based on the empirical evidence to date but remains to be explicitly empirically tested.

3.3. The pharmacology of uncertainty estimation

Theoretical work (Doya, 2002; Yu and Dayan, 2005) has highlighted the role of neuromodulators in maintaining estimates of uncertainty, adding biological plausibility to the uncertainty estimation framework. Hence, probing participants estimates of uncertainty with computational modelling may offer a window into neuromodulatory dysfunction, and tasks that orthogonalise different forms of uncertainty may aid the screening of medications that target the uncertainty estimation system (Lawson et al., 2020; Marshall et al., 2016; Pulcu et al., 2019).

Historically, the catecholamine noradrenaline (NA) was hypothesised to be the primary neuromodulator involved in signalling "unexpected uncertainty" (Yu and Dayan, 2005). Seminal studies in rodents (Dalley et al., 2001) lend support to the theoretical hypothesis that NA – synthesised in the locus coeruleus (LC) – serves as a "neural interrupt" signal to support new learning, when an increase in unexpected uncertainty suggests a change in the state of the environment. In humans, pharmacological studies manipulating NA also demonstrated its key role in signalling sudden environmental changes: for example, propranolol – which blocks the action of NA - can reduce "tonic" estimates of volatility, so that participants learn about sensory associations more slowly, and rely more on their past experience to resolve sensory uncertainty (Lawson et al., 2020). Dopamine (DA) is another catecholamine, and it is the direct precursor to NA – animal models have shown that DA signals are heavily influenced by the first-order uncertainty of rewards (Fiorillo et al., 2003; Starkweather et al., 2017). Meanwhile, in humans, haloperidol – a D2 receptor antagonist – alters learning from the behavioural relevant information in uncertain environments, irrespective of whether the source of information is social or non-social (Rybicki et al., 2022). Additionally, methylphenidate, a drug that enhances catecholamine function, modulates the ability to optimise learning rate as a function of environmental volatility (Cook et al., 2019). Finally, in a motor learning paradigm modelled with the HGF, DA and NA antagonists were shown to have a complex set of complementary and opposing effects on participants' uncertainty fingerprints (Marshall et al., 2016). Together, these studies suggest that the catecholamines play a crucial role in signalling uncertainty in service of learning.

In recent years, several studies have indicated that serotonin (5-HT) also plays a crucial role in encoding different kinds of uncertainty. One recent study recorded from serotonergic neurons in the rodent dorsal raphe nucleus (DRN) and derived estimates of 'expected' and 'unexpected' uncertainty from rodent behaviour – these estimates correlated with the firing rates in > 50% 5-HT neurons (Grossman et al., 2022). Moreover, direct recordings from the human brain demonstrates that sub-second 5-HT fluctuations track sensory uncertainty in patients undergoing deep brain stimulation (Bang et al., 2020). Pharmacological studies also indicate a role for 5-HT in learning under uncertainty, with studies in humans showing that acute doses of escitalopram (a commonly-prescribed SSRI) impairs task performance (Skandali et al., 2018), whereas chronic doses improve probabilistic reversal learning in rats (Bari et al., 2010).

Together then, a picture is emerging that the monoamines – noradrenaline, dopamine, and serotonin – all play a role in how the brain represents or encodes uncertainty. Thus, as the pharmacological treatments for many mental health conditions target monoamine systems (e.g., antidepressants, anxiolytic and antipsychotic drugs), it is possible that these treatments improve symptoms via alterations to how uncertainty is estimated and represented in the brain. Choosing which

uncertainty estimates to alter may be important for treatment stratification, and this is a problem that computational modelling strives to solve.

3.4. Summary and future directions

Overall, these studies open up new possibilities for how to modify people's estimates of uncertainty. One hypothesis is that psychotropic medication and cognitive behavioural therapies (CBT), which are often prescribed and administered transdiagnostically (Dalgleish et al., 2020), might both act on different aspects of a core mechanism: uncertainty estimation. CBT – specifically CBT focussed on intolerance of uncertainty (such as CBT-IU) – might challenge higher-order beliefs about uncertainty via threat reappraisal, while the monoaminergic medications might target neural encoding of uncertainties in the brain. Future research should investigate this possibility, since it would imply that, irrespective of diagnosis, an individual's unique and computationally assayed uncertainty profile might aid in clinical decisions about who would benefit most from mediation or from psychological therapy, or might help signal risk for any psychopathology that could be mitigated via earlier access to interventions. Further empirical work linking intolerance of uncertainty (e.g., as measured with IUS-12) and misestimation of uncertainty will also support these treatment-based areas of research.

4. Opportunities and challenges for future work

After arguing for computational modelling of uncertainty processing as a transdiagnostic framework for understanding psychopathology and intolerance of uncertainty, this final section discusses some points of caution. We begin with considering the cognitive domains of uncertainty, as well as the subjective experience of uncertainty. We will also consider how well modelling can isolate uncertainty estimation from other psychological processes.

4.1. Uncertainty in different cognitive domains

Mapping neural and behavioural differences in psychiatric conditions to specialised domains (e.g. reward, punishment, attention, emotion processing, sensory processing) is a large undertaking, and sits at the core of transdiagnostic efforts such as the Research Domain Criteria (RDoC) project (Cuthbert, 2020; Sanislow et al., 2010). Although the forms of uncertainty discussed in previous sections is domain-agnostic, computational psychiatry studies to date tend to employ domain-specific tasks for different disorders (Table 1). For instance, reward or punishment learning tasks are often used to study mood and anxiety disorders (Pike and Robinson, 2022), a moral character inference task was used to study learning in patients with borderline personality disorder (Siegel et al., 2020), and tasks probing sensory or motor contingencies were used to elucidate sensory phenomena in ASD (Arthur et al., 2021; Lawson et al., 2017; Schneebeli et al., 2022, preprint). Within the same diagnostic category, different behavioural features have also been investigated with domain-specific tasks, e.g., in schizophrenia research, hallucinations have been linked to sensory conditioning (Powers et al., 2017), and paranoia to social and non-social value-based decision-making (Reed et al., 2020; Suthaharan et al., 2021). However, it is difficult to verify domain-specificity – or domain-generality – without direct comparisons across tasks and cohorts. Indeed, recent work has reported relatively weak correlations and poor generalisability between learning rates in different domains in the same individuals (Eckstein et al., 2022). One study to date serves as an important example of how best to progress the field in this regard, Henco et al. (2020) compared four groups (depression, schizophrenia, borderline personality disorder and controls) on a paradigm that addressed probabilistic learning across two domains (social and non-social). By including various disorders and domains whilst keeping the task and model constant, they were able to identify greater reliance on social over non-social information in the schizophrenia and borderline personality disorder (BPD) groups, and found that the faster learning about volatility in BPD is domain-independent but disorder-specific. It will be important for future studies to adopt a similar approach and explicitly test whether uncertainty processing is truly transdiagnostic across several "domains of function" (Sanislow et al., 2010).

Domain-specificity is also of interest to ASD research: on one hand, the diagnostic criteria of ASD transverses social and non-social domains (American Psychiatric Association, 2013); on the other hand, theories of ASD have transitioned across domains, shifting from a focus on social cognition to greater awareness of differences in sensory processing (Bervoets and Hens, 2020; Lawson et al., 2014; Pellicano and Burr, 2012). While altered reliance on predictive relationships and inferences about volatility have been reported in the perceptual or sensory domain (Lawson et al., 2017; Schneebeli et al., 2022, preprint), the evidence is less clear for learning from volatile rewards, e.g., with null findings from a study comparing volatile and stable environments (Manning et al., 2017), but with a larger study reporting elevated learning rates on a probabilistic reversal learning task (Crawley et al., 2020). These discrepancies further emphasise the need for applying standardised tasks and models across different domains in future research, and the importance of assessing large and diverse samples. These efforts will help address both the heterogeneity within ASD, and help disentangle the contributions from any co-occurring mental health conditions, especially anxiety and depression (Hollocks et al., 2019).

Computational studies on mood and anxiety disorders have also begun to address the issue of domains, mostly on the distinction between positive and negative valences (Bishop and Gagne, 2018; Crocq, 2017; Sharp et al., 2015; Woody and Gibb, 2015). Conceptually, depression may pertain more to differences in the approach of reward, while anxiety may be linked to altered avoidance of threats (Bishop and Gagne, 2018). To differentiate between valences, probabilistic learning and decision-making tasks can incorporate different framings (e.g., to gain reward or avoid losses), or different modalities of outcomes such as monetary reward versus electric shocks (Browning et al., 2015; Gagne et al., 2020; Seymour et al., 2012). Importantly, individuals can regulate their learning rates to the volatility of rewards and punishments separately (Pulcu and Browning, 2017), which may imply a valence dissociation in uncertainty processing. Echoing this dissociation, a recent meta-analysis reported that patients with mood and anxiety disorders displayed higher punishment learning rates, but not reward learning rates (Pike and Robinson, 2022). This effect is particularly prominent in unmedicated patients (Aylward et al., 2019), and it may suggest a form of volatility overestimation that is specific to the aversive domain. However, studies that directly compare between volatile and non-volatile conditions presented a more nuanced picture: in earlier studies, trait anxiety was associated with impaired adaptation to volatility for aversive outcomes (Browning et al., 2015), but not reward (Blain and Rutledge, 2020; Browning et al., 2015); although, a more recent study compared and modelled behaviour in the two domains more systematically, and they observed a valence-independent impaired adaptation to volatility in individuals with high internalising symptoms (Gagne et al., 2020). Hence, valence-dependent and valence-independent differences may both be relevant to anxiety and depression. These distinctions, together with the distinctions between forms of uncertainty, may help explain the heterogeneity within mood disorders.

4.2. The impact of misestimating uncertainty on mood and confidence

As discussed in Section 3, appraisal of different forms of uncertainty may be modified with CBT-IU. To better examine this process, we need to understand how our subjective experiences are linked to our estimates of uncertainty. Morriss and colleagues designed a novel questionnaire to

explore the links between uncertainty and emotions, and they showed that uncertainty is not only aversive, but also modulates ongoing emotional states – when experiencing positive emotions, encountering uncertainty would decrease the intensity of said emotional state, while, for negative emotions, the intensity would be increased under uncertainty (Morriss et al., 2022). Yet, there has been little empirical work on how uncertainty estimates can influence ongoing affective experiences. One study has linked stress with the level of irreducible uncertainty in probabilistic threat contingencies (de Berker et al., 2016): self-reported stress is generally low when threat is very likely or very unlikely, but highest when there is 50% chance of threat occurrence. Moreover, the effect of uncertainty on subjective experiences may be moderated by individual differences: participants with high depressive traits have lower mood ratings in a volatile environment, but not in a stable one (Blain and Rutledge, 2020). To better understand the interactions between mood and uncertainty, it is important to develop models that jointly explain learning profiles and mood dynamics (Eldar et al., 2016). These efforts may benefit conditions where mood dynamics is the core feature of interest, such as bipolar disorder (Mason et al., 2017) and mood disorders in general (Sharp et al., 2020).

Misestimation of uncertainty may also influence metacognitive judgments, with confidence ratings expected to reflect the dynamics of uncertainty (Meyniel et al., 2015). Critically, the influence of uncertainty on confidence may be dissociable from its influence on learning: for OCD patients, while higher learning rates are apparent in how their actions were updated according to feedback, the trial-by-trial patterns of confidence ratings were mostly comparable to controls (Marzuki et al., 2022; Vaghi et al., 2017). Moreover, compulsive behaviour has also been linked to altered coupling between learning and confidence ratings in the general population (Seow and Gillan, 2020). These dissociations indicate the complex nature of the reactions to uncertainty, i.e. not everyone feels less confident in the face of uncertainty. Hence, future studies should also study the subjective and "objective" read-outs of uncertainty in parallel, and understand how they may be influenced differently by behavioural or pharmacological interventions, to help enrich the computational phenotyping of "misestimation of uncertainty".

4.3. Distinctions and interaction between different uncertainties

In Section 2, we outlined a taxonomy of uncertainty, which might give the impression that each form of uncertainty is independent. However, as emphasised by several theoretical accounts, estimates of volatility would compete with estimates of first-order uncertainties in explaining unexpected observations (Piray and Daw, 2021; Pulcu and Browning, 2019; Yu and Dayan, 2005). That is, if a participant generally assumes that there is low first-order uncertainty (i.e., the cue is always highly predictive of outcome), an unexpected outcome would likely be regarded as evidence for change, and thus result in an increase in learning rate (equivalently, one might say that the participant would infer a new context); yet, since we cannot directly measure their beliefs about first-order uncertainty, we might falsely assume that they are overestimating volatility. Conversely, apparent "failures" in accurately estimating first-order uncertainty might also be better explained with misestimation of more abstract uncertainties. These caveats are important to consider when trying to interpret these results in the context of psychopathology. Additionally, while models such as the HGF are equipped to simultaneously parameterise different kinds of uncertainty processing, parameter identifiability (uniqueness) is a topic of interest in computational research, and future studies should assess the correlation across parameters explicitly (Wilson and Collins, 2019).

Furthermore, in Sections 2 and 3, we outlined seemingly distinct boundaries between different kinds of uncertainty to draw broad parallels across different modelling frameworks and tasks. We reiterate that alternative distinctions have been proposed, often dependent on the modelling approach introduced by the authors and circumscribed to the type of tasks available to researchers. For instance, as seen in our associative learning example, there is a conceptual link between volatility and structural uncertainty – intuitively, if you infer that the probabilistic relationship has changed, you inherently recognise that the preceding context is no longer "active". However, misestimation of the number of contexts may result in very different estimates of the probabilistic relationship *between* changes. As an example, consider the evolution of the contingencies in the work of de Berker and colleagues (2016): there are several contexts to be inferred, compared to that of a serial reversal learning paradigm with only two contexts, despite similar numbers of changes. The link between mechanisms of how people infer volatility or structure is a recent and active area of research in cognitive science (Heald et al., 2023; Yu et al., 2021) and more work is needed to fully understand the interactions across these forms of uncertainty.

Another potential challenge to the distinctions in Section 1.2 is that, perhaps deviating from its broader definitions in e.g., Pulcu and Browning (2019), the same level of "unexpected uncertainty" may not accompany every contingency change: in a reversal learning task, if the contingency switches regularly (e.g., between 80% reward for option 1 and 20% for option 2 and vice versa, with one reversal every 15–20 trials), then, after one hundred reversals a participant might develop not only an accurate estimate of the two contexts (80% rewarded for option 1 and 20% rewarded for option 1), but also a fairly accurate estimate of the reversal frequency. Consequently, these initially unexpected changes gradually become more "expected". These subtleties will be important to unpack in future empirical studies, especially when building models of how uncertainty estimation evolves over longer timescales, from days up to years.

4.4. The role of other cognitive processes

Finally, it is worth highlighting that it can be difficult to completely isolate the role of uncertainty estimation, even with the help of computational models. First, every task involves an array of psychological processes (Wiecki et al., 2015): as exemplified with the probabilistic selection task (Frank et al., 2004), individual differences on this task have strong links to reward processing in cortico-striatal circuits, and also to working memory (Collins et al., 2014; Collins and Frank, 2012; Maia and Frank, 2011). Second, uncertainty increases the difficulty level of learning and decision-making tasks; this could raise concerns about confounds from general cognitive capacity or motivation, especially given the prevalence of uncertainty-related differences in case-control studies (c.f., a review on task-general cognitive deficits across psychiatric conditions; Abramovitch et al., 2021). Finally, while the HGF can obtain participant-specific trial-wise volatility estimates, its ability to do so is dependent on a set of assumptions (e.g., that participants approximate Bayesian inference in this specific manner; Mathys et al., 2011), and it is an empirical question as to whether these assumptions hold, and whether the HGF can adequately explain participant behaviour on any given task (see Marković and Kiebel, 2016, for comparison between the HGF and another approximate Bayesian model). These caveats highlight the need for corroborating evidence on the representations of uncertainty, e.g., that uncertainty is also encoded in neuromodulator systems (Section 3.3), and for extending the model space to cover more contributing psychological processes.

5. Conclusions

Intolerance of uncertainty is a transdiagnostic feature of psychopathology, in which uncertainty is experienced as aversive. Computational psychiatry can bring new light to the construct of the intolerance of uncertainty, as it considers how a person copes with different forms of uncertainty defined within behavioural tasks and applies computational models to probe the individual differences in uncertainty estimation. Across a simplified taxonomy of these uncertainties, there is a wealth of evidence to suggest that their misestimation contributes to

psychopathology. These modifiable estimates of uncertainty impact behaviour, mood, and confidence, and may represent different mechanistic routes towards finding uncertainty aversive. Future work should address the issue of domains, the interaction between uncertainties and the role of other cognitive processes, so as to confirm the role of misestimating uncertainty in psychopathology. Ultimately, there is a need to bridge the computationally defined estimates about uncertainty with the phenomenology of mental health conditions, and to verify the mechanistic roles of uncertainty estimates through causal interventions. In the future, this may help modify psychiatric nosology and develop new means of managing mental health challenges.

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