Differences in resting-state brain activity metrics related to sensitivity to punishment

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RESUMEN

Según la teoría revisada de la sensibilidad a la recompensa de Gray (rRST) (Gray & McNaughton, 2000), las situaciones en las que una persona se enfrenta a un estímulo aversivo se ven mediadas por dos sistemas neuroconductuales, el *Behavioral Inhibition System* (BIS) y el *fight-flight-freeze system* (FFFS). Estos sistemas despertarían comportamientos como la evitación defensiva en el caso del primero, y la aproximación defensiva en el caso del segundo (McNaughton & Corr, 2004). A pesar de haberse estudiado los correlatos anatómicos de la teoría de la sensibilidad a la recompensa, la actividad en reposo de las áreas implicadas sigue siendo una cuestión por explorar. El objetivo de este trabajo ha sido estudiar la relación entre la sensibilidad al castigo (SC), entendida como una manifestación cognitiva de la actividad de los sistemas neuroconductuales; con la homogeneidad regional (ReHo) y la amplitud fraccional de fluctuaciones de baja frecuencia (fALFF), dos métricas de resonancia magnética funcional en estado de reposo. Siguiendo esta idea, se han realizado análisis de regresión lineal en una muestra de 127 sujetos, tanto a nivel de todo el cerebro, como en regiones de interés compuestas por la amígdala y el hipocampo, ya que estas estructuras han sido identificadas como dos de las principales áreas implicadas en los sistemas BIS/FFFS (Adrián-Ventura et al., 2019). Basándonos en bibliografía existente (Hahn et al., 2013), esperamos encontrar correlaciones negativas entre la SC y las métricas fALFF y ReHo en amígdala e hipocampo. Tras haber realizado todos los análisis pertinentes, hemos llegado a la conclusión de que la relación esperada solo se ha manifestado entre la sensibilidad al castigo y los valores de fALFF en la amígdala e hipocampo derechos. Esta relación entre actividad basal y SC podría explicar las diferencias individuales encontradas en la activación de estas áreas ante estimulación aversiva.

PALABRAS CLAVE: Sensibilidad al castigo, fALFF, ReHo, ansiedad, amígdala, hipocampo

ABSTRACT

According to Gray's revised reward sensitivity theory (Gray & McNaughton, 2000), the scenarios where a person faces an aversive stimulus are mediated by two neurobehavioral systems, the behavioral inhibition system (BIS) and the fight-flight-freeze system (FFFS). These systems would elicit behaviors such as defensive avoidance in the case of the former, and defensive approach in the case of the latter (McNaughton & Corr, 2004). Despite all the research published about the anatomical correlates of the two systems of interest, the resting-state activity in the areas involved is still a question waiting to be properly addressed. The aim of this project has been to study the relationship between sensitivity to punishment (SP), understood as a cognitive manifestation of the neurobehavioral systems; and the regional homogeneity (ReHo) and fractional amplitude of low frequency fluctuations (fALFF), two resting state fMRI (rs-fMRI) metrics. Following this idea, linear regression analyses have been carried out in a sample of 127 subjects, with a focus on both, the whole brain, and specific regions of interest composed by the amygdala and hippocampus, as these areas have been identified as two of the main regions involved in BIS/FFFS (Adrián-Ventura et al., 2019). Based on pre-existing bibliography (Hahn et al., 2013), we expected to find negative correlations between SP measures and both rs-fMRI metrics in the amygdala and hippocampus. Once all the pertinent analyses were carried out, we came to the conclusion that the SP scores and the fALFF in the right amygdala and hippocampus yielded the expected negative correlation. This relationship between basal activity and SP could explain individual differences found in the activation of these areas when faced with aversive stimulation.

KEY WORDS: Sensitivity to punishment, anxiety, fALFF, ReHo, amygdala, hippocampus

UNIVERSITAT JAUME I

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INTRODUCTION

According to Gray's revised reinforcement sensitivity theory (rRST) (Gray & McNaughton, 2000), when a person faces a negative stimulus, two neurobehavioral systems are in charge of dealing with said situation. On the one hand, the fight-flight-freeze system (FFFS) is in charge of modulating defensive avoidance, on the other hand, the behavioral inhibition system (BIS) mediates approach-avoidance conflicts, that is, approaching the negative stimulus in order to reduce conflict (defensive approach) (McNaughton & Corr, 2004). Some of the areas identified to be part of these systems are the amygdala (fear perception), the medial hypothalamus and periaqueductal gray (defensive avoidance behaviors) and the hippocampus (defensive approach) (Adrián-Ventura et al., 2019).

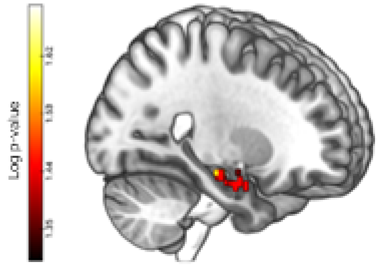
Different neuroimaging studies have been conducted with the goal of understanding the neuroanatomical correlates of FFFS/BIS, but few have focused on resting state brain functional connectivity, including functional connectivity (Costumero et al., 2021), and local measures such as fractional amplitude of low frequency fluctuations (fALFF) and regional homogeneity (ReHo) (Hahn et al., 2013). These metrics have also proved to be sensitive measures when evaluating neural dysfunctions in different anxiety disorders (Mizzi et al., 2021; Shen et al., 2020; Cui et al., 2020). The objective of this study is to further understand and cement the scarce knowledge about the resting state brain activity related to FFFS/BIS, based on sensitivity to punishment (SP) scores. We expect to find a negative correlation between SP scores and the previously mentioned resting state fMRI (rs-fMRI) metrics in the amygdala and hippocampus.

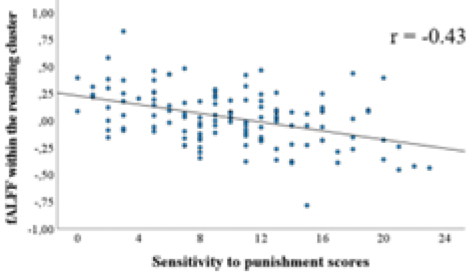
METHODS

- **Participants**: The final sample consists of 127 participants after subject exclusion due to excessive head movement (64 women; age: mean = 23.94, SD = 7.28, range = 18-49). All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). No participant referred a history of neurological, psychiatric or severe medical disorders, traumatic brain injury with loss of consciousness, or were under psychoactive medications.
- **Personality assessment**: All participants completed the Sensitivity to Punishment (SP) scale from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001). This scale is intended for assessing the reactivity and responsivity of the BIS/FFFS by evaluating behavioral responses toward potential aversive or conflicting situations.
- **Image acquisition and preprocessing**: 1.5T Siemens Avanto scanner. A 3D image was acquired using a T1-weighted MPRAGE sequence. For the rs-fMRI, a total of 200 volumes were recorded using a GRE T2*-weighted EPI sequence. rs-fMRI data was preprocessed via Data Processing Assistant for Resting-State fMRI Advance Edition (DPARSFA), following the standard steps suggested for the software. Differences between fALFF and ReHo preprocessing were set following Yan & Zang (2010).
- **Statistical analysis**: Once the ReHo and fALFF metrics were obtained for each participant, the resulting standardized maps were analyzed in the SPM's 2nd level. Whole brain and region of interest (ROI) regression analyses were conducted for both metrics, taking the SP scores as covariate of interest, and age and sex as covariates of no interest. Amygdala and hippocampus ROIs were extracted from the Hammers atlas. The statistical inference for the whole-brain and ROI analyses was calculated via threshold-free cluster enhancement (TFCE).

RESULTS

- **ReHo**: No statistically significant positive or negative results were found when analyzing the relationship between SP and ReHo at a whole-brain level, nor at a ROI level.
- **fALFF**: No significant positive or negative results were found when analyzing the relationship between SP and fALFF at a whole-brain level. However, the ROI analysis did yield a statistically significant result for the right hemisphere ROI. Specifically, a negative correlation between the SP scores and the ROI's fALFF (k = 21 voxels; pFDR-corrected = 0.010; TFCE = 43.05).





DISCUSSION

Contrary to what was hypothesized, we found no association between the scores on a SP scale and the regional homogeneity resting state metric. However, we did find a negative correlation between said SP scores and the fALFF of the amygdala and hippocampus. This relationship between basal activity and SP could explain individual differences found in the activation of these areas when subjects are faced with aversive stimulation (see Stein et al., 2007; Krug & Carter, 2010), as a higher level of basal activation in non-anxious subjects would lead to a reduced activation contrast during negative events. The inability to replicate previous results (Hahn et al., 2013) could stem from the differences in sample size (27 to 127) or from methodological aspects such as age distribution.

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