Reduced top-down connectivity as an underlying mechanism for psychotic experiences in healthy people

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Abstract

Perception results from our brain's ability to make predictive models of sensory information. Recently, it has been proposed that psychotic traits may be linked to impaired predictive processes. Here, we examine the brain dynamics underlying prediction formation in a population of healthy individuals with a range of psychotic experiences. We designed a novel paradigm, which incorporated both stable and volatile sound sequences by manipulating their probability. We measured prediction error with electroencephalography and gauged prediction formation explicitly by behaviourally recording sensory 'regularity' learning errors. Critically, we show that top-down frontotemporal connectivity may be a neural mechanism by which impaired regularity learning influences psychotic experiences. These findings further our understanding of the neurobiological underpinnings of prediction formation and provide evidence for a continuum of psychosis in the healthy, non-clinical population.

Keywords: prediction, volatility, psychotic, mediation, effective connectivity

One Sentence Summary

Healthy individuals with psychotic experiences have impaired sensory learning, mediated by reduced top-down frontotemporal connectivity.

In a stable environment, sensory perception is facilitated by prior beliefs about what is likely to happen next (*1, 2*). By estimating the probability of forthcoming events, we can form a predictive model about the world and its regularities (*3*). When circumstances are 'volatile', such that previously learnt regularities change, having a flexible predictive model is more advantageous (*4-6*). Previous literature has shown that healthy individuals are able to optimally estimate environmental volatility (*6*), adopting a greater learning rate in the face of ever changing, volatile circumstances (*6, 7*). This motivates exploratory behaviour and continuous updating, as well as suppression of top-down prior beliefs (*8*). However, this state of constant learning is inefficient as a long-term strategy in stable environments (*9, 10*). Stable environments allow for the development of a robust predictive model, which simultaneous enables an efficient encoding of sensory stimuli while minimising the spending of cognitive resources (*5*). Poor estimation of environmental volatility has been found to have negative consequences on social cognition and decision-making in individuals with autism, anxiety and schizophrenia (*11-13*). These patient groups have aberrant representations of volatility; either over-estimating it, leading to imprecise, weak predictive models, or under-estimating it, leading to rigid and maladaptive predictive models (*14*).

Emerging theoretical accounts of psychosis postulate that psychotic experiences arise due to an impairment in the brain's predictive ability to infer internal and external sensations (*14-16*). Individuals experiencing psychosis (such as schizophrenia) may misattribute saliency to irrelevant sensory information leading to the formation of unfounded odd beliefs. There are many converging lines of evidence that support the theory that psychosis arises due to an impaired predictive model (*17, 18*). The most robust and replicable empirical evidence for this arises from attenuated neurophysiological responses to surprising sounds embedded in a sequence of predictable sounds, in so-called oddball paradigms (*19-21*). This is thought to reflect a sensory *prediction error* deficit that results from a failure to form accurate predictions

about forthcoming predictable stimuli (*15, 22, 23*). Reduced prediction error (PE) response in schizophrenia has been linked to alterations in brain connectivity between the frontal and the temporal cortex as well as within the inferior frontal gyrus (IFG) and auditory cortex (*24, 25*). Alterations in the neurophysiology of PEs have been shown to increase as psychotic traits increase, suggesting that the degree of PE aberrancy aligns on a continuum of psychosis (*26, 27*) – the idea that nonclinical individuals in the general healthy population may display a range of psychotic traits. However, the underlying brain networks, presumably also altered along the continuum remain unknown. The psychosis continuum comprises the full spectrum of psychotic experiences, from healthy individuals who experience a range of psychotic-like experiences, to prodromal individuals with subclinical symptoms, and to those with florid psychosis at the very end of the spectrum (*28, 29*). One of the benefits of investigating psychosis in relation to neural dynamics (*30*) and PE response (*31, 32*) on the healthy end of the spectrum is the possibility to eschew the confounds of medication and illness severity.

The aims of this study were three-fold. The first aim was to examine the relationship between regularity learning and sensory PE measured with electroencephalography (EEG). Secondly, we wanted to elucidate the neural dynamic underpinnings of prediction formation during regularity learning. For this purpose, we developed a novel auditory oddball task with either fixed sound probabilities (stable conditions) or varying sound probabilities (volatile conditions; see Figure 5). The third aim was to investigate whether aberrations in prediction formation are aligned on a continuum of psychosis. Specifically, we examined the relationship between regularity learning, PE responses and the brain networks engaged in prediction violations. We hypothesised that disruptions in intrinsic and top-down brain dynamics (*24*) mediate the influence of impaired prediction formation on increased psychotic experiences.

Results and Discussion

Our first aim was to compare the strength of the predictive models established in stable and volatile in a regularity learning task. For this purpose we examined the event-related potential (ERP) recorded at frontocentral channel (Fz), and in line with the vast oddball literature we found that responses to deviant sounds were larger than responses elicited by standard sounds, regardless of volatility ($F(1,30) = 45.33$, $p < 0.001$, $\eta^2 = 0.60$). Moreover, we found a significant interaction between PE response and volatility ($F(1,30) = 11.06$, $p = 0.002$, $\eta^2 = 0.27$). Critically, a follow-up analysis revealed that PEs were larger under the stable compared to the volatile conditions, $t(30)=-3.33$, $p = 0.002$, $d = -0.60$ (see Figure 1a and 1b). Increased PEs in stable conditions, compared to volatile, have been identified in previous studies (*33, 34*). PEs signal a violation between what the brain predicts will happen and what is actually experienced. As such, PEs are fundamental teaching signals that drive updating of the brain's predictive model of the sensed world (*35, 36*). Thus, greater PE responses to regularity violations indicate a stronger (i.e., more precise) prediction model in *stable* than volatile conditions (*36, 37*).

We next examined differences in mean percentage errors in probability estimation (regularity learning error) and mean confidence ratings during stable and volatile conditions. The data show that participants had fewer errors in regularity learning during stable conditions ($M = 9.30\%$, $SE = 0.87$), compared to volatile conditions ($M = 12.38\%$, $SE = 1.07$), $t(30) = -2.40$, $p = 0.023$, $d = -0.43$. In addition, participants had greater confidence in their probability estimates during stable conditions ($M = 2.57$, $SE = 0.07$), compared to volatile conditions ($M = 2.19$, $SE = 0.05$), $t(30) = 4.78$, $p < 0.001$, $d = 0.86$ (see Figure 1c). This shows that regularity learning and confidence are enhanced in stable, more predictable environments, than in more volatile, less predictable, environments. In addition, we asked whether regularity learning errors were related to the degree of PE response. Pearson's correlations and Bayesian analysis

revealed a very strong, significant correlation between regularity learning errors and PEs (at the ERP level) in stable conditions (p = 0.003 ($p_{adjusted}$ < 0.01), BF_{+0} = 33.99; see Figure 1d, Table S2), hence demonstrating that greater PEs in *stable conditions* are associated with better sensory regularity learning. Regularity learning is the process by which the brain learns the statistical structure in the environment and forms predictive models of what is likely to happen next (*38-41*). Previous studies have demonstrated that individuals are able to implicitly learn the statistical structure of sensory events in the environment (*3, 23*). Crucially, by simultaneously recording PE responses and behaviourally measuring regularity learning, we show for the first time that greater sensory PEs are associated with improved explicit ability to gauge the sensory regularities within one's environment.

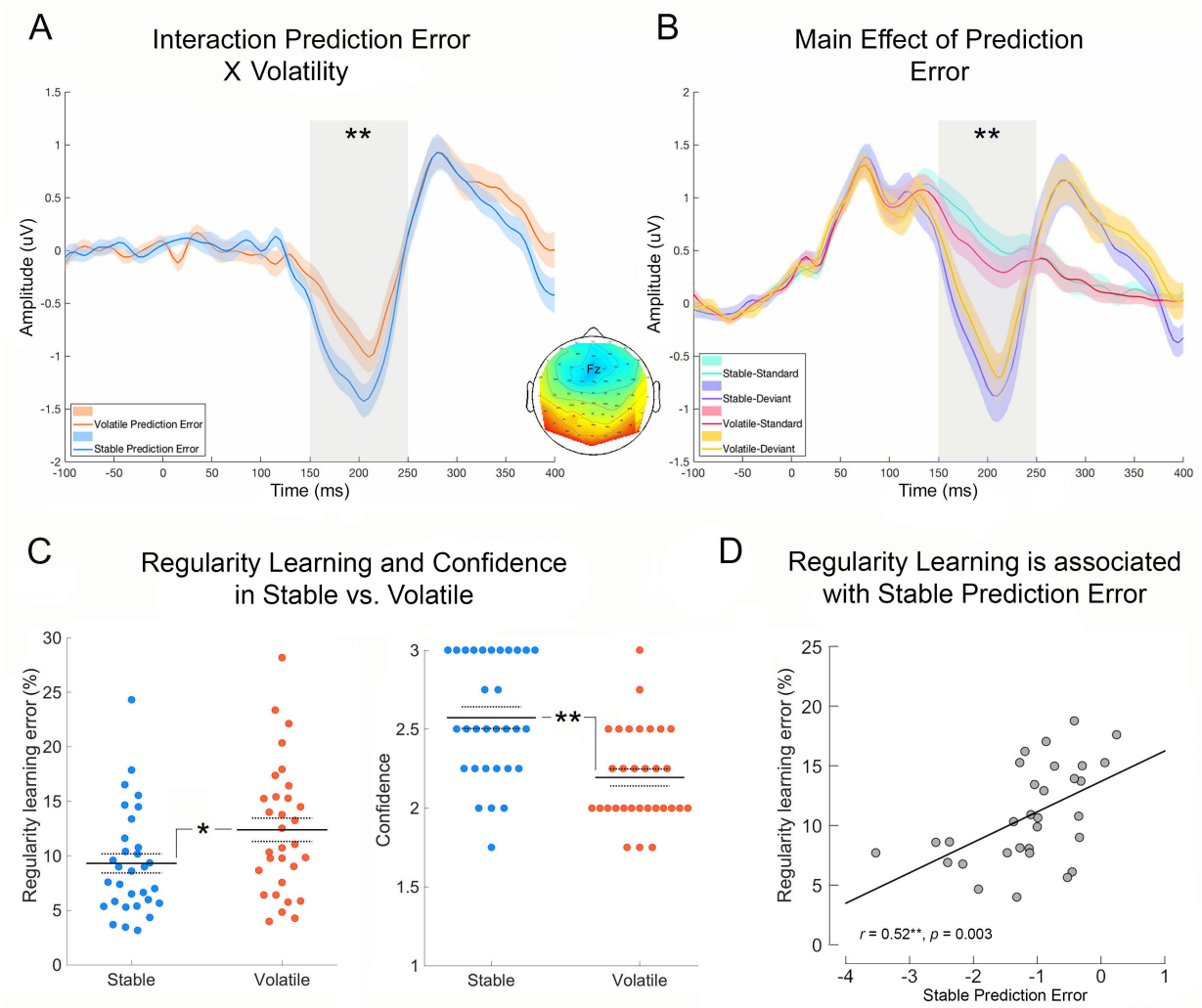

Fig. 1. Greater prediction errors and regularity learning indicate a more precise prediction model in *stable* than *volatile* conditions. A) Significant interaction between volatility (stable – blue – versus volatile – orange) and brain PE responses, B) Significant main effect of PE, showing brain responses evoked by standards (green, red) and deviants (purple and yellow) in the context of stable and volatile conditions. Solid lines represent mean and lighter shading represent standard error of the mean, C) Fewer regularity learning errors and greater confidence in stable (blue) than volatile (orange) conditions, D) Significant correlation between regularity learning errors and prediction errors in stable conditions. * $p < 0.05$; ** $p < 0.001$.

To further investigate the sensory PEs evoked by regularity violations with fewer spatial and temporal constraints, we ran a general linear model for the whole spatiotemporal volume of brain activity. Firstly, we replicated previous auditory oddball findings by showing a significant main effect of PE response (standard sounds vs deviant sounds) peaking at 205 ms (peak-level $F = 170.92$, $p_{FWE} < 0.001$), 290 ms (peak-level $F = 240.99$, $p_{FWE} < 0.001$; frontocentral and occipitoparietal channels), and 25 ms (right frontal channels; peak-level $F = 25.26$, $p_{FWE} = 0.004$). Moreover, we found a significant interaction between PE response and volatility, at 165 ms over occipitocentral channels (peak-level $z = 4.27$, $p_{FWE} = 0.015$, see Figure 2a). Next, we asked whether regularity learning errors were related to neuronal activity. To address this question, we conducted a spatiotemporal multiple regression analysis at the interaction between PEs and volatility (Stable PEs > Volatile PEs) with regularity learning error as the predictor variable. Our data show that a decrease in regularity learning errors significantly predicted an increase in brain activity at 165 ms (peak-level $z = 3.64$, cluster-level $p_{FWE} = 0.034$, see Figure 2b). In order to determine where in the brain this effect came from we used source reconstruction techniques (*42*), which uncovered an increased activity in the right superior frontal gyrus (peak-level $z = 2.19$, $p_{uncorrected} = 0.014$) and the right fusiform gyrus (peak-level $z = 1.89$, $p_{uncorrected} = 0.029$, see Figure S2b). This finding demonstrates that the difference in PEs in stable and volatile environments (ability to attune to volatility) increases as regularity learning improves, associated with activity in right frontotemporal regions. This finding is concordant with the idea that healthy individuals are optimally attuned to different

environments, such that in volatile environments there is a greater reliance on local probability (smaller PE) (*43*), whereas stable environments enable stronger neuronal representations, or more precise predictive models (larger PE), of global regularities (*44*).

Source-level analysis revealed that stable PEs engaged frontoparietal regions, such as the middle frontal gyrus (peak-level $z = 4.23$, $p_{FWE} = 0.02$), the primary motor area (peak-level $z = 4.45$, $p_{FWE} = 0.009$), and the inferior parietal lobule (peak-level $z = 4.56$, $p_{FWE} = 0.006$). In comparison, volatile PEs engaged occipitoparietal regions, such as the precuneus (peak-level $z = 5.05$, $p_{FWE} = 0.001$) and the middle occipital gyrus (peak-level $z = 4.39$, $p_{FWE} = 0.011$, see Figure 2c). These results are in keeping with prior studies suggesting that higher hierarchical frontal regions (engaged for stable PEs) are associated with formation and representation of prior beliefs (*45-47*) and activity in inferior parietal regions is associated with the evaluation of prior beliefs (*48, 49*). In comparison, lower hierarchical occipital regions (engaged for volatile PEs) are associated with sensory processing (*46*), which drive prior belief updating.

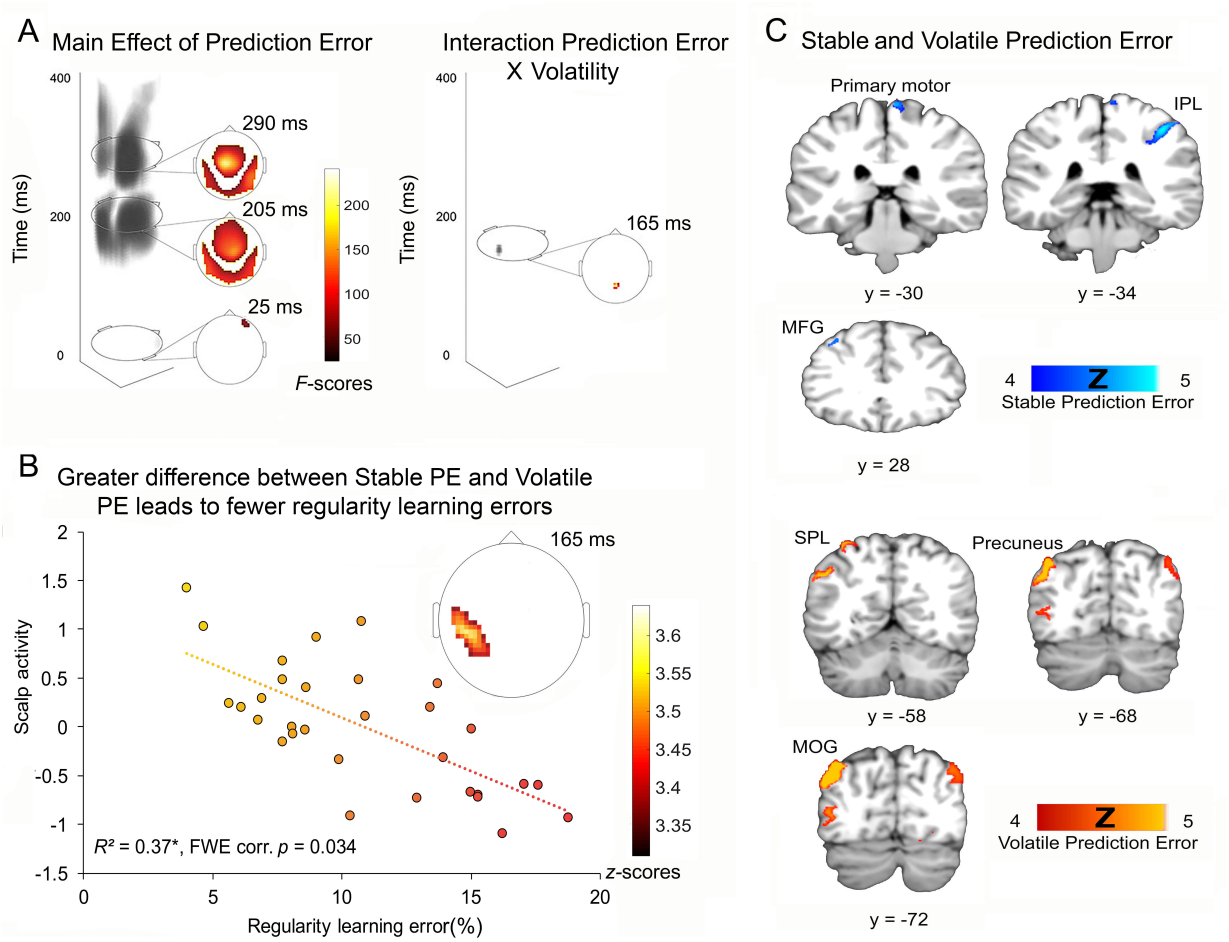

Fig. 2. Brain responses underlying volatility attuning and regularity learning. A) Spatiotemporal univariate statistical analysis revealed a significant main effect of PE (left column) over frontal and occipitoparietal channels; and PE x volatility interaction (right column) over occipitocentral channels. B) Spatiotemporal multiple regression analysis revealed a negative relationship between regularity learning errors and spatiotemporal activity during the interaction (Stable PE > Volatile PE) at 165ms. C) Source reconstruction analysis revealed significant clusters for stable PEs in frontoparietal regions versus for volatile PEs in occipitoparietal regions. IPL = inferior parietal lobule; MFG = middle frontal gyrus; SPL = superior parietal lobule; MOG = middle occipital gyrus. All maps are displayed at $p < 0.05$, FWE whole-volume corrected.

The network architecture underlying PE response has been extensively studied previously (*50, 51*), with robust findings demonstrating that a three-level hierarchical brain model underlies the generation of PEs evoked in auditory oddball paradigms. In the current study, we focused on the pattern of connections that best *differentiates* PE responses under stable and volatile environments. The high temporal resolution of EEG data enables improved estimation of the underlying neurobiological interactions, providing insights into the brain's

effective connectivity (*52, 53*). Here, we were interested in, 1) the effect of contextual volatility on neuronal responses, and 2) the effective connectivity related to psychotic traits.

Bayesian model comparison was performed on thirty-six different dynamic causal models (see Figure S3), which were based on the functional brain architecture shown to underlie PE responses (*50, 51*). Results from Bayesian model selection using random effects family-level analysis indicated that the best model included connections amongst six *a priori* defined regions, with inputs to left and right primary auditory cortex (A1); intrinsic connections within the A1; bilateral connections between: A1 and superior temporal gyri (STG), STG and inferior frontal gyri (IFG); as well as lateral connections between left A1 and right A1, and left STG and right STG (model 7; see Figure 3a). In the optimal model, larger PEs in stable compared to volatile blocks were caused by enhanced modulations in backward, forward and intrinsic connections (see Figure 3a). Forward connections are thought to convey PEs, whereas backward connections covey predictions (i.e., beliefs about sensory input), and intrinsic connections emulate local adaptation of neuronal responses and are thought to reflect the precision (strength) of neuronal representations (*53, 54*). This finding is in keeping with the predictive coding account of the mechanisms underlying perception of an auditory oddball sequence (*55*), and suggest that more precise models about sensory input are enabled by greater brain connectivity in stable than volatile PEs.

In order to test the evidence for a continuum of psychosis, we examined the altered neural dynamics, behaviour and neurophysiology related to psychotic traits in the general healthy population. First, we examined brain connectivity estimates by applying Bayesian model averaging across all models (weighted by their probability) and participants. Critically, we found a strong, significant correlation between psychotic experiences and top-down connectivity from the right IFG to STG (frontotemporal) ($p = 0.005$ ($p_{adjusted} < 0.05$), $BF_{-0} = 18.28$; see Table S3). This shows that a greater degree of psychotic traits in healthy people was

associated with weaker top-down connectivity from inferior frontal to superior temporal regions. Precisely the same connection has previously been found aberrant in patients with schizophrenia (*24*), as well as high-risk individuals with a genetic predisposition for schizophrenia (*56*), and is aligned with the dysconnectivity hypothesis for schizophrenia, observed particularly between frontotemporal regions (*57, 58*). Next, we asked if aberrations in behaviour (greater regularity learning errors) and neurophysiology (attenuated PE) are also aligned on the psychosis continuum. Pearson's and Bayesian correlations were conducted on psychotic experiences, regularity learning errors, as well as PEs (at the ERP level) in stable and volatile conditions. We found a moderate, significant correlation between psychotic experience and errors in regularity learning ($p = 0.028$, $BF_{+0} = 4.37$; see Table S2), meaning that healthy individuals with greater psychotic experiences were worse at learning about sensory regularities.

Our final analysis explored if the top-down frontotemporal connection, which was weaker in individuals with more psychotic experiences, was the underlying mechanism by which regularity learning errors influenced psychotic traits. For this purpose, we employed a mediation analysis, which seeks to establish the mechanism that enables a predictor to influence an outcome (*59*). Multiple regressions were conducted to asses each component of the mediation analysis (see Figure 3c). The results demonstrated that regularity learning error was a significant predictor of top-down frontotemporal connectivity ($b = -0.009$, $p = 0.02$), and that top-down frontotemporal connectivity was a significant predictor of psychotic experience ($b = -4.98$, $p = 0.04$), supporting the mediation hypothesis. Regularity learning was no longer a significant predictor of psychotic experiences after controlling for the mediator, top-down frontotemporal connectivity ($b = 0.08$, $p = 0.17$), consistent with a full mediation (see Figure 3b). The results indicate a significant indirect effect (*ab* = total effect - direct effect) of regularity learning on psychotic experience through top-down frontotemporal connectivity (*ab*

= 0.05, Bias Corrected and Accelerated Bootstrap (BCA) CI [0.004, 0.14], P_M = 0.38 - percent mediation: percent of the total effect accounted for by the indirect effect). Critically, these findings identify top-down frontotemporal connectivity as a potential mechanism by which poorer regularity learning influences increased severity of psychotic experiences in healthy people.

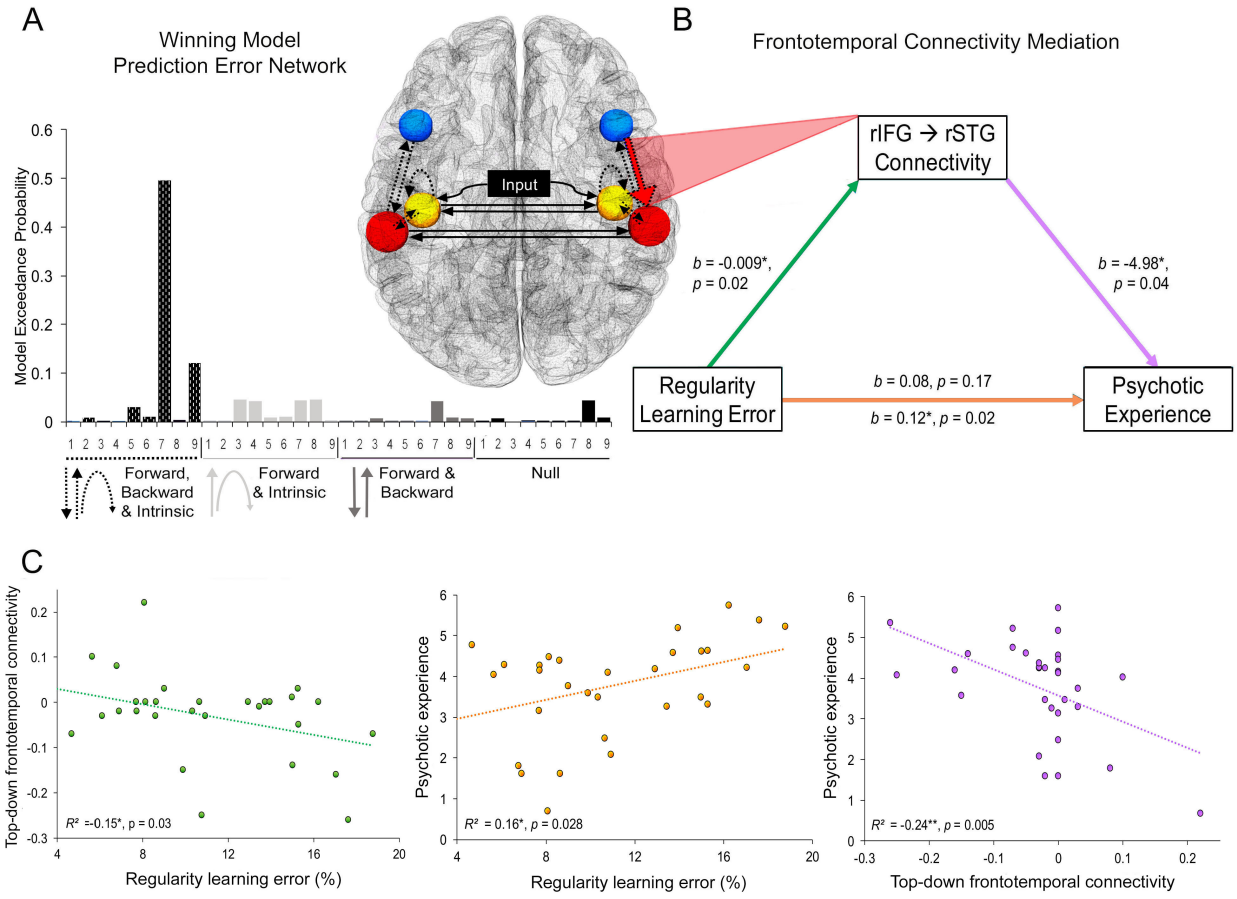

Fig. 3. Top-down frontotemporal connectivity mediates the relationship between regularity learning errors and severity of psychotic experiences in healthy people. A) 36 competing connectivity models tested the modulation of connections for stable > volatile PEs. The winning model architecture had connections between all six regions bilaterally (model 7), and included volatility-dependent (stable > volatile) modulations in forward, backward and intrinsic connections, B) The mediation analysis revealed a significant full mediation, with an indirect effect of regularity learning on psychotic experience through top-down frontotemporal connectivity, C) Regression plots, demonstrating that regularity learning errors predict top-down frontotemporal connectivity (green) and psychotic experiences (orange), and that top-down frontotemporal connectivity predicts psychotic experiences (purple).

In the current study, we explored the brain dynamics underpinning regularity learning under uncertainty, and the relationship between disruptions to predictive processes and psychotic experiences in healthy individuals. We found that individuals learn better and their brain PE responses are greater during stable than volatile conditions. At the neural level, there is a greater engagement of higher hierarchical regions, such as the middle frontal gyrus, as well as greater modulation of intrinsic, forward and backward connections. Importantly, our data show that aberrations in the brain's predictive model are aligned on a continuum of psychosis, in the sense that healthy people with more psychotic traits have poorer regularity learning abilities, mediated by weaker top-down frontotemporal connectivity. Our findings have implications for understanding the neurobiological underpinnings of impaired prediction formation, with the potential to inform the application of neuromodulation therapies for psychosis targeting the frontotemporal network.

Methods

Participants

Thirty-one, healthy adults were recruited through the Psychology Research Participation Scheme (SONA) and online newsletter to staff and students across the University of Queensland. Prior screening confirmed that all participants did not have a history of psychiatric or neurological disorders, and were not currently taking medication or using any illicit drugs. The highest level of education, smoking habits and alcohol consumption were recorded. Participants also completed the 92 Item - Prodromal questionnaire (PQ), which measures positive and negative symptoms and is typically used to assess psychotic experiences in healthy individuals (*60*). The PQ scores were weighted by the frequency of the psychotic experience (i.e. "Daily" scored 4; "A few times per week" scored 3; "Once a week" scored 2; "1-2 times" scored 1; "Never" scored 0), in all the analyses we used the log transformed,

weighted PQ scores. For further information on the demographics of the sample and the weighted PQ scores per participant, as well as the positive and negative symptom frequencies, please see Table S1, Figure 4 and Figure S1. Participants provided written informed consent for taking part in our study after reading and understanding the information sheet, which included a full description of the study and procedure. Participants received monetary reimbursement for their time. This research was approved by the University of Queensland Human Research Ethics.

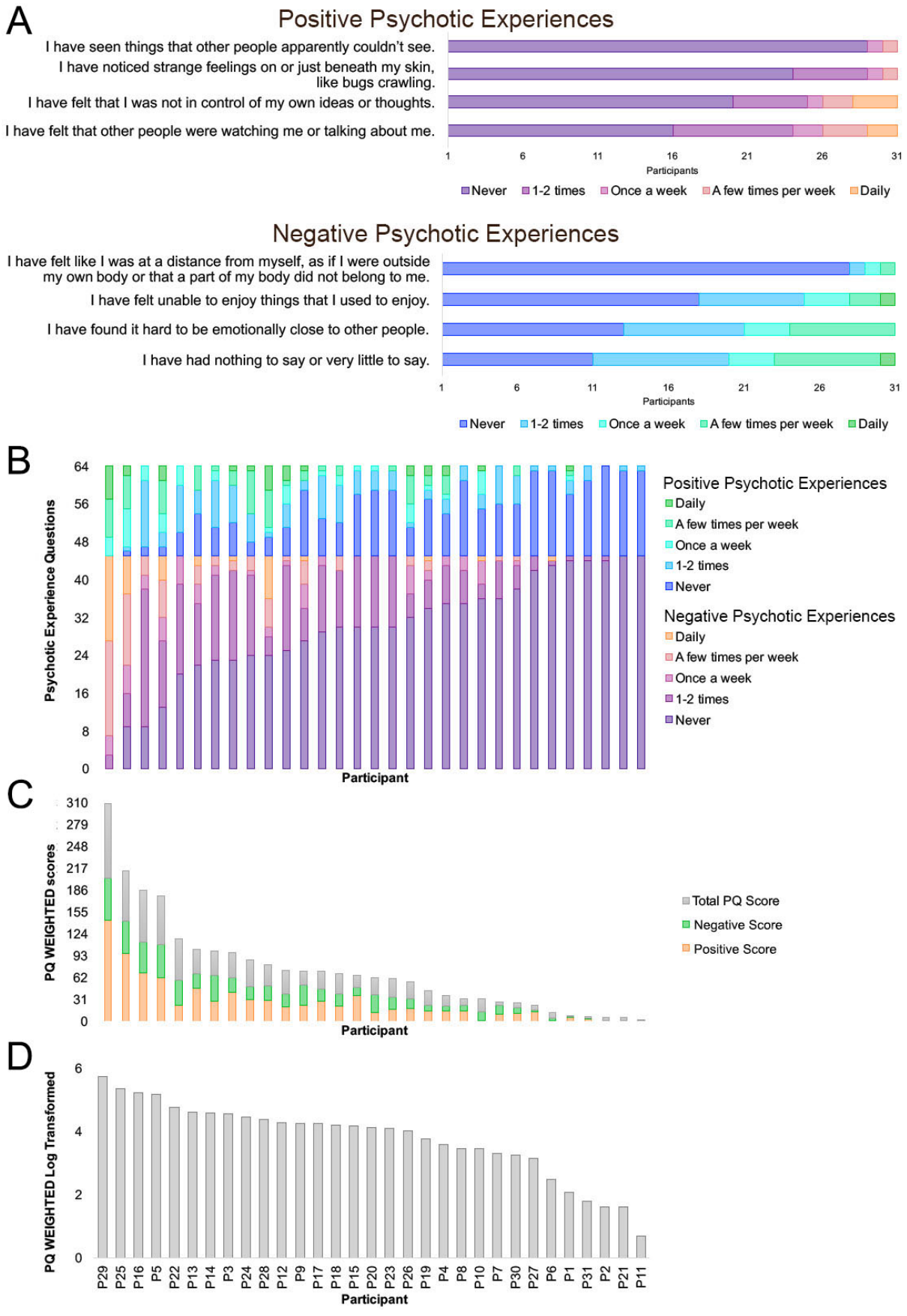

Fig. 4. Prodromal questionnaire (PQ) scores. A) Frequency of a subset of positive psychotic experiences (purple to orange) and negative psychotic experiences (blue to green) in the

sample, for the full list of positive and negative psychotic experiences please see Figure S1, B) Frequency of psychotic experiences for each participant, displaying positive psychotic experiences (purple to orange) and negative psychotic experiences (blue to green), C) PQ scores weighted by frequency for each participant, displaying total PQ weighted scores (grey), negative weighted scores (green) and positive weighted scores (orange), D) Log transformed PQ weighted scores for each participant.

Materials and Procedure

Volatility task. An auditory 'duration' oddball paradigm was modified so that the probability of different sounds varying in duration was either stable or volatile (adapted from Weber and colleagues (*61*)). In a stable experimental run, a particular sound was always more likely than another sound (e.g. short sounds had 80% probability and long sounds had 20% probability). In volatile experimental runs, a particular sound, which was more likely in the first block, was then less likely in the second block, with eight blocks and eight reversals of probability in total. The Volatility task is represented in Figure 5.

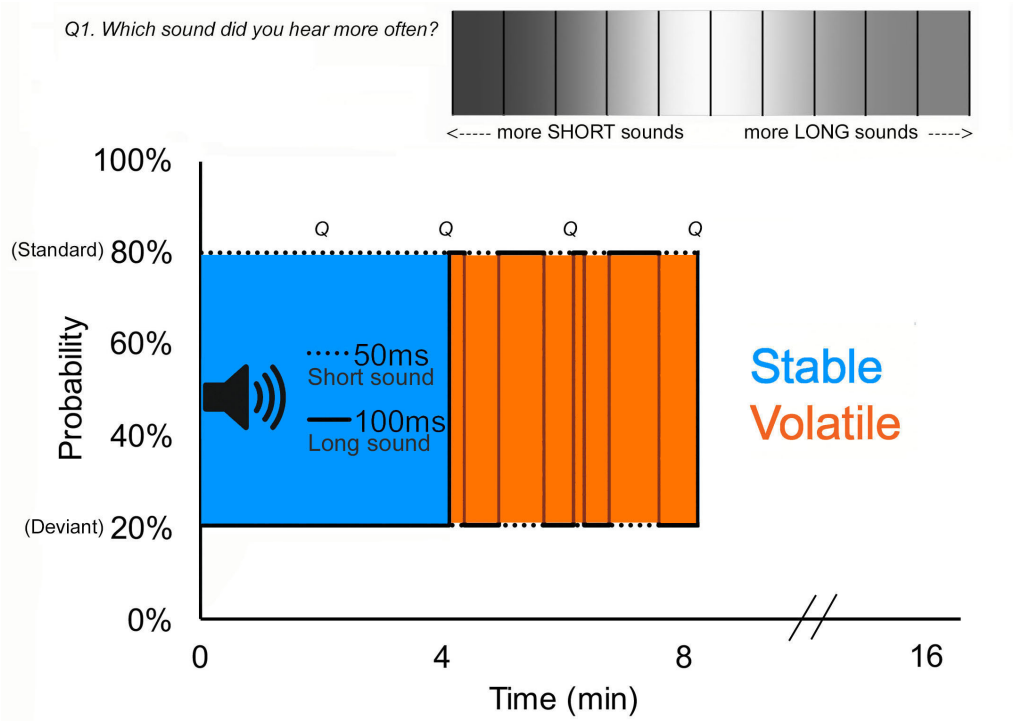

Fig. 5. Volatility task. A schematic diagram showing an example of a stable and volatile run. In the stable run the short sound (50 ms) was more probable (80%) throughout, whereas in the volatile run the long sound (100 ms) was more probable in the first block, then the short sound was more probable in the second block, with eight blocks and eight reversals of probability in

total. Participants were asked to listen to the sounds and estimate the probability (top Q1) of the most frequent sound and rate their confidence on this judgment, every 2:08 min.

Auditory stimuli and experimental design. The Volatility paradigm consisted of 2000 pure tones played over eight experimental blocks (2:08 min each). The tones varied in duration such that short tones lasted 50 ms and long tones lasted 100 ms. All tones had an identical frequency of 500 Hz and a smooth rise and fall periods of 5ms. The tones were presented in a pseudorandom order, with each presentation of 5 tones including a deviant tone in a randomly assigned position; the deviant tones were always separated by at least one standard tone. The tones were delivered binaurally via insert earphones for ~2 min every 500 ms. Sound intensity was kept constant between participants at a comfortable level. The order of stable and volatile blocks was counterbalanced across participants.

Procedure. During the Volatility task participants were seated on a comfortable chair in front of a desk and computer screen, in a dimly lit Faraday cage testing room. Prior to the experiment, the participants were familiarised with the different sound types and trained with two short practice runs of the task. Participants were asked not to move while the sounds were played and to look at a fixation cross at the center of the screen. The participants were instructed to pay attention to the sounds in order to judge the proportion of different sound types and rate their confidence on this judgment. Participants were required to make these estimates every 2:08 min using a computer keyboard and a mouse. The total duration of the Volatility task was approximately 20 minutes (including short breaks).

EEG recording and preprocessing

A Biosemi Active Two system recorded continuous electroencephalography (EEG) data from 64 scalp electrodes at a sampling rate of 1024Hz. Electrodes were arranged according to the international 10-10 system for electrode placement (Oostenveld, R. & Praamstra, P, 2001). Pre-processing and data analysis were performed with SPM12

(http://www.fil.ion.ucl.ac.uk/spm/). Data were referenced to standard BioSemi reference electrodes, down-sampled to 200Hz and high-pass filtered at 0.5 Hz using the Butterworth filter. Eye blinks were detected and marked using the VEOG channel at an eyeblink threshold of 4, the Berg method was used to correct for eye blinks. The data were epoched offline with a peri-stimulus window of -100 to 400ms. Further artefact rejection was performed by thresholding all channels at 100uV, robustly averaging across trials (*62*), applying a low-pass Butterworth filter of 40 Hz, and baseline correcting between -100 to 0 ms. We analysed event-related potentials from the onset of standard and oddball tones, separately for stable and volatile conditions.

Data Analysis

In the current study the analyses conducted followed both a frequentist approach and a Bayesian approach. As well as applying the Bayesian approach for model comparison and model averaging to investigate brain connectivity (explained in more detail in the Dynamic Causal Modelling section), we also calculated Bayes factors for the correlation analyses. Bayes factors were used to explore the robustness and the strength of evidence for the associations, and as they are resistant to multiple comparisons (*63*). Briefly, Bayes factors are based on Bayes' rule, displayed in the equation below. The observed data (the posterior; $p(H_1|data)/p(H_0|data)$), equals the prior odds- the odds of the null and alternative hypotheses ($p(H_1)/p(H_0)$) before the data is observed, multiplied by the Bayes factor ($p(data|H_1)/p(data|H_0)$) or the change (update) from prior to the posterior (*64*).

$$\underbrace{\frac{p(\mathcal{H}_1 \mid \text{data})}{p(\mathcal{H}_0 \mid \text{data})}}_{\text{The Posterior}} = \underbrace{\frac{p(\mathcal{H}_1)}{p(\mathcal{H}_0)}}_{\text{The Prior}} \times \underbrace{\frac{p(\text{data} \mid \mathcal{H}_1)}{p(\text{data} \mid \mathcal{H}_0)}}_{\text{Bayes factor } BF_{10}}$$

The subscript '10' in BF_{10} indicates that in the equation H_1 (the alternative hypothesis) is in the numerator and H_0 (the null hypothesis) is in the denominator, and subscript '01' indicates the reverse. In the current study, Bayesian factors were computed using BF_{10}, which indicates testing the alternative hypothesis over null hypothesis. The Bayesian analyses were conducted using the JASP package (https://jasp-stats.org/). The frequentist analyses were conducted using the SPSS package (IBM Corp, 2012), multiple correlations were corrected using the Šidák method (*65*).

Single-channel and behavioral analyses

Single-channel analysis. We conducted a full factorial 2x2 within subjects ANOVA design on mean ERP values with Environment (Stable and Volatile) and PE (Standard and Deviant) as factors. Mean ERP values were obtained by averaging across the preselected time window of interest, which is typical for PE latency: 150 – 250 ms, over a frontocentral channel (Fz), in which PE responses are typically seen in oddball paradigms (*66*). We contrasted evoked responses to deviant and standard sounds, under stable and volatile conditions. Significant interactions were further analyzed using paired-samples t-tests.

Behavioural analysis. We conducted paired t-tests on mean percentage errors in probability estimation (a proxy for regularity learning) and mean confidence in probability estimation, in stable vs. volatile conditions. This was done in order to assess the effect of environment (Stable vs. Volatile) on regularity learning and confidence in estimating probabilities. Next, we computed Pearson's and Bayesian correlations to assess the association between psychotic experience, regularity learning errors, and PEs in stable and volatile conditions (see Table S2).

Spatiotemporal maps and Source Reconstruction

Three-dimensional spatiotemporal images were generated from averaged ERP data for each participant and condition. A two-dimensional matrix, corresponding to the scalp electrode space was produced, for each time bin from 0 to 400ms in steps of 5ms. The images were assembled according to their peristimulus temporal order, which resulted in a three-dimensional spatiotemporal image (32 × 32 × 81) per participant. These images were then smoothed at full width half maximum of 12 mm × 12 mm × 20 ms. In addition, we performed source reconstruction of the spatiotemporal image volumes in order to make inferences about the cortical regions that generated the scalp data. We co-registered the sensor data with a single sphere head model in order to obtain the source estimates on the individuals' cortical mesh. Next, we conducted forward computations of the effect each dipole on the cortical mesh has on the sensors. Finally, we inverted the forward computations with the multiple sparse priors algorithm under group constraints (*67, 68*), these inverse reconstructions were summarized as images (smoothed at $8mm^{3)}$ for each of the four conditions in every participant.

For both spatiotemporal and source level, data were analysed using a mass-univariate general linear model method. We conducted a full factorial analysis, with factors: Environment (Stable and Volatile) and PE (Standards and Deviants). We computed contrast images for main effects, interactions and t-tests, in order to gauge the differential effect between deviants and standards during stable and volatile conditions. In addition, we conducted multiple regression analyses with regularity learning error as the predictor and activity at the scalp and source level as the outcome. This was done to relate regularity learning ability to PE response at the neural level. Age was added into all models as a covariate, since attenuation in PE response occurs with age (*69*). The order of volatile and stable conditions was also included as a covariate as it has been shown to influence PE responses (*33, 34*). Finally, psychotic experience was added as a covariate in order to exclude any potential differences in volatile and stable conditions due

to psychotic symptoms. All statistical maps are reported at a threshold of $p < 0.05$ family-wise error (FWE) corrected for multiple comparisons for the spatiotemporal peak/volume or source region.

Dynamic Causal Modelling

Dynamic causal modelling (DCM) was employed, which similarly to source reconstruction also uses a spatial forward model. However, in addition to this, DCM incorporates a biologically informed temporal forward model, which places empirically-derived constraints on the inversion and allows inferences about the source connectivity (*70*).

In the model specification, we defined the brain architecture based on previous robust findings (*50, 51*), demonstrating that a three-level hierarchical brain model underlies the generation of PE responses evoked in auditory oddball paradigms. This model included: bilateral primary auditory cortices (A1; MNI coordinates: left [-42, -22, 7] and right [46, -14, 8]; chosen as the cortical input sources), bilateral superior temporal gyri (STG; left [-61, -32, 8] and right [59, -25, 8], and bilateral inferior frontal gyri (IFG; left [-46, 20, 8] and right [46, 20, 8]). We considered nine competing model architectures that differed in source regions and the pattern of intrinsic, backward, and forward connections (See Figure S3). In order to model the effect of environment on effective connectivity, we examined the differences in PE response for stable versus volatile conditions. For this, the ERPs for each condition (Stable Standard, Stable Deviant, Volatile Standard, Volatile Deviant) were merged into either Stable PE (Stable Deviant – Stable Standard) or Volatile PE (Volatile Deviant – Volatile Standard). The full details of the model specification have been described by Garrido, Friston, Kiebel, Stephan, Baldeweg and Kilner (*55*). Briefly, we modelled each source region with a single equivalent current dipole; an input time delay with a prior mean of 60 ms; drift was modelled

with a direct cosine transform of 1, and eight modes were selected for the 0 to 400 ms peri-stimulus time window, over stable PE and volatile PE trials.

The explanatory models were grouped by families based on the modulations placed on intrinsic and extrinsic connectivity, i.e. (I) Forward and Intrinsic family; (II) Forward and Backward family; (III) Forward, Backward and Intrinsic family; and (IV) Null family (no modulation in connectivity). We conducted Bayesian model selection, with a random-effects approach at both the model and family levels (*71*). We computed both expected and exceedance probabilities for the different families of models. The exceedance probability for a model indicates how well this model explains the data in comparison to the other models. We also conducted Bayesian model averaging in order to determine the strength of the effective connectivity at each connection, weighted by the likelihood of all models, and across all participants.

We conducted Pearson's and Bayesian correlations to assess the association between psychotic traits and the effective connectivity estimates. Only the top-down, right frontotemporal (right IFG to right STG) connection demonstrated a strong, significant association with psychotic experiences ($p = 0.005$, $BF_{-0} = 18.28$; see Table S3). The association was followed up with a mediation analysis using Preacher and Hayes (*72*) bootstrap method (PROCESS in SPSS) to directly investigate whether top-down connectivity was a mechanism by which regularity learning influenced the severity of psychotic experiences (*59*).

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Author contributions

Author ID designed the paradigm, conducted the experiment, analysed the data and wrote the first draft of the manuscript. Author MIG assisted in the design of the paradigm; authors MIG and RR assisted in the analysis of data. All authors contributed to and have approved the final manuscript.

Competing interests

Authors declare no competing interests.

Data and materials availability:

The article's supporting data and materials have been made available. Please find raw data files and the behavioural/connectivity scores here:

https://espace.library.uq.edu.au/view/UQ:724759.

Supplementary Materials

Materials and Methods

Figures S1-S4
Tables S1-S3

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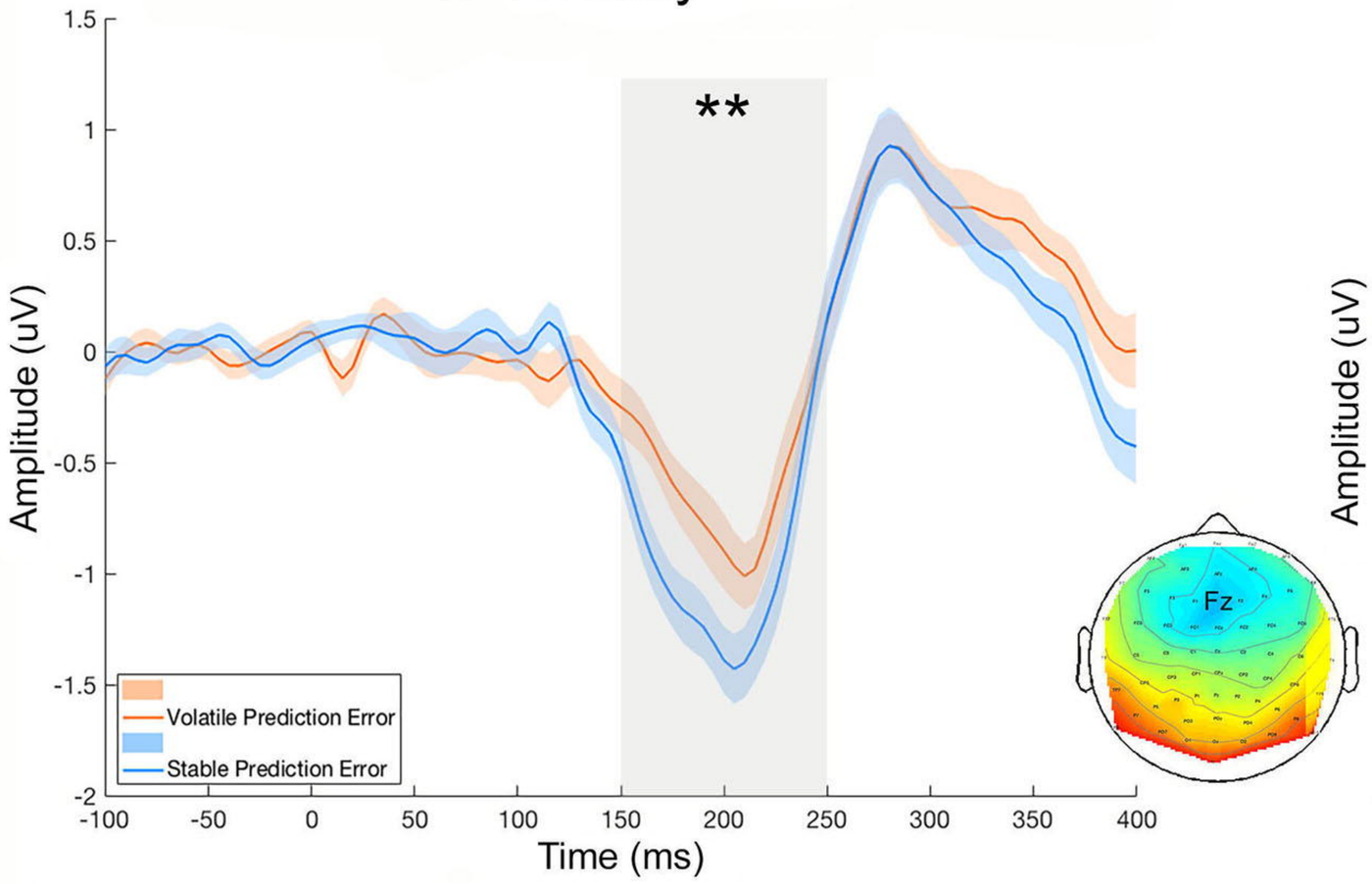
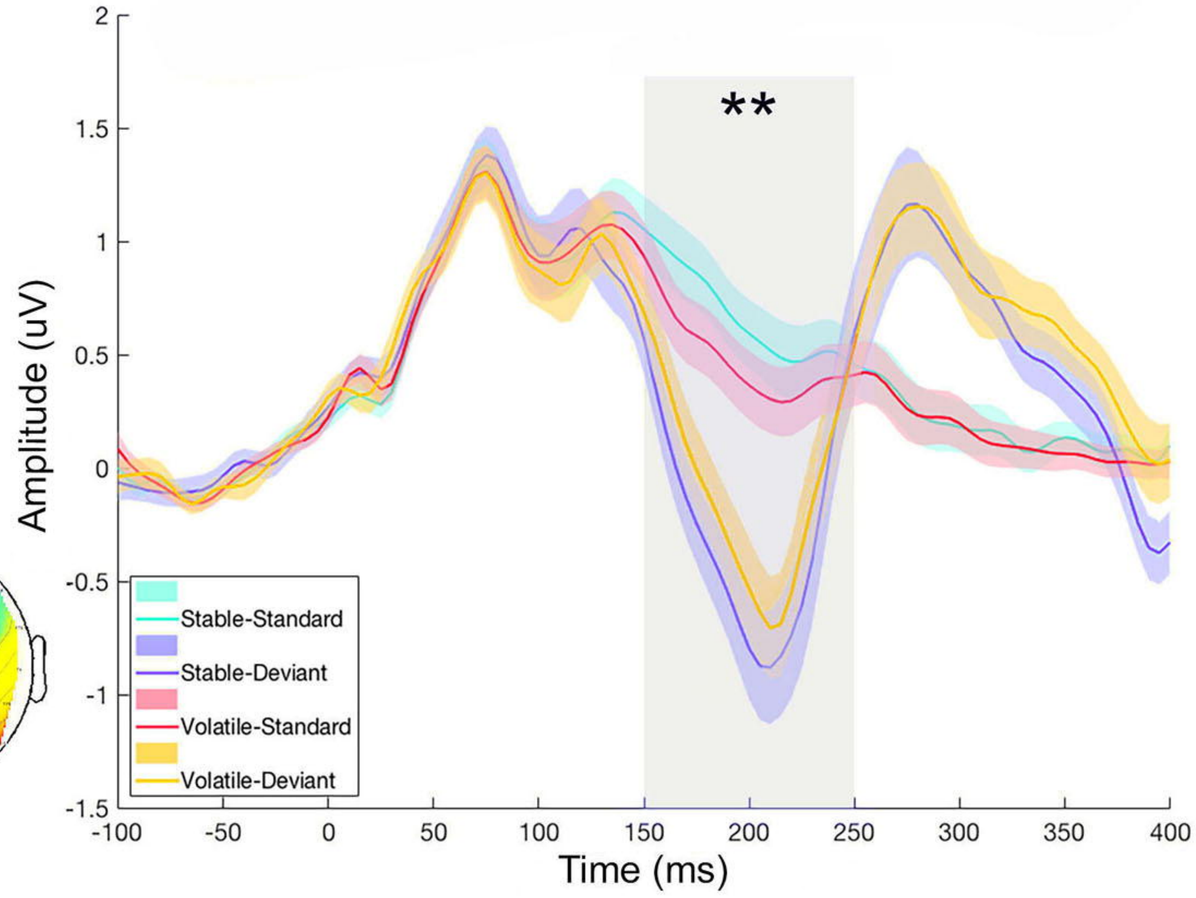
A

Interaction Prediction Error X Volatility



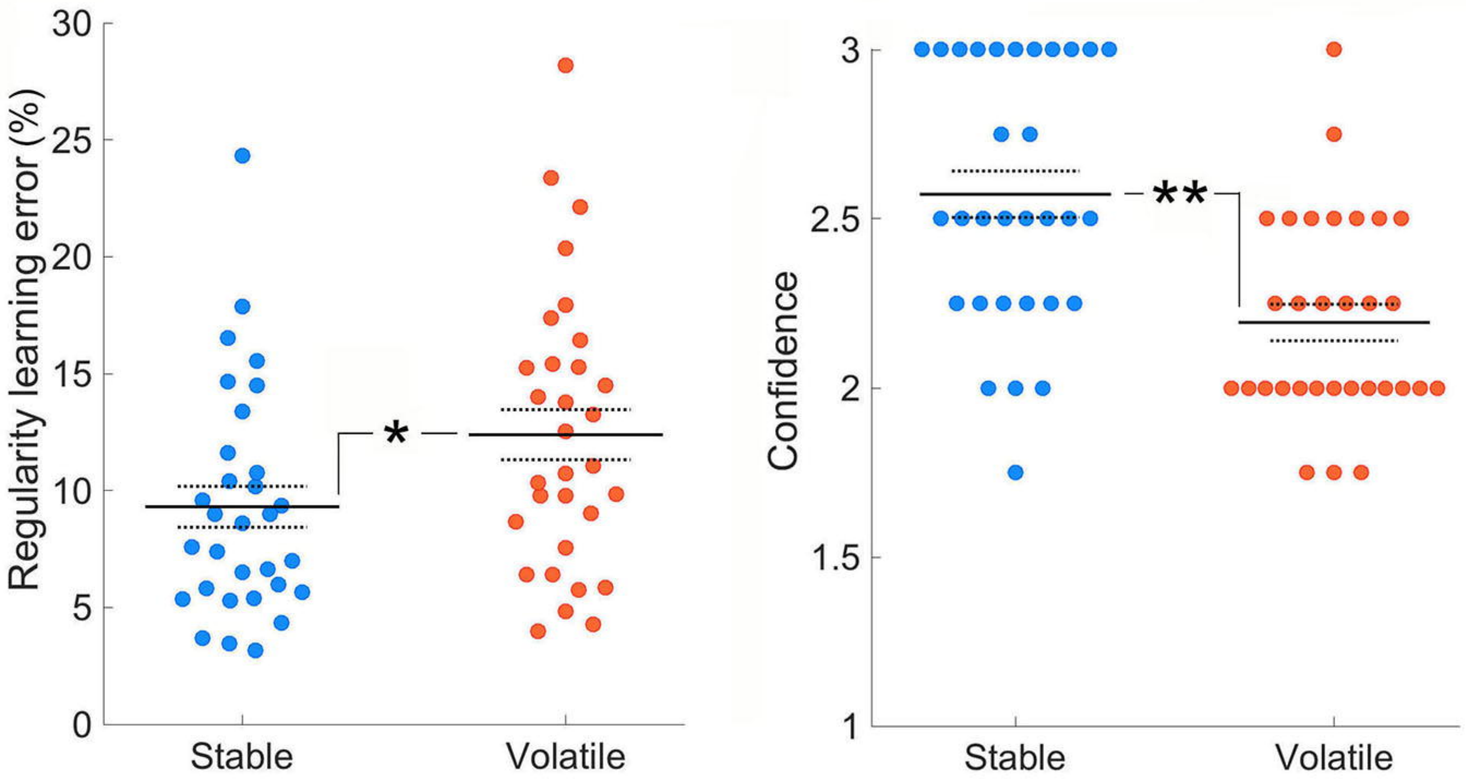
B

Main Effect of Prediction Error



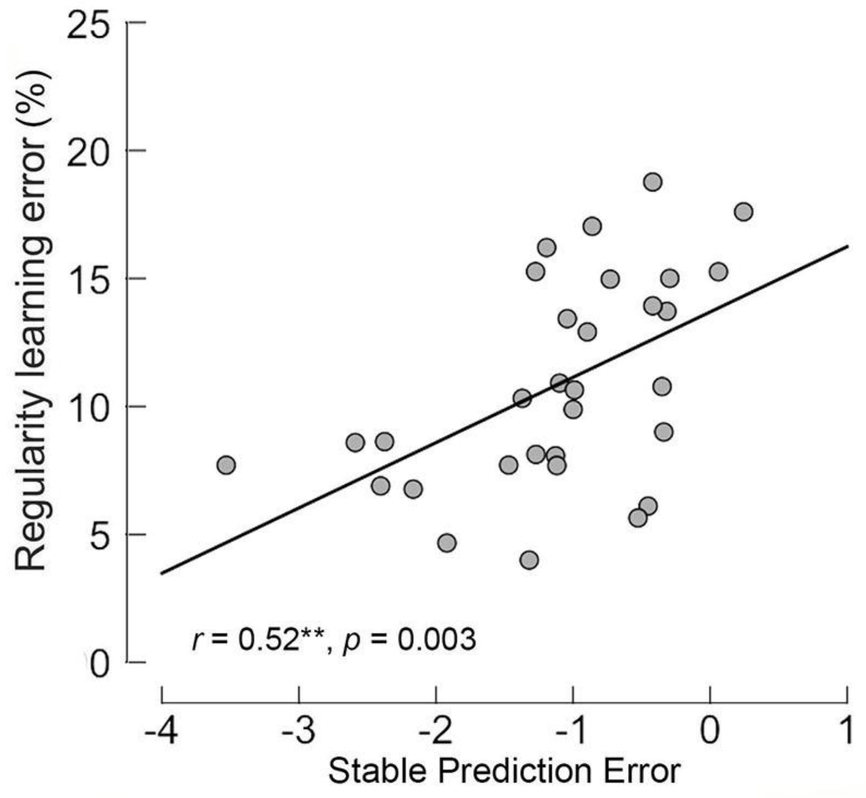
C

Regularity Learning and Confidence in Stable vs. Volatile



D

Regularity Learning is associated with Stable Prediction Error



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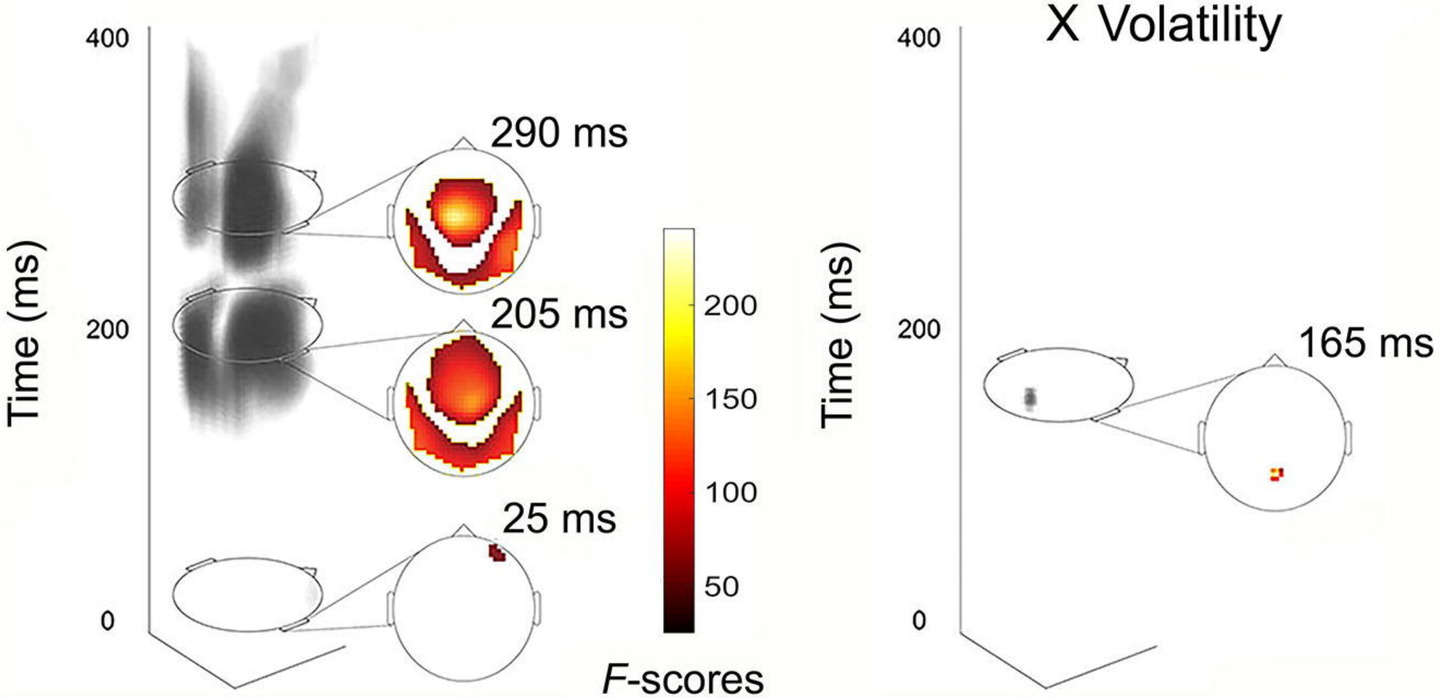

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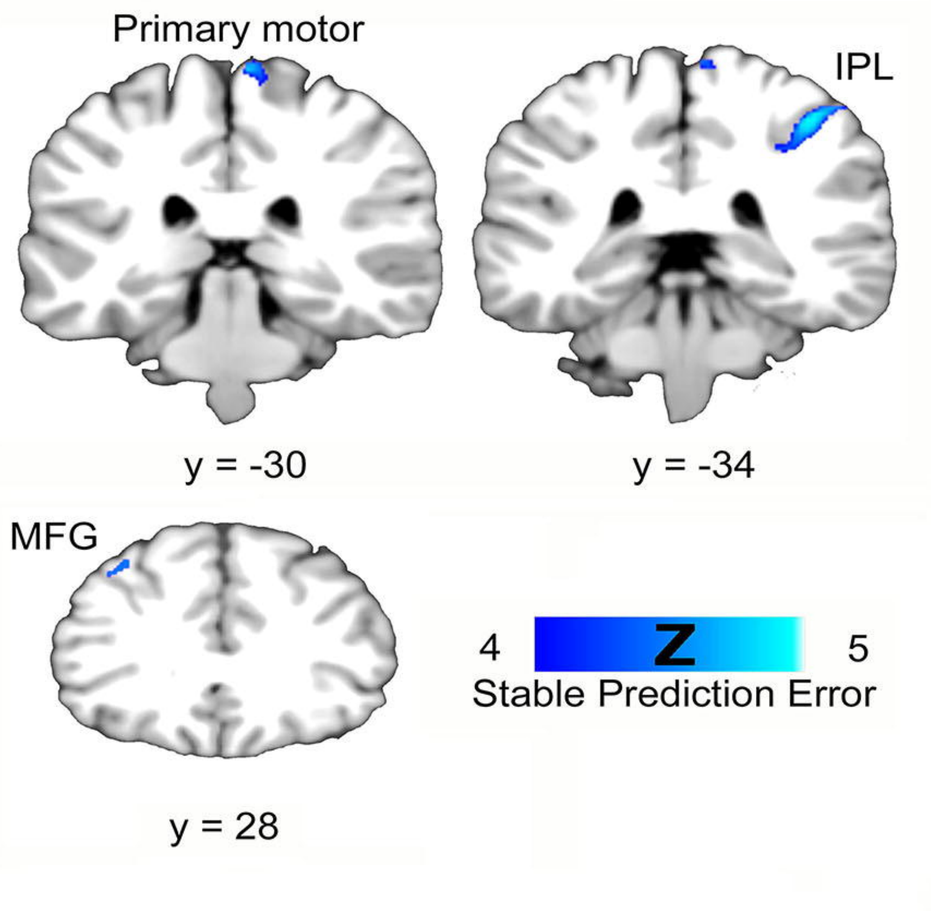

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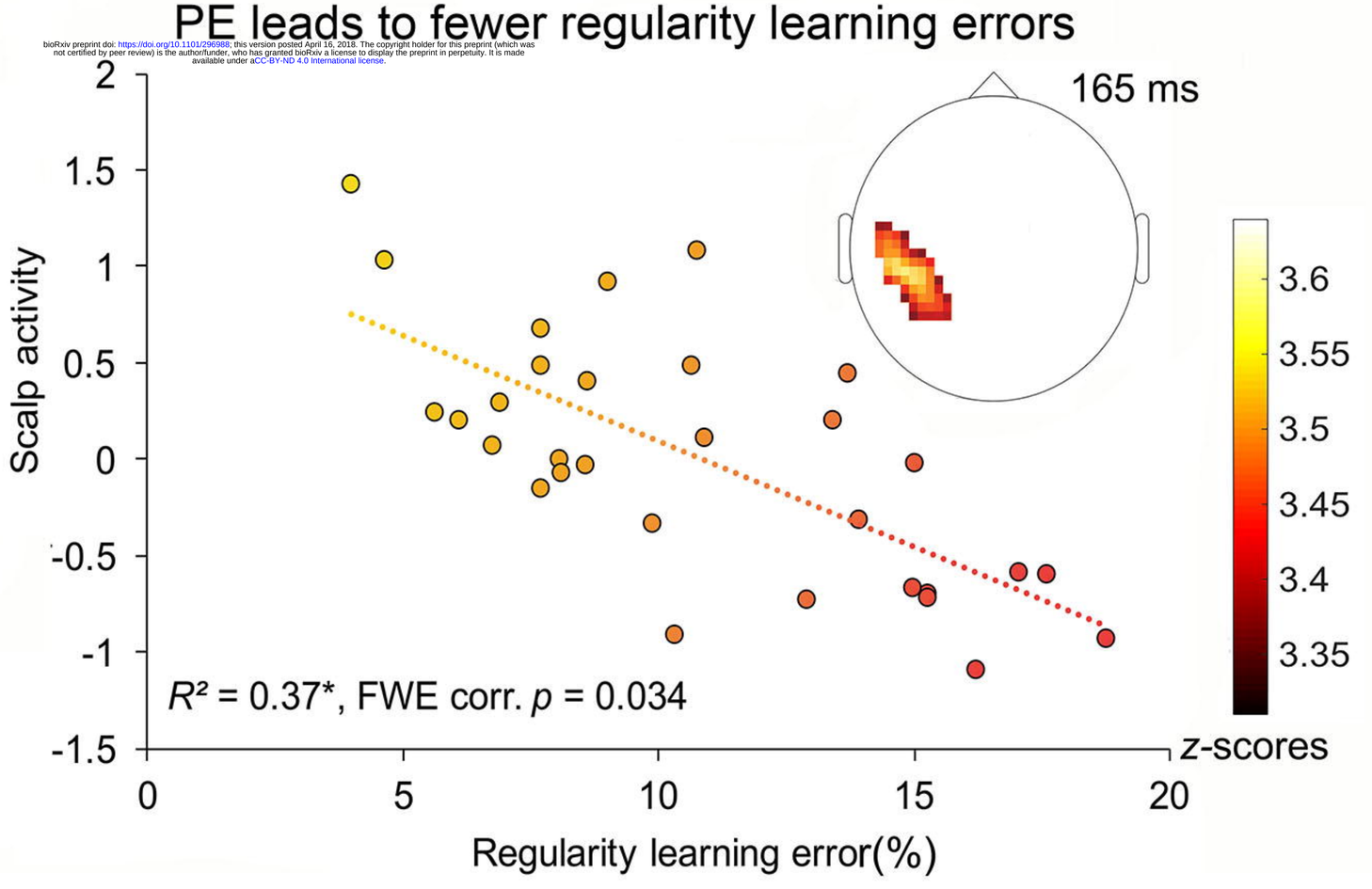
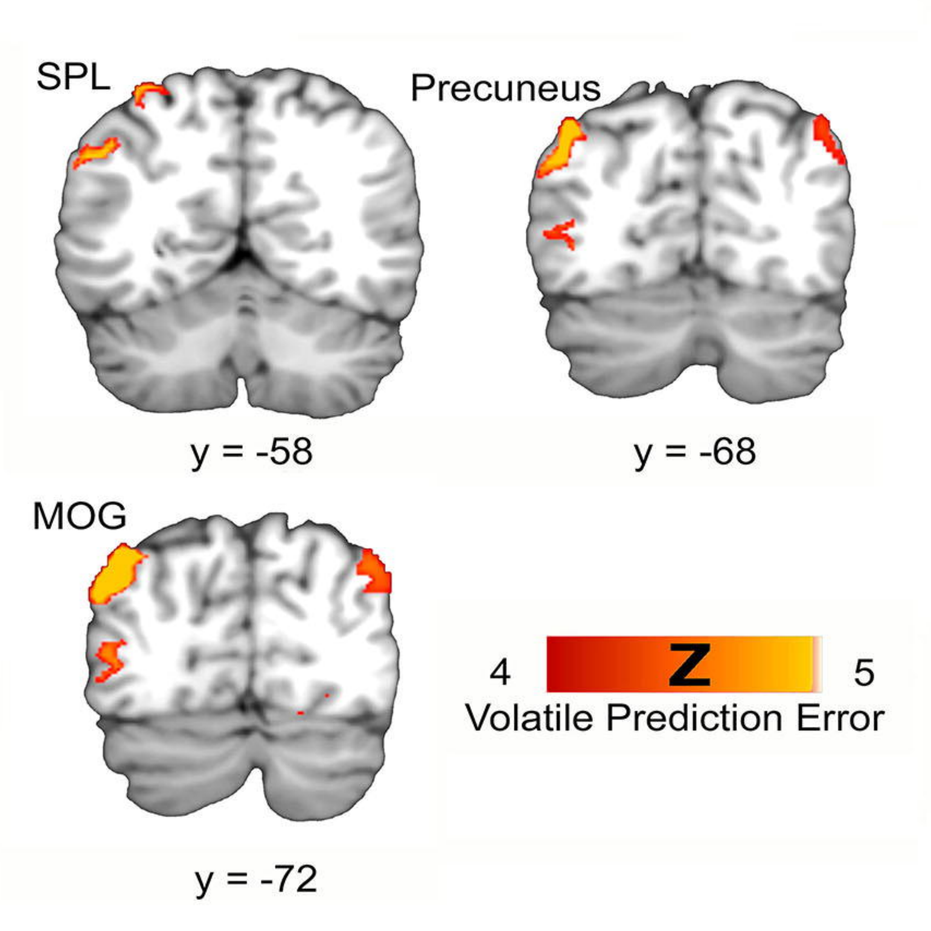
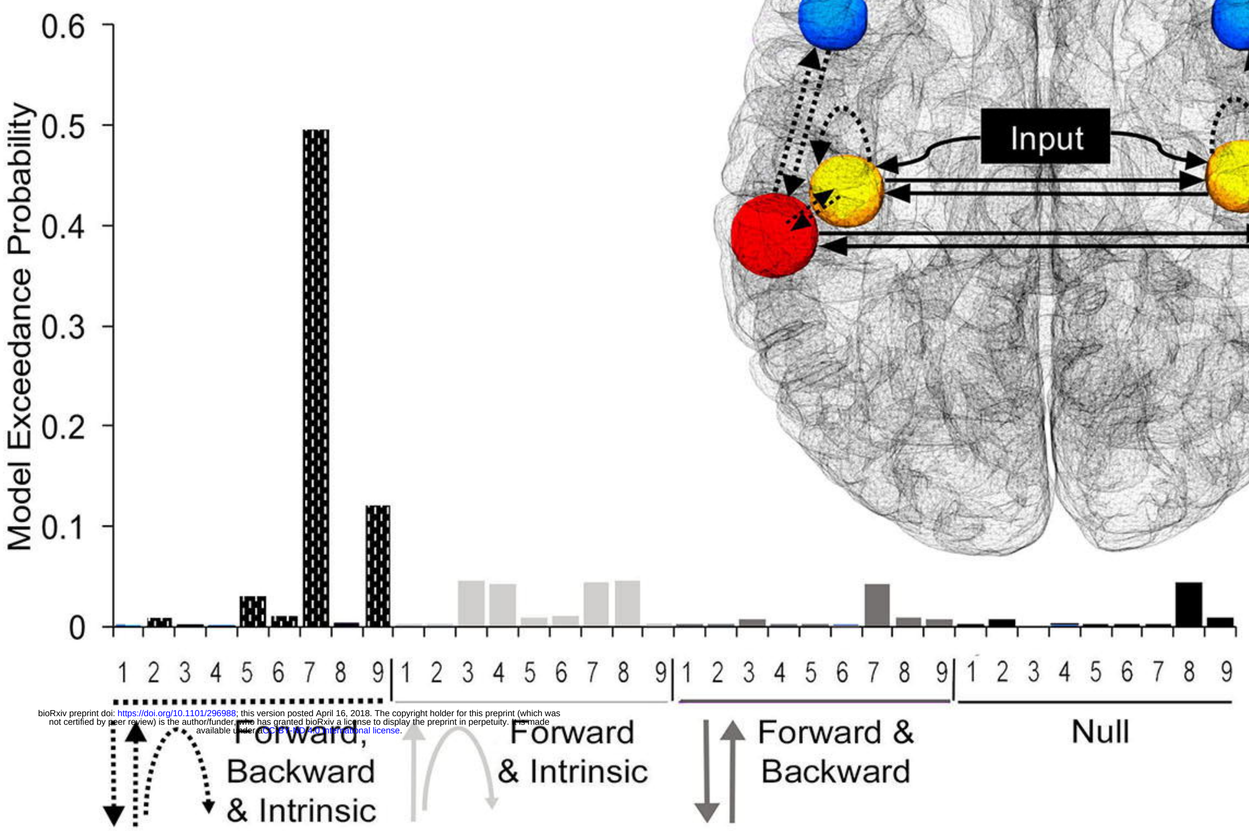




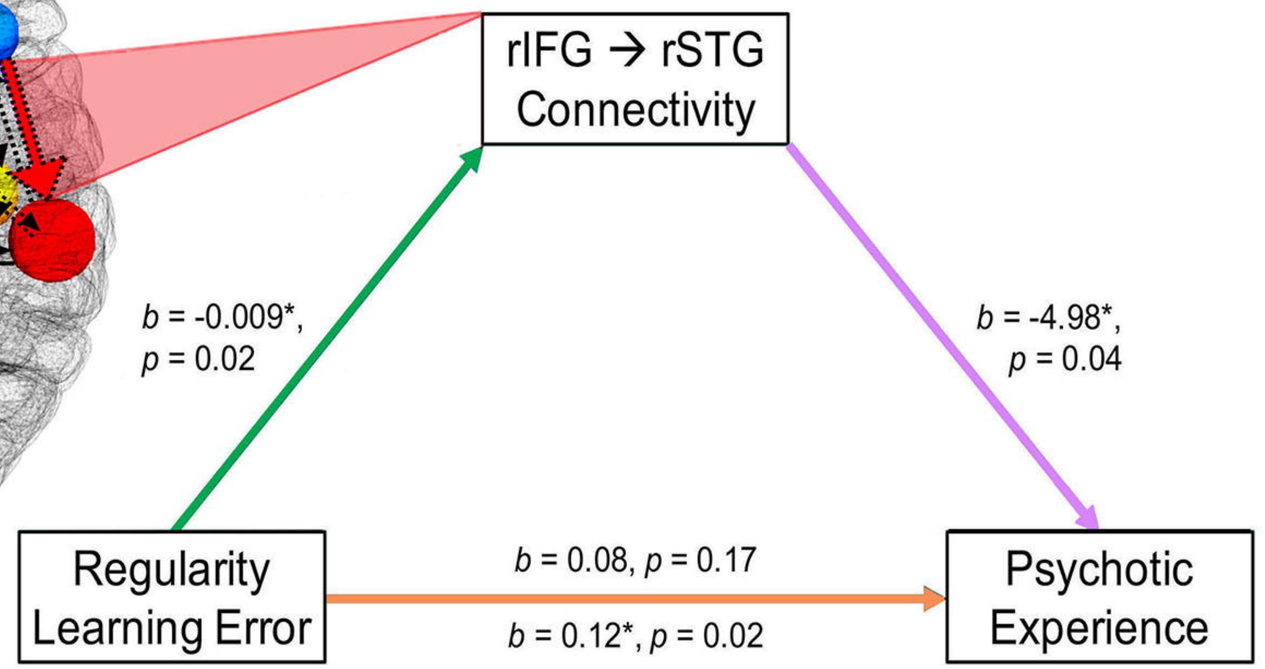
A

Winning Model
Prediction Error Network



B

Frontotemporal Connectivity Mediation



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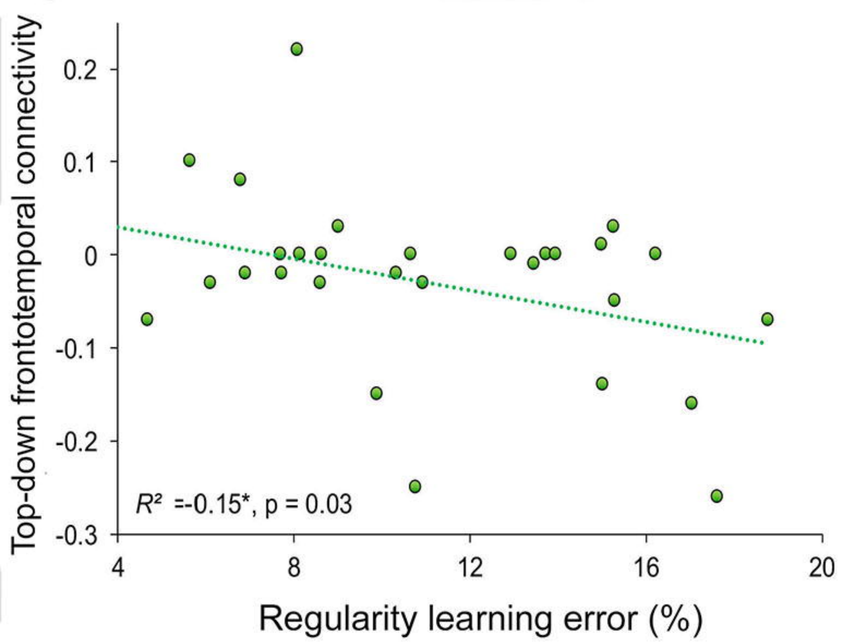

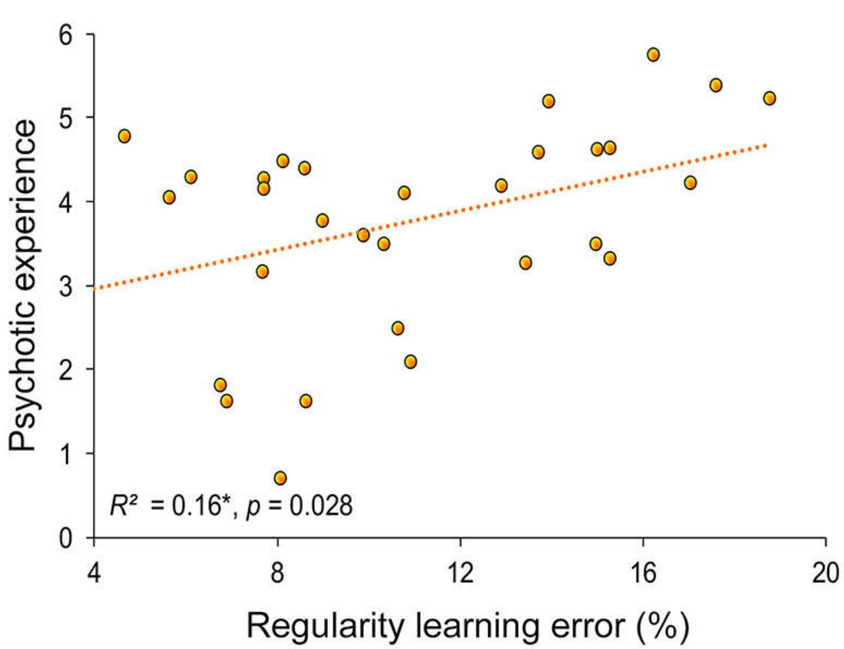

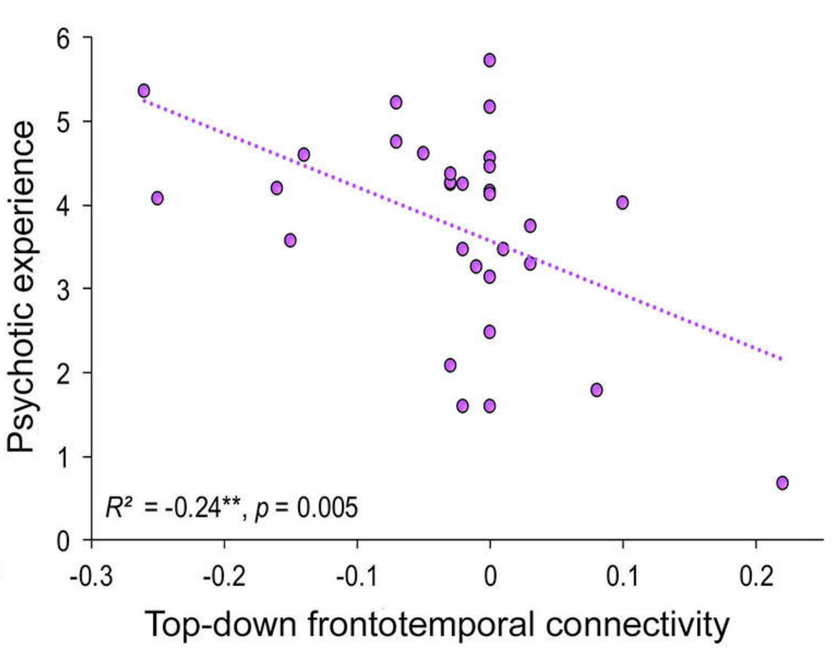

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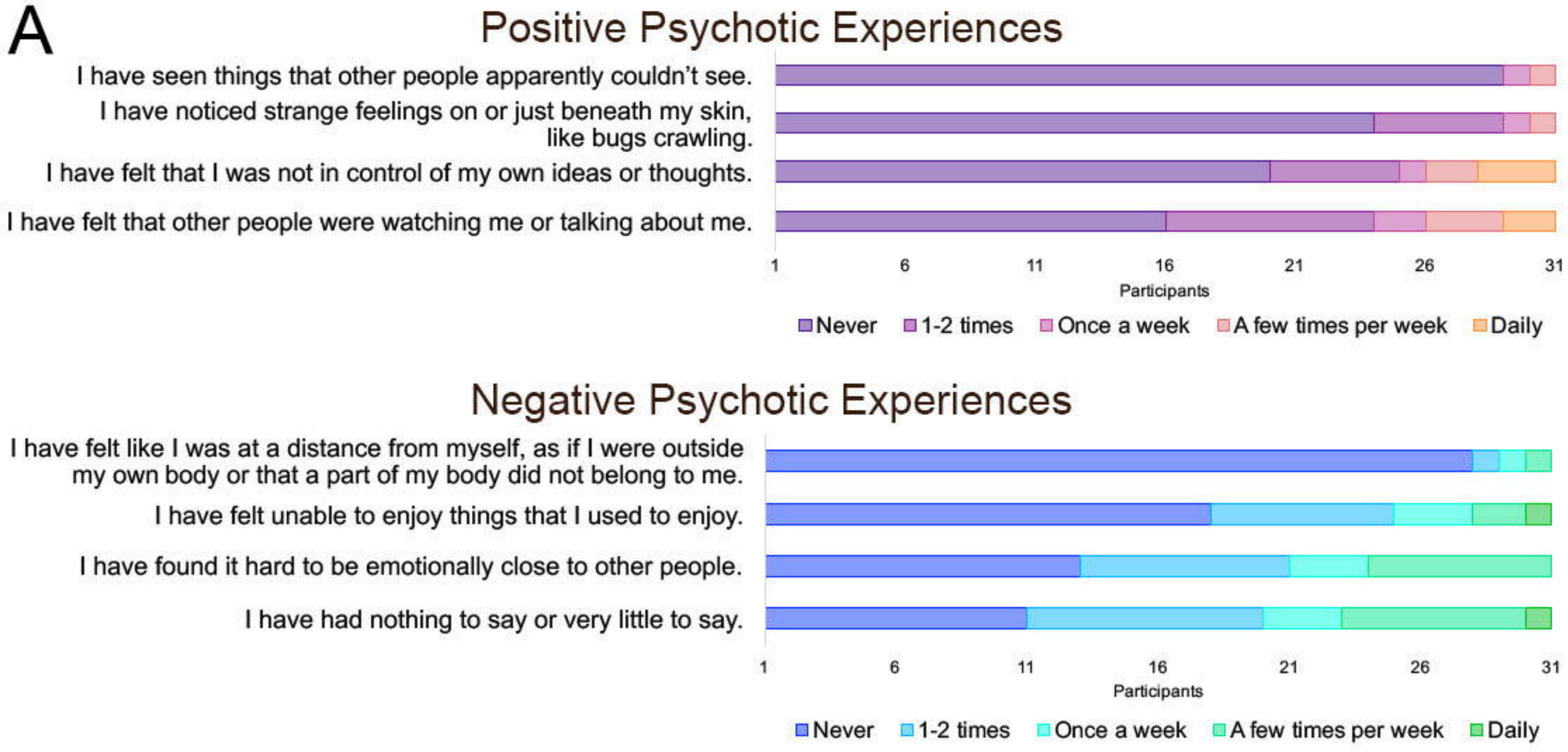

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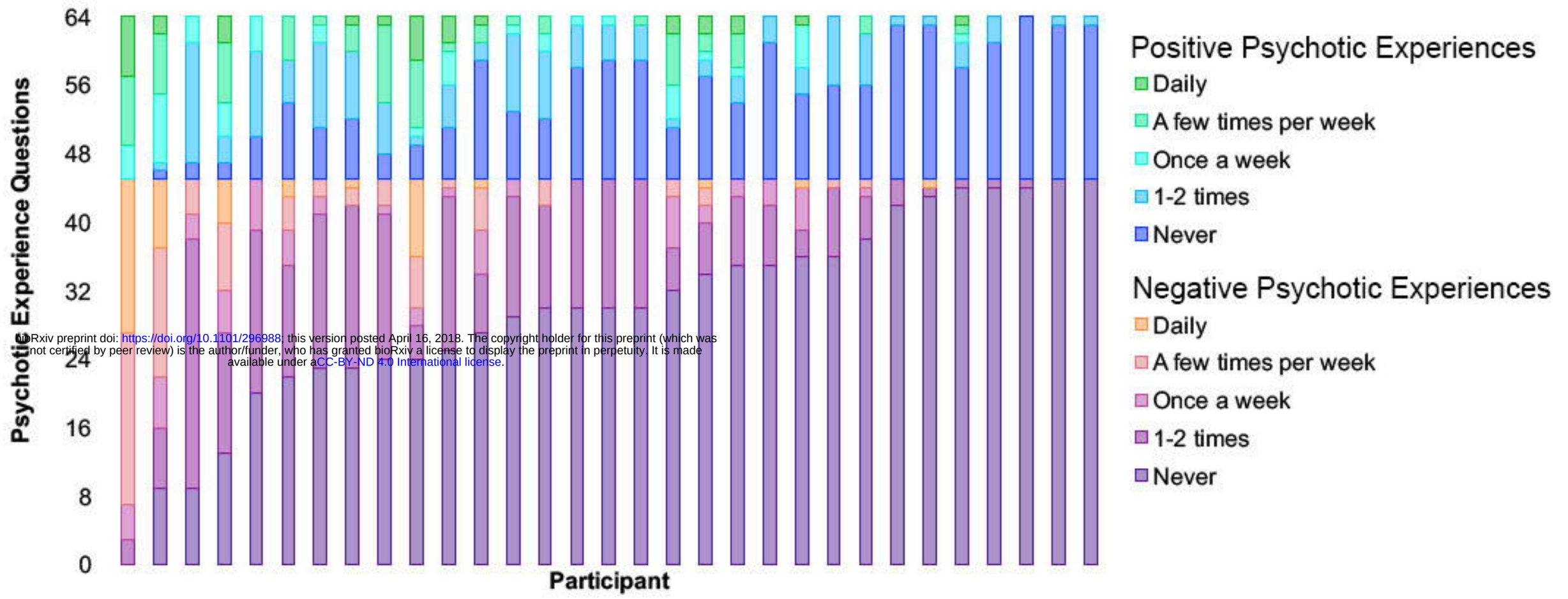

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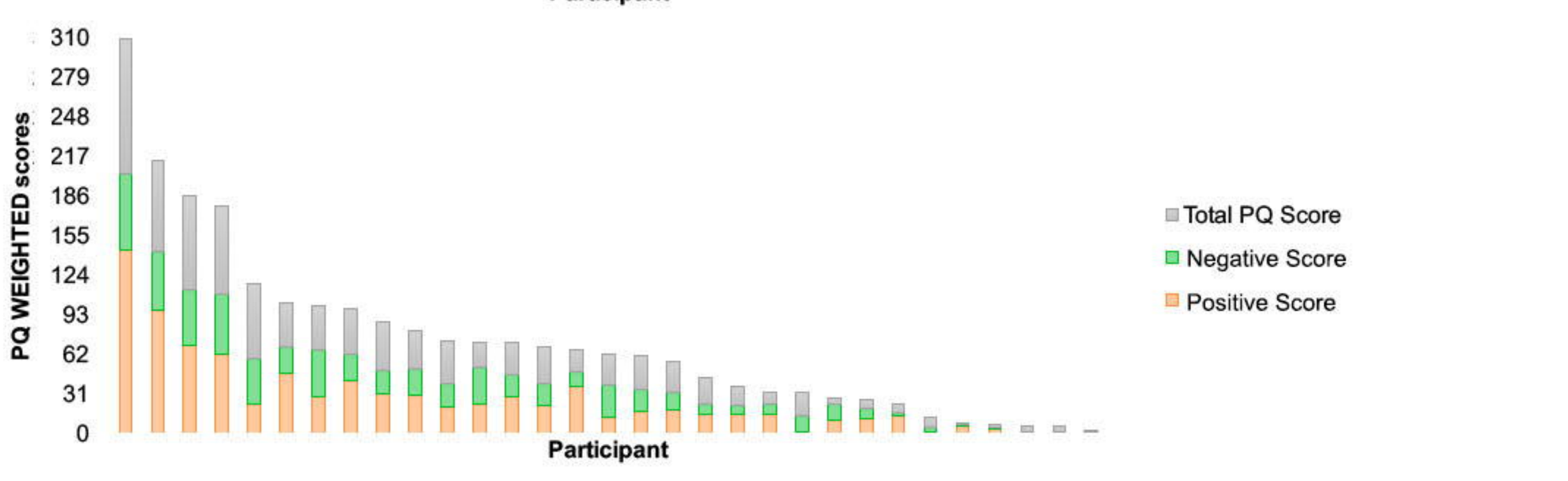

D