Previous work has established that schizophrenia risk increases in proportion to the degree of *C4A* expression[10]. To investigate whether the increased engulfment of synaptic structures by iMGs in the patient-derived cellular models was due to the risk variant in the *C4* locus, the authors first determined the genotype and expression level of the *C4* locus in the schizophrenia patient-derived lines. They then applied a complement activation assay to assess neuron-specific C4 expression. In the immune system, C4 induces C3 activation, allowing the covalent attachment of C3 onto its targets and subsequently promoting the engulfment of targets by phagocytic cells. The authors therefore examined C3 deposition to evaluate the level of C4 activation. Since *C4A* expression is largely dependent on the copy number of the long form of *C4A* (*C4AL*), Sellgren et al. hypothesized that, if *C4AL* increases neural complement deposition through increased neural *C4A* expression, the C3 deposition should correlate with the *C4AL* copy number in their model[13]. That was indeed what the authors observed: the C3 complement deposition was strongly positively correlated with *C4AL* copy number in induced pluripotent stem cell-derived neural cultures from schizophrenia patients, but not with the copy number of the short or the long form of *C4B*[13]. Strikingly, the authors also identified an effect of *C4AL* copy number on complement-dependent engulfment of synaptic structures by iMGs[13]. Taken together, these results show an association between increased synapse engulfment and the schizophrenia risk variant.

Minocycline, a broad-spectrum tetracycline antibiotic capable of penetration into the brain, has been speculated to have therapeutic potential in some neurological diseases through its anti-inflammatory effects[14]. The authors therefore asked whether minocycline could decrease synaptic pruning in their cellular model. They pretreated iMG cultures with minocycline in a series of clinically relevant doses and revealed a dose-dependent decrease in synapse engulfment[13].

Sellgren et al. hypothesized that chronic exposure to minocycline or the similar brain-penetrant drug doxycycline during adolescence might decrease schizophrenia risk. Because these two medications are commonly prescribed for the treatment of acne vulgaris, the authors investigated electronic health records from two large academic medical centers with many years of follow-up and identified individuals between the ages of 10 and 18 who received at least one electronically prescribed antibiotic from several similar brain-penetrant drugs. This investigation revealed that minocycline or doxycycline exposure for at least 90 days was associated with significantly decreased risk of incident psychosis[13].

Sellgren et al. raise the exciting possibility that minocycline may have a beneficial effect on the hyperactive synaptic pruning associated with schizophrenia, pointing to a potential early therapeutic intervention. More broadly, the results of the study highlight the power of coupling experimental results and clinical data. Altogether, these data support a novel point of view on microglia activation and a potential way to intervene early.

Several limitations of this intriguing story are worth noting. First, although the co-culture of microglia and neurons derived from schizophrenia patients provides a novel avenue to study synaptic pruning in addition to human clinical and animal studies, it remains unclear to what extent this method recapitulates the in vivo condition, given that the molecular signature of iMGs differs from that of human freshly isolated microglia[15] and that synaptic pruning in vivo requires motor or sensory inputs. Second, although this study has established a correlation between *C4A* copy number and synapse engulfment, further genetic-manipulation experiments are needed to clarify to what extent the *C4* variant contributes to increased synaptic pruning. In addition, as the effect of *C4* risk variant was observed in neural lines but not in iMG lines, the factors that cause an increased phagocytosis by microglia merit further exploration. Finally, future studies are needed to understand the effects of minocycline on microglial function and the use of minocycline as an early therapeutic intervention for schizophrenia. ❐

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Published online: 22 February 2019
https://doi.org/10.1038/s41593-019-0343-1

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Competing interests

The authors declare no competing interests.

COMPUTATIONAL PSYCHIATRY

Post-traumatic stress disorder as a disorder of prediction

Disproportionate reactions to unexpected stimuli and greater attention to perceived threat are cardinal symptoms of post-traumatic stress disorder. Computational psychiatry helps explain how these responses develop and result from abnormalities in learning and prediction during and after traumatic events.

Peggy Seriès

Following a terrifying event, such as military combat or rape, 5–30% of individuals[1] will develop post-traumatic stress disorder (PTSD). For them, the intense fear they have experienced leaves a debilitating trace that will interfere with their future life. PTSD symptoms include flashbacks, nightmares, hyperarousal, and severe anxiety, as well as uncontrollable

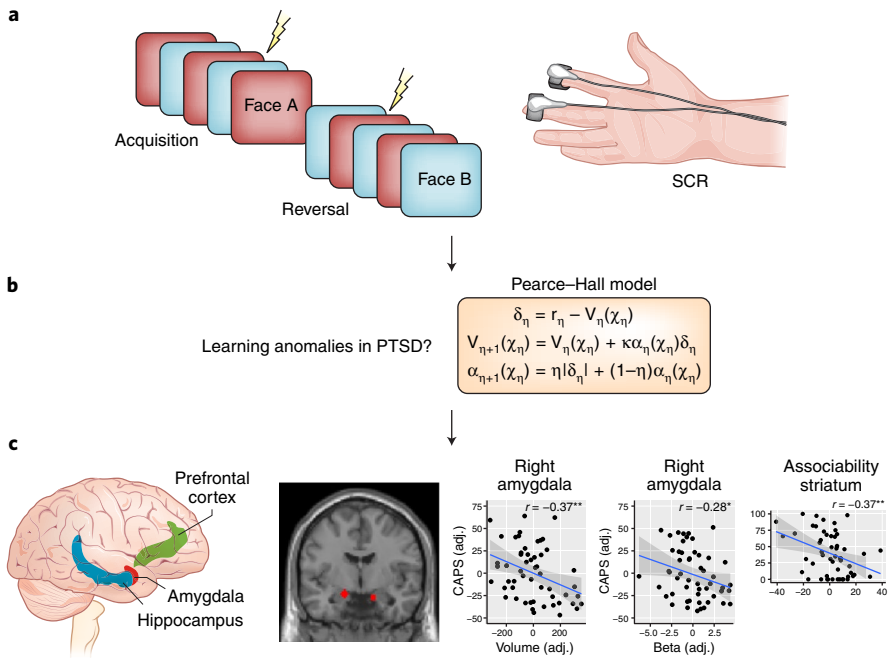

Fig. 1 | A computational psychiatry approach to investigating possible learning anomalies in PTSD. a, Homan et al.[2] recorded SCR during a fear-conditioning experiment in combat-exposed veterans. Face A was first paired with a mild electric shock. After reversal, Face B was paired with the shock while Face A was no longer associated with it. **b**, They then modeled the SCR data using various reinforcement models which compute a value, *V*, for each face cue, *x*, iteratively updated at each trial, *n*, based on the discrepancy between the expected ($V_n(x_n)$) and obtained outcome r_n, i.e., the prediction error δ_n. The best fitting model was found to be a hybrid Pearce–Hall model, which includes an associability variable (α_n) that reflects attention allocation to cues previously accompanied by surprise. They determined the best-fitting parameters of the model for each individual and found that PTSD severity was associated with increased prediction error weight, η. **c**, The model-based time-series was then convolved with the hemodynamic response function and then regressed against functional MRI data with a focus on regions known to be involved in PTSD, i.e., the amygdala, the striatum, the hippocampus and the dorsal anterior cingulate cortex (dACC). They found that the neural computations that were shaped by these altered prediction-error weights contributed to the symptoms of PTSD: aversive value encoding in the amygdala and striatum; and associability computations in the striatum, dACC, and hippocampus. They also found that the right amygdala computations contributed to the symptomatology above and beyond the effects of smaller amygdala volumes, suggesting additive effects of right amygdala volume and function.

thoughts about the event and behavioral strategies to avoid environments that may trigger the symptoms.

Why does PTSD develop for a fraction of but not all individuals submitted to similar experiences? Is there a biological vulnerability for the disorder or a biological signature of its consequences that could be used as a diagnostic marker and guide the development of new therapies? Recent studies by Homan et al.[2] and Brown et al.[3] in combat-exposed veterans show how computational psychiatry can help answering those questions. As with other mental disorders[4], the key might be to model PTSD as resulting from (subconscious) inferential biases and impaired belief updating.

Common theories propose that PTSD results from abnormalities in learning during and after the traumatic event[5]. Fear conditioning could explain why neutral stimuli (people, places, sounds, etc.) that have been associated with the traumatic event acquire the capacity to trigger and maintain anxiety long after the trauma itself. Why this association doesn't weaken over time has been attributed to either the fact that it was abnormally strong in the first place or—more likely—to deficits in extinction processes, i.e., a failure for the association to weaken when the same cues are encountered without leading to the traumatic event. This could be a result of patients' avoidance strategies: individuals with PTSD avoid encountering such cues again and thus may never experience them as being safe. Other theories assume, on the contrary, that PTSD is related to basic deficits in acquiring associations between specific cues and the traumatic event. This would result in associating the trauma with the environment as a whole, causing heightened contextual anxiety and/or overgeneralization of fear to all cues resembling the initial cues. In environments not related to the traumatic event, PTSD patients have also robustly been found to exhibit reduced habituation of responses to repeatedly presented novel, intense, or fear-relevant stimuli, as well as greater sensitization of fear-related autonomic responses. Despite the popularity of those theories, the specific components of anomalous learning in PTSD remain unclear.

Computational modeling is ideally placed to help formalize and quantitatively test hypotheses regarding such potential abnormalities. In the laboratory, we can explore how individuals learn to predict the association between different cues and threats (such as electric shocks) and their flexibility in using, updating, or forgetting those predictions. Computational modeling can then reveal interindividual differences in internal learning and evaluation processes that are otherwise inaccessible to raw-data analysis[4].

Homan et al.[2] used a fear-conditioning task with a group of combat-exposed veterans presenting a wide range of PTSD symptoms (Fig. 1). Participants had to passively learn the pairing between two face images and mild electric shocks. Face A was paired with an electric shock in one third of the trials, while Face B was never paired with the shock. The acquisition phase was immediately followed by a reversal phase. After reversal, face B was now likely to lead to the shock, while face A was no longer paired with the shock. To assess conditioning, the authors measured skin conductance response (SCR). Interestingly, PTSD severity had no effect on the acquisition of the conditioned response before or after the reversal: all participants seemed to learn equally well. However, a modeling approach uncovered subtle differences.

Homan et al. used a basic reinforcement-learning (Rescorla–Wagner) model and a Pearce–Hall hybrid model to fit the SCR data. Both types of reinforcement models compute a 'value' for each face cue, iteratively updated at each trial, based on the discrepancy between the expected and obtained outcome, i.e., the prediction error. However, the hybrid model replaces the constant learning rate of the Rescorla–Wagner model with a dynamic 'associability' parameter, which reflects attention allocation to cues that had been previously accompanied by surprise. Associability dynamically modulates value

learning by accelerating it for cues whose predictions are poor (large prediction errors) and decelerating it when predictions become reliable.

In line with previous studies[3,6], Homan et al. found that the hybrid model accounted for the SCR data better than the basic model. Moreover, after fitting the model to individual participants' data, they found that PTSD severity was associated with one particular model quantity: the prediction-error weight, which can be seen as a learning rate for associability. In line with Brown et al.[3], they found that highly symptomatic combat veterans were more influenced by prediction errors, weighting them more strongly as they adjusted trial-by-trial attention to cues.

Using model-based functional MRI, they went one step further and asked about the neural correlates of such differences: where and how strongly the computations of value, prediction errors, and associability are reflected in the neural activity. One of the main structures implicated in PTSD is the amygdala, considered as the threat-processing center and locus of associative learning[1]. The amygdala has been found to be smaller in size and hyperactive in PTSD. Other structures are also involved in providing context and meaning to the traumatic events, in particular, the prefrontal cortex and the hippocampus. PTSD patients typically show reduced activation of the prefrontal cortex and hippocampus, which is thought to correspond with reduced top-down inhibitory control of the amygdala, possibly explaining the hyper-responsivity of the amygdala to fearful stimuli[1].

Homan at al. found that neural activity in the amygdala was associated with the computation of value for the face images. PTSD was associated with lower neural tracking of value in the amygdala and the striatum, in addition to smaller amygdala volumes. Moreover, and departing from the findings of Brown et al.[3], the authors found lower tracking of associability (and less so of prediction error) in the striatum, hippocampus, and dorsal anterior cingulate cortex in individuals with higher PTSD severity. They suggest that the higher weights assigned to prediction errors might be a compensatory adjustment for the decreased neural tracking of associability.

Computational psychiatry of PTSD is in its infancy, and quantifying individual differences in internal learning and evaluation processes is an important first step. By examining PTSD in a predictive-coding framework, these recent findings may provide new keys to understanding the disorder: the increased weight given to surprising outcomes might explain the disproportionate reactions to unexpected stimuli or events, as well as heightened orienting and attentional biases toward negative information[3]. It could also explain the aberrant learning and synaptic plasticity long postulated to be at the core of PTSD[1], that aversive outcomes could be experienced as less predictable and less avoidable, and the documented aversion to ambiguity in aversive environments in PTSD[7].

The next steps will be to clarify how those results compare with previous findings[5] and whether they extend (or not) to other frameworks such as instrumental[3] and reward[8] learning. It will be crucial to verify that these individual differences correspond to vulnerabilities for the disorder (as opposed to its consequences) and how they relate to the different dimensions of PTSD symptoms (re-experiencing, avoidance, hyperarousal). It will be also important to show that they are specific to PTSD, as opposed to depression[3] or other anxiety disorders[9], which have also been found to relate to learning rates of associative learning in dynamic aversive environments[10]. Ultimately, computational studies will need to focus on developing models that can integrate theories of abnormal learning during and after traumatic events with the explanation of some or all symptom clusters into a single framework.

Importantly, such learning mechanisms are also at the core of the therapies that have shown to be effective in PTSD[11]: prolonged exposure, cognitive processing therapy, and trauma-focused cognitive–behavioral therapy. These treatments all try to counteract avoidance strategies and to directly address—and update—the associations (memories, feelings, thoughts) made during the traumatic events. Despite the relative success of these techniques, the mechanisms behind both their strengths and their weaknesses are inadequately understood, and it has been suggested that up to 33% of people with PTSD are resistant to treatment[12]. We need to understand how those therapies work when they do, possibly by identifying the relationship between individual learning differences (such as increased attention to surprising outcomes) and treatment success. Ultimately we will need to design new therapies informed by a better understanding of the role of inference and learning in the genesis and maintenance of psychological distress[13]. ❐

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Published online: 22 February 2019
https://doi.org/10.1038/s41593-019-0345-z

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