Process inspired EEG pattern predicting failure-sensitivity as indicated by fMRI mapping and/or ic recordings activity (D3.15 – SGA3)

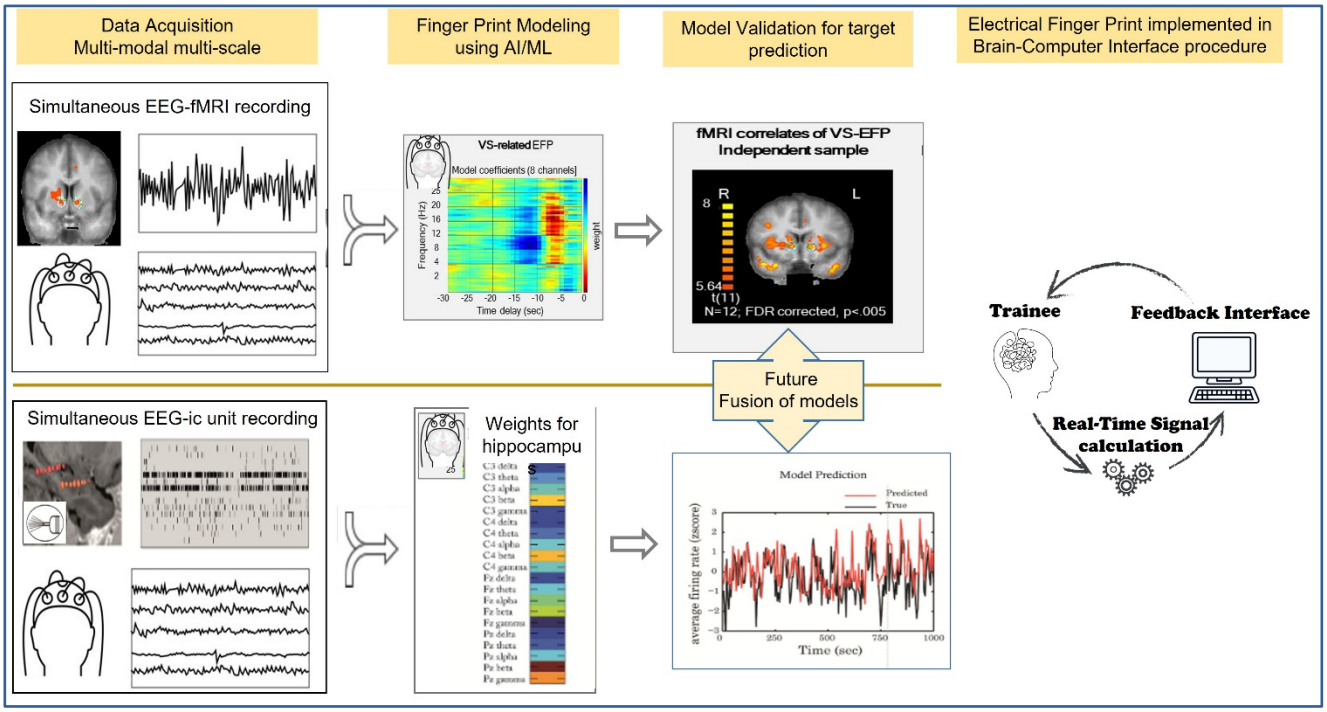

Figure 1. fMRI and Intracranial inspired EEG models used for brain-computer interfaces.

Schematic illustration of modelling fMRI or Intracranial EEG recordings to scalp EEG through machine learning algorithms. These EEG models are derived from activity in regions relevant for failure processing and learning (e.g. hippocampus and ventral striatum including Nucleus Accumbens), thus could be used in the future for monitoring and self-neuromodulation via Brain-Computer Interfaces in a scalable way. Figure adapted from Singer et al., 2023 (PLUS P4058) and Yamin et al., 2023 (PLUS P4053), see further explanations in section 2.7.

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Description in GA:	Models, developed relying on EEG/fMRI or ic/scalp EEG recordings and ML, are used to produce EEG patterns, which successfully predict failure sensitivity, as indicated, by fMRI mapping and/or ic recordings.
Abstract:	In this task, we focused on gathering human neuroimaging data from different scales and modalities in order to decipher the neural signature of *learning from failure* in a motivational context. This work has been inspired by our previous brain-mapping studies showing that under a motivational conflict, mesolimbic nuclei, hippocampus, and medial-PFC regions determine the tendency of individuals to learn from failure more than from reward and that such learning underlies tendencies to avoid rewards under risky conflict and reduce reward sensitivity. Accordingly, we assumed that failure driven tendency for avoidance and/or lower reward sensitivity could lead to psychopathologies such as social anxiety, substance used disorders, traumatic stress, and depression. The overarching goal of this task was to develop a *neural signature of the response to and learning from failure*, with the expectation to implement it for monitoring and neuromodulation of failure bias processes in vulnerable individuals. Our task was achieved through several sub-projects: 1. Using fMRI to demonstrate the association between abnormal neural processing of failure and depressive psychopathology. 2. Using intracranial recordings (unit activity and LFP) to reveal electrical markers of learning from failure and responsivity to reward. 3. Using fMRI to demonstrate the relevance of neural sensitivity to reward (versus punishment) to the clinical trajectory of real-life traumatic stress. 4. Using reinforcement-learning perspective to provide a theoretical framework for *learning from failure* (and success) in the context of self-neuromodulation (Neurofeedback) training.5. Using fMRI to portray the neural correlates of learning from failure in Neurofeedback. 6. Demonstrate the feasibility of developing EEG fingerprints of fMRI or intracranial activity in the deep brain regions related to *learning from failure*.

Keywords:	*fMRI, Intracranial Recordings, EEG, Reward, Reinforcement Learning,* PTSD
Target Users/Readers:	Neuroscientific community

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1. Introduction

Our activity in this task was focused on gathering human neuroimaging data from different scales and modalities in order to decipher the neural signature of learning from failure in a motivational context. This work has been inspired by our previous brain-mapping studies with fMRI and intracranial recordings (as described below in section 1&2), showing that under a motivational conflict, mesolimbic nuclei, hippocampus, and medial-PFC regions determine the tendency of individuals to learn from failure versus learn from reward (Gonen et al 2016, Gazit et al. 2020). These findings have nurtured our assumption that biased tendency for avoidance after failure and lower reward sensitivity could lead to psychopathologies such as social anxiety, substance used disorders, traumatic stress, and depression related disorders. Accordingly, the overarching goal of this task was to develop a *neural signature of the response to and learning from failure*, with the expectation to implement it for monitoring and neuromodulation of failure bias mechanism in vulnerable individuals (as depicted in Figure 1). Our task was achieved through several objectives:

1) Demonstrate the clinical relevance of abnormal failure processing during motivational conflict via fMRI
2) Reveal electrical markers of learning from failure using intracranial recordings (unit activity and LFP)
3) Demonstrate responsivity to reward and punishment at the level intracranial single unit activity
4) Demonstrate the relevance of sensitivity to reward versus punishment to the clinical trajectory of real-life traumatic stress
5) Formulating learning from failure and success in Neurofeedback through the lens of reinforcement learning
6) Reveal the neural correlates of success and failure in Neurofeedback, beyond the neuromodulation target
7) Demonstrate the feasibility of developing EEG fingerprints of fMRI or intracranial activity in the deep brain regions related to learning from failure.

2. Multi-scale Neural Depiction of Learning from Failure in Humans

2.1 fMRI study of approach under goal-conflicts in patients with Peri-Menstrual Dysphoric Disorder (PMDD)

This study follows our previous finding with healthy controls using the Punishment Reward Incentive MOtivation (PRIMO) task. This interactive game-like task enables the assessment of individual tendency to approach or avoid rewards under concomitant risk of punishment (i.e., dealing with an approach avoidance conflict) (Gonen et al., 2016). The paradigm is comprised of four runs altogether lasting ~30min. The goal of participant was to earn as much money as possible by catching coins and avoiding balls (Figure 2).

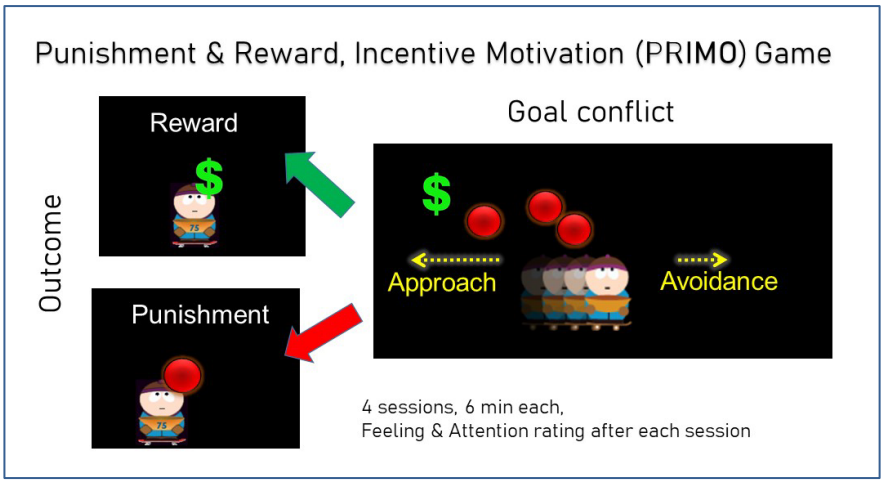


Figure 2. The PRIMO Paradigm.

In previous work on healthy participants, we showed that approaching rewards under risk of punishment) involves the mesolimbic circuit including ventral striatum and ventral tegmental area (VS and VTA). More so the personal tendency to such an approach behaviour corresponded to a certain personality profile (more extroverted and reward seeking and less introverted, neurotic and risk seeking) (Figure 3).

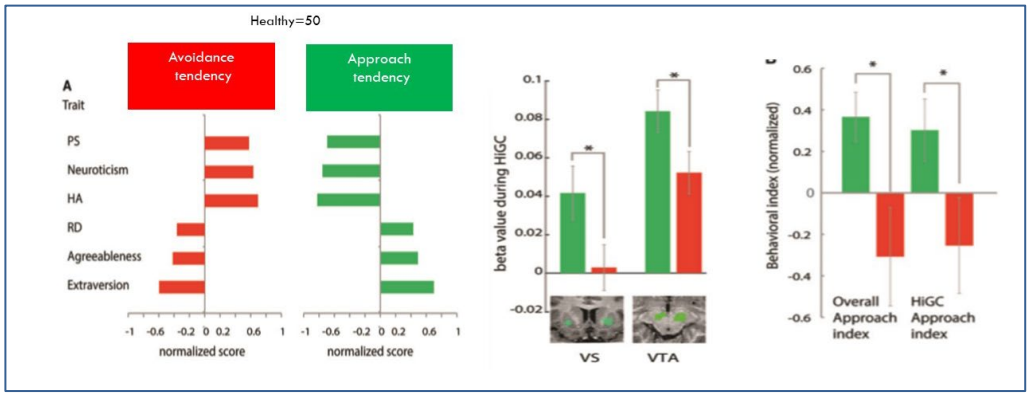


Figure 3. Behavioural tendencies and personality profiles.

Anxious personality profile (Neuroticism, punishment sensitivity and avoidance) corresponded to less recruitment of mesolimbic activity and less approach behaviour under high goal conflict. Adapted from Gonen et al., 2016.

In the current study as part of T3.13 we tested 25 women (32.6+/- 6.2 years, Table 1) suffering from premenstrual dysphoric disorder (PMDD). These patients suffer from severe physical discomfort

around their menstrual period accompanied by emotion dysregulation manifested as enhanced anger bursts and difficulty to keep social and occupational functioning.

Table 1: Characteristics of study participants

Characteristic	Score				
Symptoms (years)	11.4 ± 7.4				
Menarche age (years)	12.6 ± 1.6				
Oral contraception (y/n)	12 / 13				
Psychological treatment (y/n)	14 / 11				
Physical training (y/n)	11 / 14				
PMTS-OR	*Depression* 3.5 ± 0.5	*Anxiety* 3.4 ± 0.7	*Lability* 3.7 ± 0.5	*Anger* 3.3 ± 0.5	*Total* 34.0 ± 4.2
BFI	*Extraversion* 27.4 ± 4.8	*Neuroticism* 25.8 ± 4.4	*Agreeableness* 34.1 ± 4.3	*Conscientiousness* 31.1 ± 4.0	*Openness to experience* 38.9 ± 5.9
CGI-S	5.2 ± 0.4				

Additional information for Table 1 above. ***PMTS-OR; variation in severity of premenstrual symptoms, BFI; Big five personality inventory, CGI-S; overall severity of illness.***

During approach under risk, compared to the healthy controls (Gonen et al., 2016) the patients showed diminished activity in mesolimbic core regions, excessive activity in somatosensory and high order visual areas and less recruitment of medial prefrontal cortex (frontal part of the default mode network) (Figure 4, Figure 5-Left Panel). Behaviourally, PMDD patients exhibited similar emotional feelings regarding rewards and punishment and more tendency for approach overall compared to healthy controls (Gonen et al 2016). However, PMDD patients showed less differentiation between approaching under high- and low goal conflict situations (Figure 5-Right Panels).

These finding point to the possibly that patients have lower capacity to deal with the risk of failures in the game (i.e., being hit by a ball). This stands to 1. Less reward related brain activity when approaching rewards under high-risk and 2. Poorer behavioural/mental consideration of the risk (thus approaching high and low risk similarly). We are currently further analysing the data with respect to relation between neural and behavioural manifestations as well as their relation to symptoms.

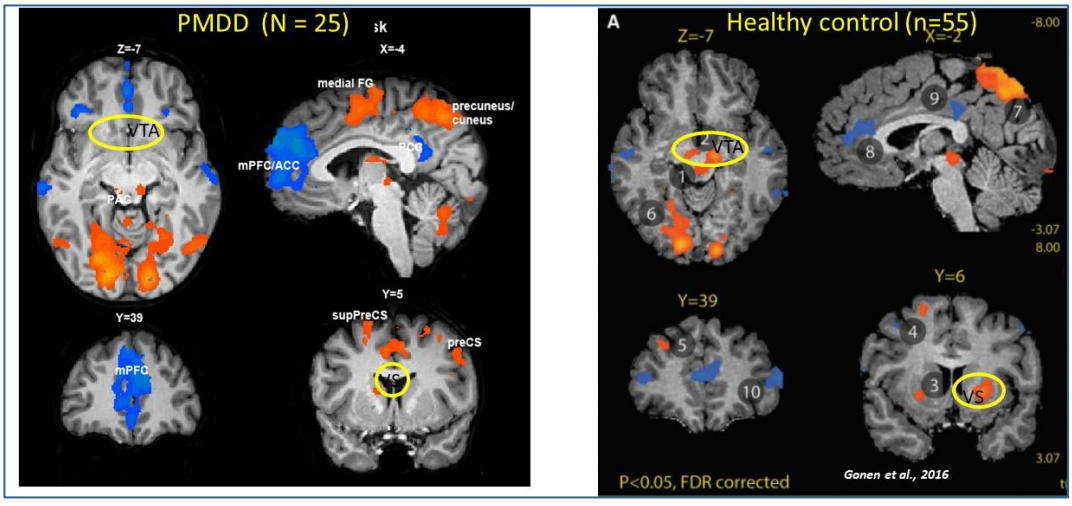


Figure 4. Whole brain results of PMDD and Healthy controls.

Whole brain analysis of Approach High Risk vs. Approach Low Risk from PMDD patients (N=25) and healthy controls (N=55).

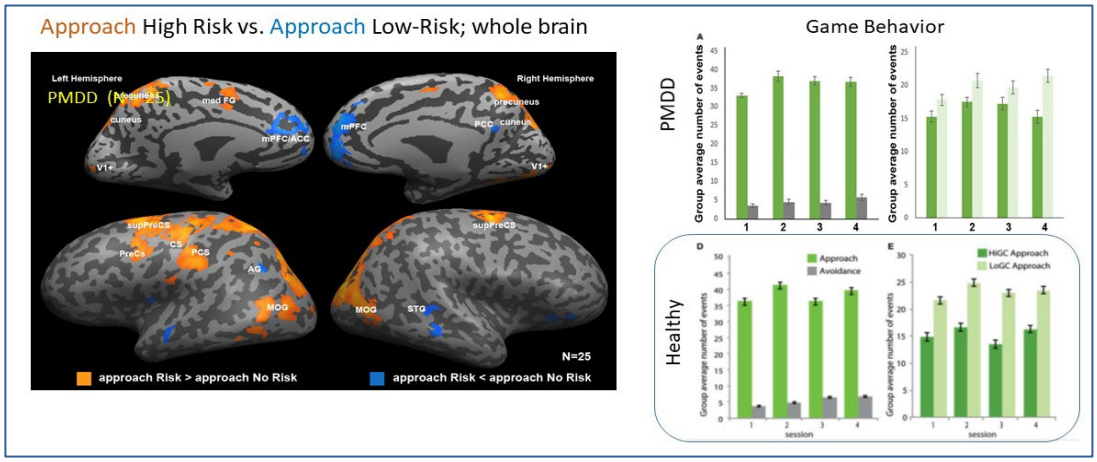


Figure 5. Whole brain analysis and behavioural patterns.

2.2 Intracranial recordings (units and LFP) of goal-conflict processing

In a recent study from our lab (Gazit et al. 2020), we used the same task described in the previous sections, while recording single-units and local field potentials from epilepsy patients implanted with intracranial depth electrodes. The results showed that mPFC units were more selective to punishment than rewarding outcomes during goal-directed behaviour. Importantly, while mesial-temporal units were not selective to the value of outcomes (reward or punishments), the firing-rate following punishment was linked with a lower probability for approach behaviour in the next trial (Figure 6).

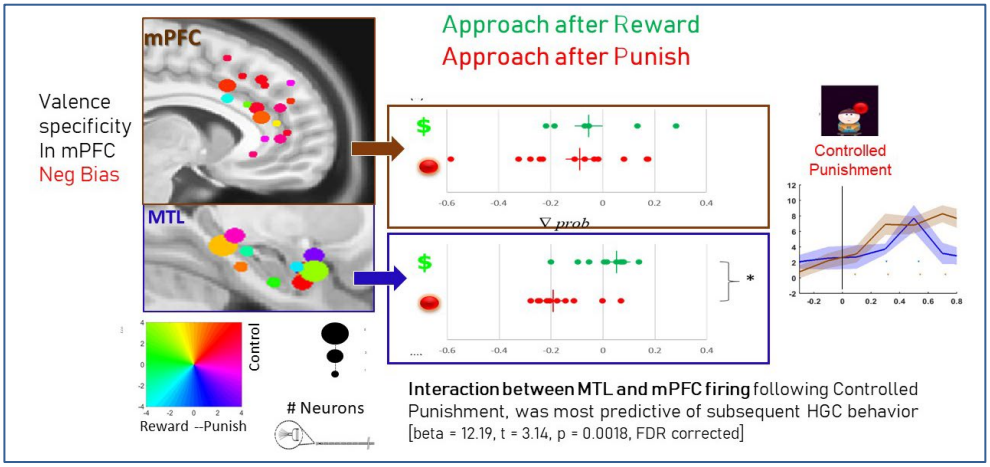


Figure 6. Predicting behaviour under goal conflict from neuronal response to prior outcome.

Together these findings suggest a differential role for mPFC and MTL in processing goal-directed behaviour under conflict. Adapted from Gazit et al., 2020.

In T3.13 we further explored this notion with an analysis of local field potentials from the same group of patients with epilepsy. Looking at data from macro contacts lying in the Hippocampus and mPFC we analysed high frequency power changes following the different task conditions. A non-parametric cluster-based permutation test was used on time-frequency spectrograms of reward and punishment outcomes in both regions. We found a cluster of broadband gamma power (30-100HZ) showing decreased power following reward (compared to punishment) in the hippocampus [p=0.002] but not in the mPFC (see below Figure 7 A, B). Brain-behaviour effects of LFP gamma power changes were tested with separate General Linear Models for reward and punishment outcomes. Gamma power was averaged for each trial within the significant cluster found in the permutation analysis comparing reward and punishment outcomes. Following punishment outcomes, a significant interaction was found between Region and Behaviour in the subsequent trial [F (3,212) =2.951; p=0.034]. A further inspection of each region with respect to goal-conflict behaviour, showed that

such gamma power decrease following a punishment outcome, **was greater before an avoidance behaviour** on the next risky trial [hippocampus F(1,7)=12.93, p=0.007; mPFC F(1,7)=15.4, p=0.006; see Figure 7C]. This finding point to an electrical marker for reduced approach behaviour under goal conflict (i.e., approaching reward under risk for punishment), a common real-life situation exacerbated by stress.

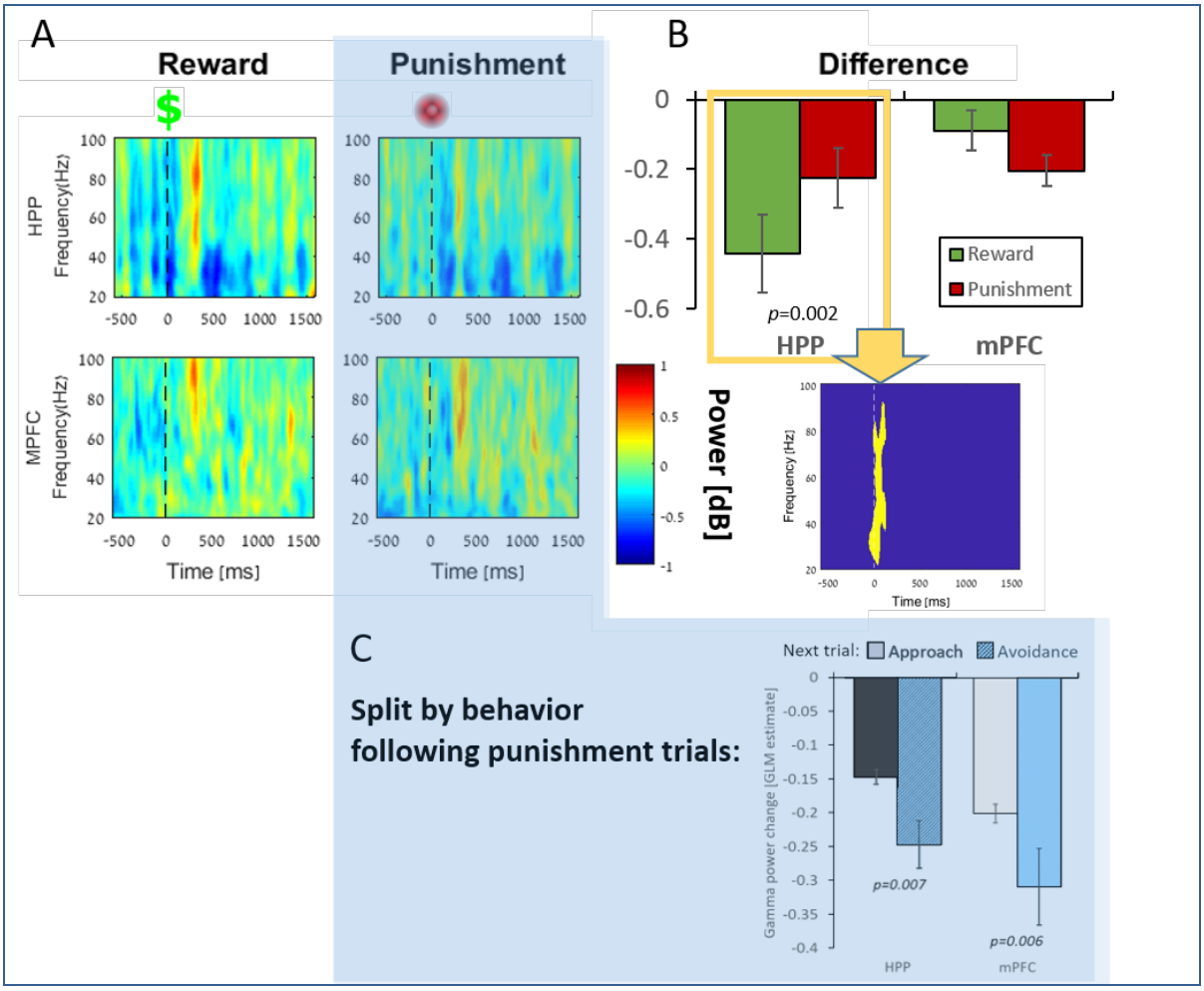


Figure 7. Local field potentials from the hippocampus and mPFC in the PRIMO paradigm.

2.3 Single unit responsivity to reward and punishment in humans.

Using a risky-choice task previously used in our lab in fMRI studies (Kahn et al 2001, Assaf et al 2009), we recorded activity from single units in Epilepsy patients implanted with depth electrodes. 24 playing sessions were recorded from 21 patients with electrodes mainly in mesial temporal and prefrontal regions. The task (see below Figure 8) is a 2-player competitive gambling game played for 14 min, in which participants are required to make risky choices in order to win (The safe or risky domino choice paradigm; SRDC). The effectiveness of the SRDC game to detect individuals' sensitivity to risk, punishment, and reward was previously validated in both healthy and clinical populations.

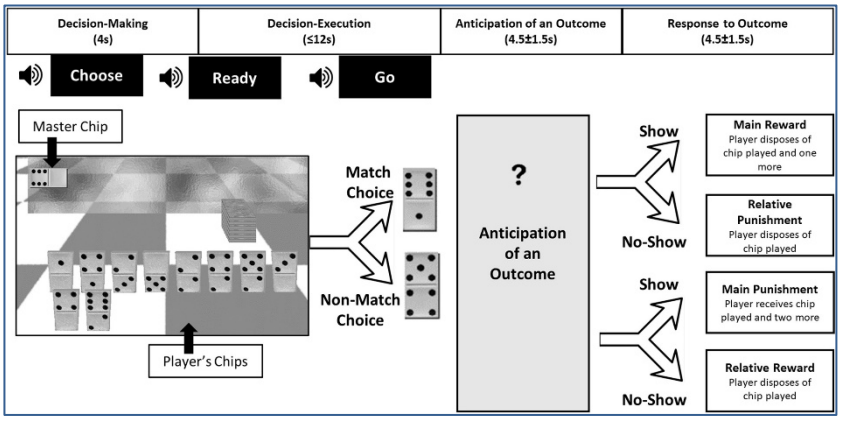


Figure 8. Outline of The Safe or Risky Domino Choice paradigm.

Raw data were recorded at 30000Hz using Blackrock Microsystems amplifier and neural signal processing unit. Spikes were detected using an adaptive threshold after raw data was filtered between 300-3000Hz. Units were sorted in a semi-automatic manner using wave_clus3 (Chaure et al., 2018) based on spike shape, variance, and the presence of a refractory period for the single units, and spike times for each cluster were documented. Raster plots of spike times were binned to non-overlapping windows of 200ms length to create FR per window and summed across trials to create peri-stimulus time histograms (PSTH). For evaluating neuron responsiveness, we concentrated on the time period of 200–800 ms post outcome (reward or punishment) stimulus. Figure 9 shows representative examples of responsive units, from different regions. Figure 9A displays the response of a single unit from the amygdala of one patient following the Show-Match (reward) and Show-Non-Match (punishment) conditions. This specific unit shows a non-selective increased firing response to the type of outcome (although with different dynamic; later response to punishment). Figure 9B displays a unit from medial pre-frontal region, showing a selective response to the punishment outcome. Figure 9C displays a unit from anterior cingulate cortex showing a differential response with firing increased for the reward outcome and decreased for the punishment outcome.

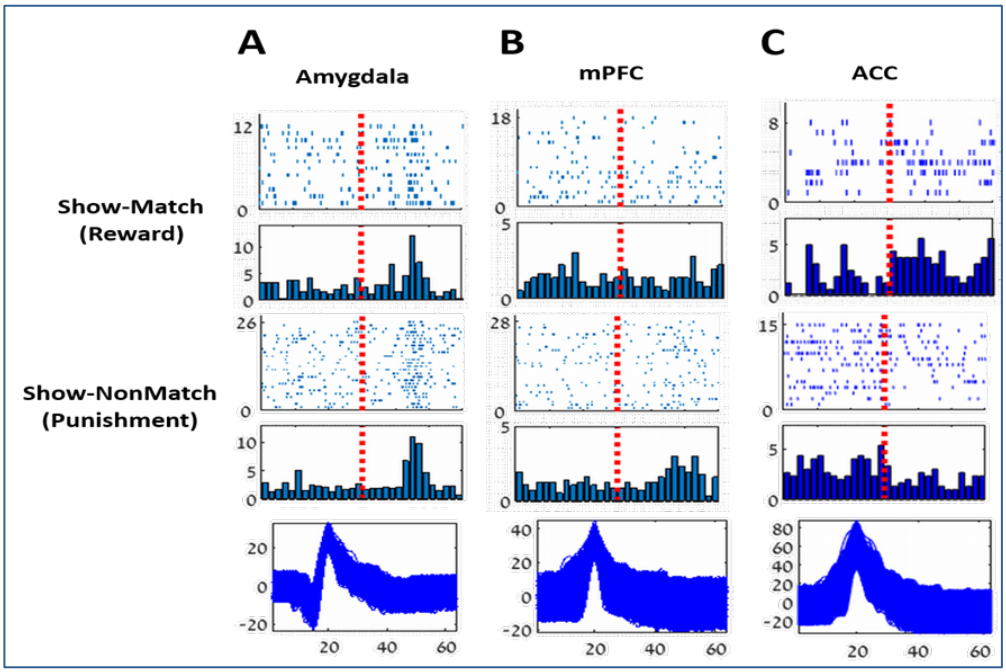


Figure 9. Differential single unit responses to the SRDC paradigm in different regions.

2.4 Motivation related neural activity predicting PTSD trajectory in trauma survivors.

2.4.1 Study 1: Neural response to punishment versus reward predicts PTSD following trauma.

171 adults (87 women, mean age 34.22 years, range 18-65 years) who were admitted to a general hospital's emergency department after a traumatic event underwent clinical assessments and fMRI scans, at one-, six-, fourteen- and about 36 months following trauma (T1, T2, T3 and T4, respectively). PTSD diagnosis and severity at each TP were determined by a comprehensive clinical interview conducted by trained and certified clinical interviewers using the CAPS-5, the current gold standard for PTSD diagnosis. During TP1-TP3, participants played a 2-player competitive gambling game for 14 minutes in the fMRI scanner, in which they were required to make risky choices in order to win (The safe or risky domino choice paradigm; SRDC, see above). The effectiveness of the SRDC game to detect individuals' sensitivity to risk, punishment, and reward was previously validated in both healthy and clinical populations (Kahn et al 2001, Assaf et al 2009). Our focus was on the neural responses to-outcome; rewards vs. punishments as reflected in activation in the VS and amygdala, respectively and the functional connectivity between these regions and PFC ROIs as target regions.

Partial correlations were computed between neural indicators of valence processing at 1 month post trauma (TP1) and PTSD severity at 6 and 14 months post trauma (TP2 and TP3, respectively), while controlling for participants' age, gender, trauma type, and initial symptom severity (i.e., CAPS-5 total scores at TP1). In line with our hypothesis, both increased amygdala activation to punishments relative to rewards, and decreased VS activation to rewards relative to punishments at TP1 were significantly predictive of more severe PTSD symptoms at TP3. Specifically, higher CAPS-5 total scores at TP3 were associated with greater left amygdala activation at TP1 (n = 108, r = 0.197, p = .022) (Figure 10A) and decreased right VS activation at TP1 (n = 111, r = −0.235, p = .007) (Figure 10B).

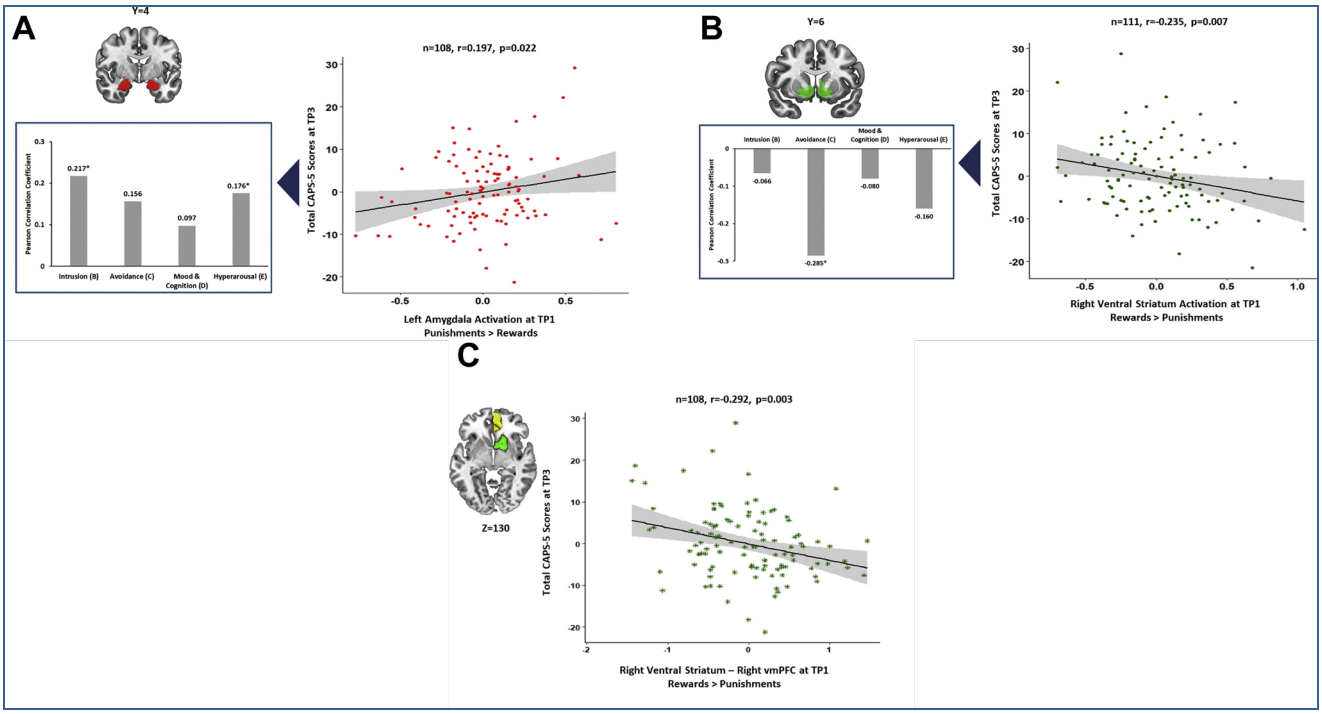


Figure 10. Correlations between functional connectivity and PTSD symptoms.

Exploratory analysis of the relation to specific symptom clusters revealed a trend toward a significant association between increased amygdala activation to punishments versus rewards TP1 and more severe hyper arousal (r = 0.176, p = .037, pFDR = .074) and intrusion symptoms at TP3 (Panel A, r = 0.217, p = .027, pFDR = .074). Moreover, decreased VS activation to rewards versus punishments at TP1 was significantly associated with more severe avoidance symptoms at TP3 (r = −0.285, p = .001, pFDR = .004). Adapted from Ben-Zion et al., 2021, PLUS P3220.

Examining the predictive power of functional connectivity patterns of the neural components of the two valence systems at TP1 for predicting symptom severity at TP3 revealed such a relationship only for the VS. Specifically, decreased VS-vmPFC connectivity during rewards versus punishments at TP1 was associated with more severe PTSD symptoms at TP3 (n = 108; right VS-right vmPFC: r = −0.292,

p = .003, pFDR = .036), indicating that individuals with decreased VS-vmPFC connectivity when processing rewards versus punishment at TP1, developed more severe symptoms at TP3 (Figure 10C). To identify the relative importance of each predictor compared with others, importance values were calculated using the SHAP analytic approach. In terms of absolute feature importance, VS-vmPFC connectivity during rewards versus punishments at TP1 was the best predictor of PTSD symptoms at TP3, followed by VS activation to rewards versus punishments and amygdala activation to punishments versus rewards (Figure 11).

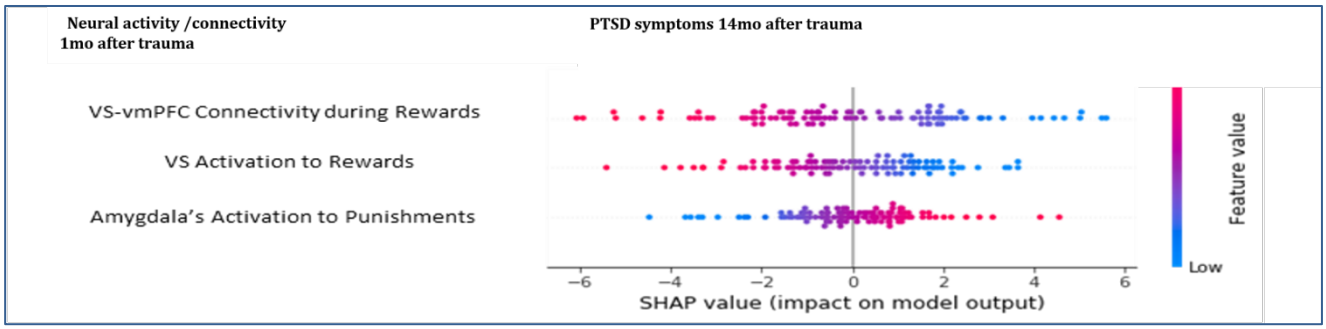


Figure 11. Predictor importance for PTSD symptom model.

2.4.2 Study 2. Neural response to goal conflict predicts more PTSD following trauma.

37 trauma survivors from the above study came back to lab after about 36 months from the trauma. Participants played the PRIMo game described above during fMRI. Each participant played three 6-minute rounds during their scanning session. Whole brain analysis of the reward-punishment contrast showed positive activation in the reward system including the VS and VTA. Clinical assessments during TP4 were compared to the previous time points and a symptom improvement trajectory was calculated for each participant using the slope of the linear equation combining all assessments. Activity in the reward system was negatively correlated with the PTSD symptom trajectory (VTA r=-0.39, p=0.016; Nacc r=-0.28, p=0.09; combined r=-0.35, 0.03), such that a steeper symptom trajectory was related to greater activity during the reward compared to punishment outcome (Figure 12). In light of the above finding with LFP from the hippocampus and mPFC, this long-term association between less mesolimbic reward activation and more PTSD, could be related to diminished gamma following punishment when facing a stressing goal-conflict. Accordingly, upregulating gamma in these areas through self-neuromodulation might enhance resilience to stress and trauma.

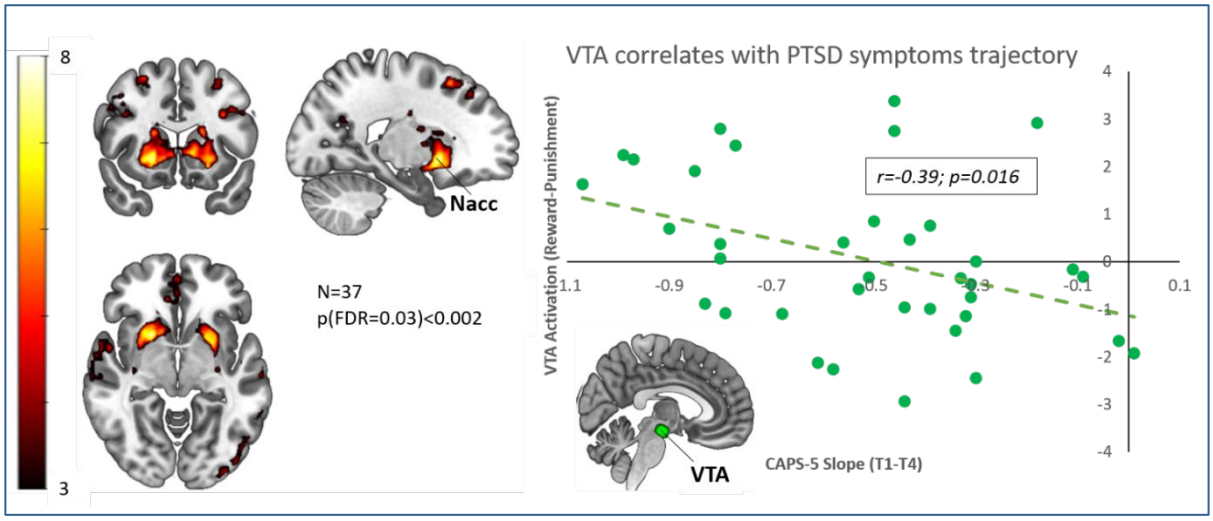


Figure 12. Neural correlates of symptom trajectory in PTSD

2.5 Neurofeedback success or failure in the lens of reinforcement learning.

Neurofeedback (NF) is a collection of Brain-Computer Interface procedures through which individuals learn to self-regulate their own neural dynamics, by receiving reinforcing feedback regarding desired changes in neural activity/connectivity patterns. NF protocols differ with respect to various task characteristics. However, the two most critical dimensions that define structurally different learning regimes are the goals of regulation as instructed to participants before practice, and the timing of feedback presentation. The goals of regulation may be specified through explicit instructions, or through an implicit protocol. In **T3.13** we focused on explicit regulation protocol, in which participants are asked to search actively in a trial-and-error manner for mental strategies (eliciting some kind of a mental content involving perceptual, imaginative, cognitive, or meta-cognitive components) that result in a defined neural change (e.g., the up or down regulation of a neural pattern). Sensory feedback reporting the change then informs participants about their reward. In term of the timing of feedback presentation, sensory feedback may be given either during or following periods of neural regulation attempts. The explicit protocols in **T3.13** used continuous sensory feedback regarding changes in neural patterns during regulation attempts. The ultimate reward is a function of this sensory feedback (e.g., if the reported neural change is appropriate for at least a minimal period of time). Animal NF studies have shown it is possible to boost the activity of a single neuron whilst suppressing the activity of neighbouring neurons – for essentially arbitrary choices of neurons, in a reasonable training period. This seems an extraordinarily hard search and exploration problem – and we currently do not know how it is solved. Human NF paradigms currently operate with far less precision – with still some substantial evidence of neural regulation learning effects (see Figure 13 for learning ability in humans).

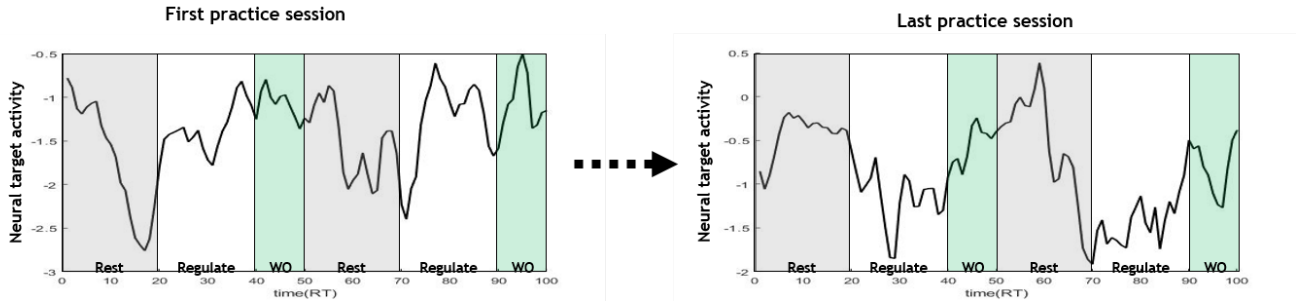
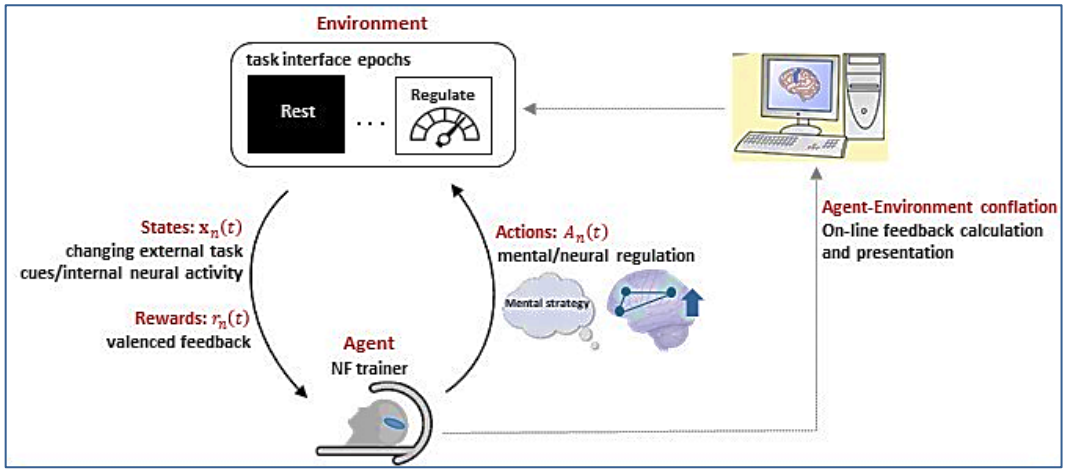


Figure 13. Neurofeedback learning abilities in human participants

In **T3.13,** we formulated NF through the lens of **Reinforcement Learning (RL),** addressing the puzzle underlying training efficiency. In a recent perspective article, we attempted to set the stage for a computational solution to this puzzle by placing the practice of NF under the analytic considerations of RL. Our characterization licenses comparisons between typical NF protocols in terms of their unique advantages and limitations and puts in sharper perspective unattended aspects of NF learning, such as credit assignment and exploration of actions, that are extensively investigated in RL including algorithmically (Figure **14**, adapted from Lubianiker et al., 2021).

Figure 14. Reinforcement Learning modelling of Neurofeedback.



2.6 Success and failure in Self-Neuromodulation; fMRI perspective of beyond the target mechanism

In order to further explore the brain networks involved in success and failure during self-neuromodulation, we gathered 140 patients from four separate studies using an Amygdala real-time fMRI down-regulation protocol. Patients were diagnosed with either chronic (N=69) or acute (N=26) form of post-traumatic stress disorder or fibromyalgia (N=45) and enrolled in a clinical study with baseline and post intervention fMRI sessions. During the baseline session, patients performed one run of amygdala neurofeedback training with an interactive interface providing continuous real-time feedback on their brain activity. Each trial was divided into a 'Watch' period where the instruction was to passively observe a figure skateboarding on the screen and a 'Regulate' period where the instruction was to actively decrease the figure's speed. Amygdala activity in each repetition of the regulate period was compared to the average activity in the watch period and displayed to the participant via a speedometer reflecting the current speed. First, we looked at group-level whole brain activations of the watch vs regulate periods showing a distributed network of activated and deactivated regions, including the target region of the amygdala (see Figure 15A). Next, we divided the entire group into successful (N=84) and unsuccessful (N=56) modulators, based on the beta estimate of the amygdala region of interest activation. Looking at the whole brain activations in each subgroup we observed two distinct networks involved in either success or failure of performing the task (see Figure 15B, C).

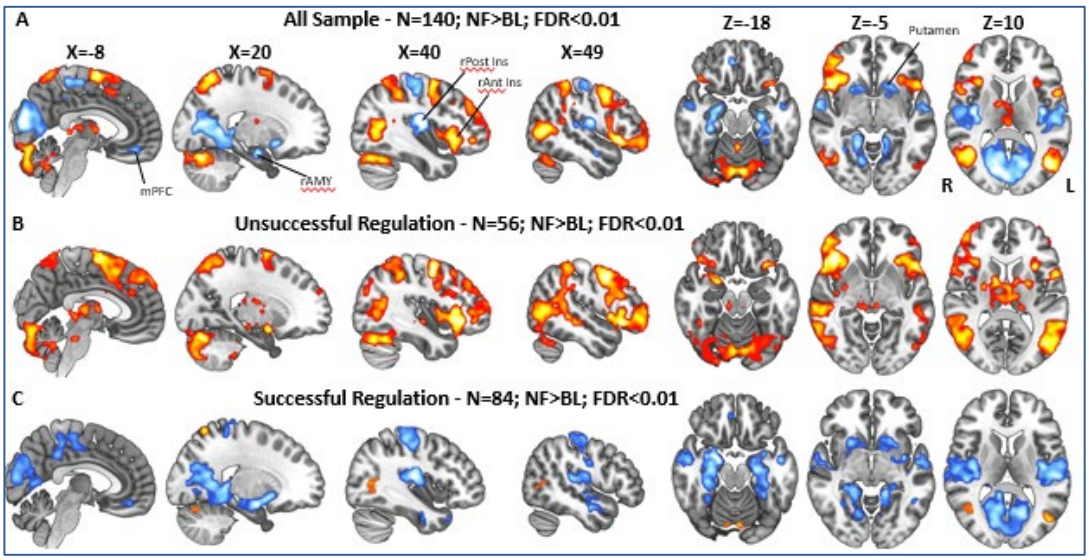


Figure 15. Regulation vs. Baseline in successful and unsuccessful modulators

A subgroup of all patients (N=75) went through Amygdala-Electrical Fingerprint training during the intervention period lasting between 10-15 weekly sessions. We examined this subgroup at the post-intervention time point, while performing the Amygdala rtfMRI down-regulation task in another scanner session. In the entire EFP-NF training group, the whole brain activation network of the regulation task was similar, although weaker than the baseline session. When looking on Amygdala deactivation during this session, it was only marginally correlated with an overall measure of EFP learning throughout the intervention period. To explore other regions involved in successful modulation during rtfMRI we evaluated other clusters, which were modulated along with the amygdala in the successful group (Figure 16, whole brain).

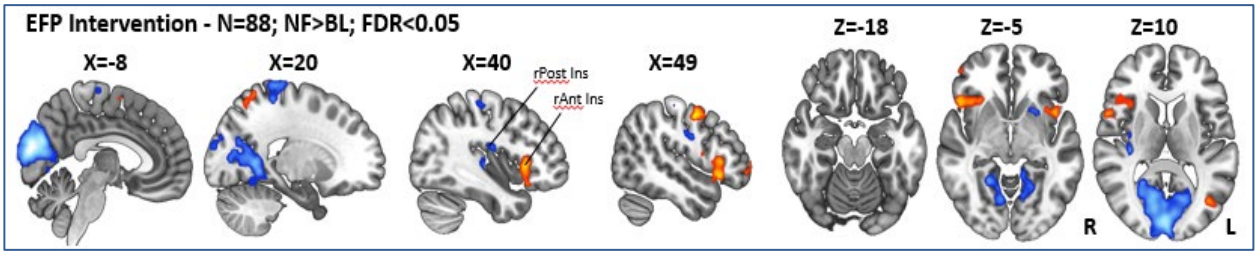


Figure 16. Regulation vs. Baseline in post-training scans

Interesting a significant correlation was found between posterior insula deactivation and EFP-learning, but only in subjects who were successful in down regulating their amygdala BOLD during the second session (Figure 17; left panel). Introducing a mediation model, we show that the effect of EFP learning on Amygdala down-regulation following treatment is mediated by posterior insula deactivation (Figure 17; right panel).

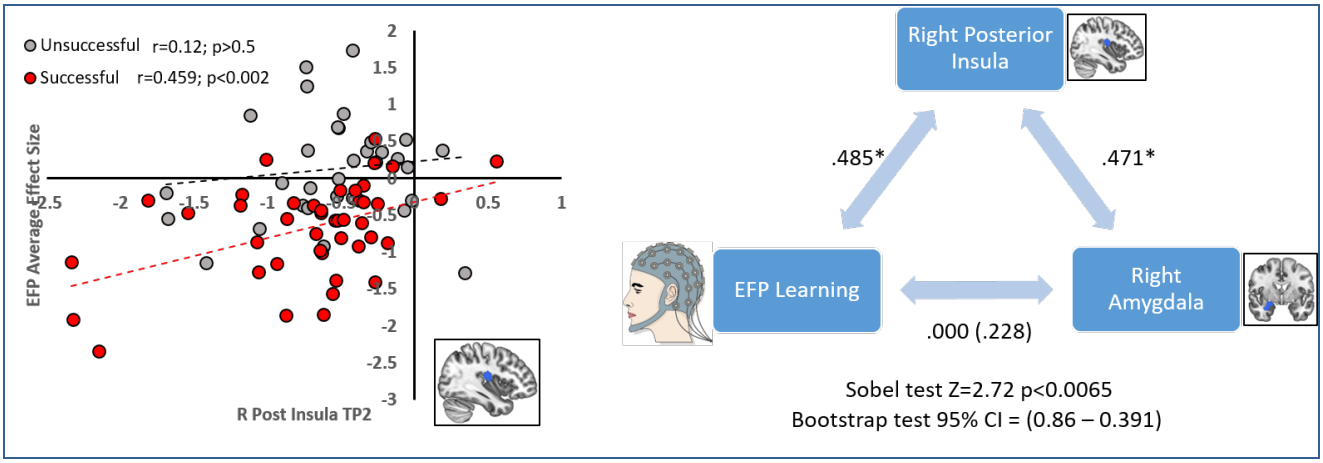


Figure 17. Correlation between learning and modulation

2.7 EEG signatures derived from fMRI activation and intracranial recordings in regions related to motivational conflict.

2.7.1 From fMRI to Scalp EEG

The possible scalability of neural markers of failure processing that is derived from fMRI activation during motivational conflict as described in section 2.1, is demonstrated in our recent work showing that fMRI activation during hedonic experience could be modelled into a validated EEG model using machine learning procedure. In this work, recently published in Singer et al., 2023 PLUS P4058, we developed and validated a scalable, fMRI-informed EEG model related to reward processing in the nucleus accumbens (Nacc). The Nacc is a core node of the brain's motivation system, also shown by us using fMRI to be involved in processing approach behaviour under high-risk (see Figure 4). An EEG based model of such activation may enable scalable and ecological monitoring of motivation-related

neural processing in contexts that preclude use of the stationary and costly fMRI technique. To develop the EEG model, we acquired simultaneous EEG/fMRI data from 17 healthy individuals while they listened to individually tailored pleasurable music – a highly hedonic stimulus known to engage the Nacc. We used these cross-modal data to construct a generic regression model for predicting the concurrently acquired BOLD signal from the Nacc using spectro-temporal features from the EEG signal (termed Electrical Finger Print; EFP). The performance of the extracted model was examined using a series of tests that were applied on the original dataset and, importantly, on an external validation dataset, which was collected from a different group of 14 healthy individuals who underwent the same EEG/FMRI procedure. The validation analyses revealed that the Nacc-related EFP model predicted Nacc-BOLD activation from the simultaneously acquired EEG, as well with additional functionally relevant regions, to a greater extent than a model derived from another anatomical region. The functional validity of the developed Nacc-related EFP was supported by showing that it is modulated by musical pleasure and predictive of the Nacc-BOLD during a monetary reward task, further indicating its functional relevance. These findings highlight the feasibility of modelling activation related to Nacc via EEG only, and pave the way for future use of such a scalable neural probing approach for self-guided neuromodulation or neural monitoring (Figure 18).

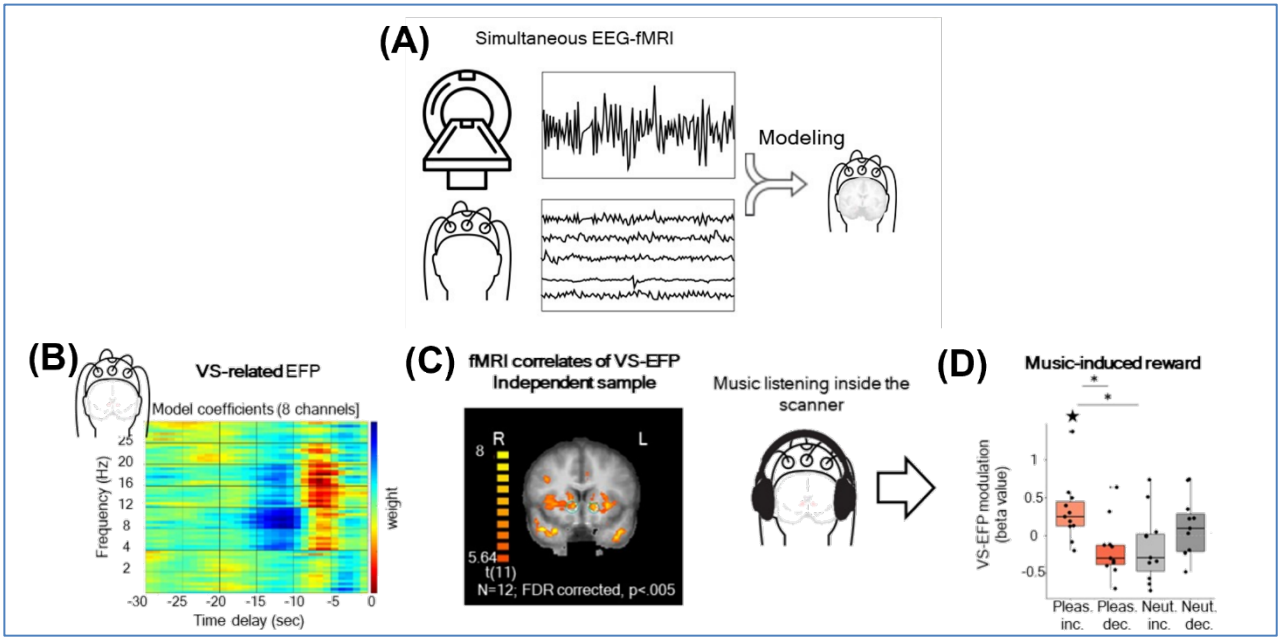


Figure 18. The development of EEG inspired model of fMRI activity in the Nucleus Accumbens

Schematic description of fMRI-informed EEG modelling. (A) Simultaneous EEG-fMRI recording is combined with Machine learning algorithms to predict fMRI activation from the Nacc using the EEG features, resulting in "Electrical FingerPrint" (EFP) Model. (B) The EFP model is a weighted time-frequency EEG representations of fMRI Nacc activity. (C) Validation: Whole-brain FMRI analyses showing that the EFP signal predicted BOLD activity in the target regions and related brain areas in an independent sample (green contour). (D) Process-Assessment. Increase in Nacc-related-EFP model was evident during moments of increase in pleasure ratings while listening to pleasurable music, indicating reward-related modulation. Adapted from Singer et al., 2023 PLUS P4058.

2.7.2 From Intracranial recording to scalp-EEG

The possible scalability of neural markers of failure processing that is derived from intracranial hippocampus recording as described in section 2.2, is demonstrated in our recent work showing that intracranial unit recording from the amygdala and hippocampus could be predicted by scalp EEG electrodes. Linking scalp electroencephalography (EEG) signals and spontaneous firing activity from deep nuclei in humans is not trivial. To examine this, we analysed simultaneous recordings of scalp EEG and unit activity in deeply located sites recorded overnight from patients undergoing pre-surgical invasive monitoring. We focused on modelling the within-subject average unit activity of two medial temporal lobe areas: amygdala and hippocampus. Linear regression model correlates the units' average firing activity to spectral features extracted from the EEG during wakefulness or non-REM sleep. We show that changes in mean firing activity in both areas and states can be estimated from EEG (Pearson $r > 0.2$, $p<0.001$). Region specificity was shown with respect to other areas. Both

short- and long-term fluctuations in firing rates contributed to the model accuracy. This demonstrates that scalp EEG frequency modulations can predict changes in neuronal firing rates, opening a new horizon for non-invasive neurological and psychiatric interventions (Figure 19, adapted from Yamin et al 2023, PLUS P4053). This work paves the way for our final deliverable of an electrical signature depicting avoidance following failure in light of our results from LFP in the hippocampus.

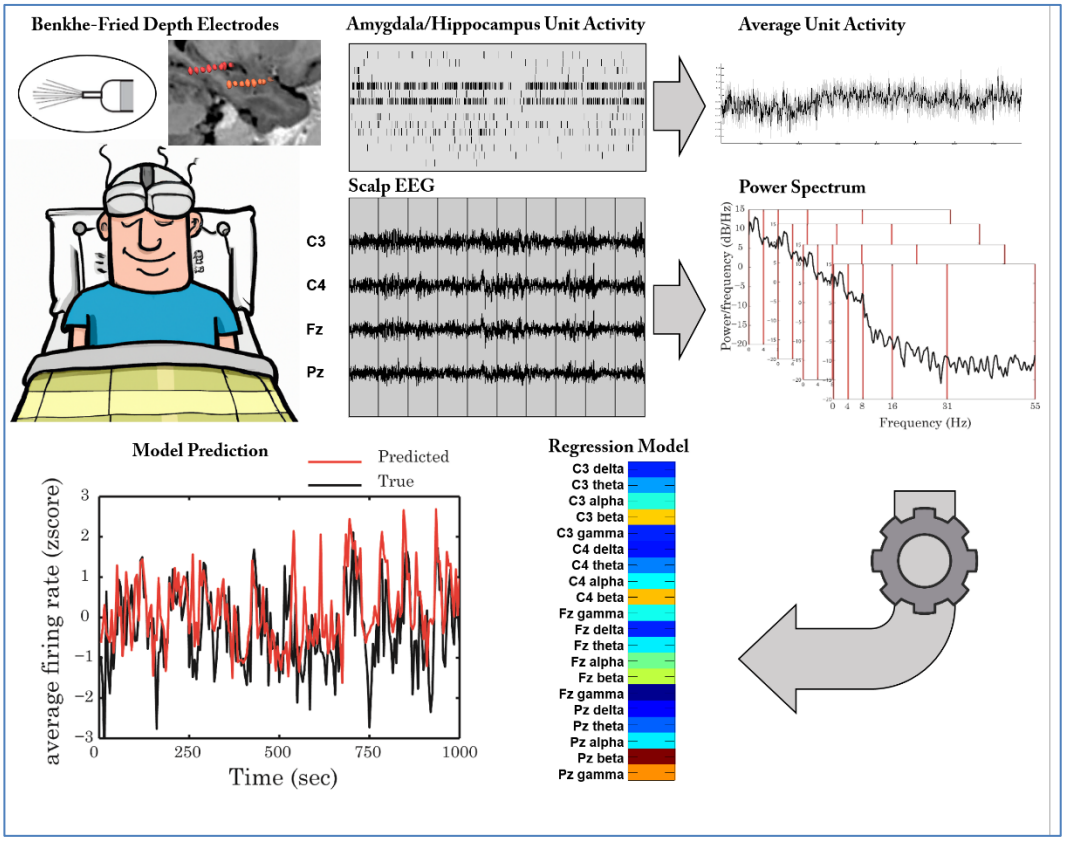


Figure 19. Overview of the Amygdala/Hippocampus unit activity model adapted from Yamin et al 2022 PLUS P4053

3. Looking Forward

Based on the current findings we plan to further pursue the development of EEG signatures of failure biases, using data from multiple modalities combined with scalp EEG such as intracranial recording and fMRI. Our aim is to go beyond neuroanatomical characterization of failure by acquiring the data during relevant process activation (e.g., Reinforcement learning, approach-avoidance-conflict, and risky choice tasks). We intend to develop EEG signatures which are derived from more than one region involved in the processing of failure (e.g., hippocampus and mesolimbic, hippocampus and prefrontal). In addition, we plan to establish and pipeline for obtaining family of signatures, which could be later optimized to individual's need. After developing and validating the signatures, we plan to test their functional utility in neurofeedback as therapeutic procedure in addiction or depression. Lastly, once having a scalable EEG signature, it will be possible to also monitor individuals in real life settings while accounting to daily challenges or stressful events.