Neural Signatures of Human Conditioned Fear Extinction: a Meta-analysis of fMRI Studies

MA Fullana[1,2,3], J Radua[4,11], C Soriano-Mas[5,6], N Cardoner[3,7], B Vervliet[8], O Benet[9], A Albajes-Eizagirre[4], BJ Harrison[10]

(1)Anxiety Unit, Institute of Neuropsychiatry and Addictions, Hospital del Mar, CIBERSAM, Barcelona, Spain; (2) IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; (3) Department of Psychiatry, Autonomous University of Barcelona, Barcelona, Spain; (4) Department of Translational Neuroimaging, FIDMAG Germanes Hospitalàries-CIBERSAM, Sant Boi de Llobregat, Barcelona, Spain; (5) Department of Psychiatry, Bellvitge University Hospital-IDIBELL, CIBERSAM, Barcelona, Spain; (6) Department of Psychobiology and Methodology of Health Sciences, Autonomous University of Barcelona, Barcelona, Spain; (7) Depression and Anxiety Unit, Mental Health Department, Parc Taulí Sabadell University Hospital, Barcelona, Spain; (8) Center for Excellence on Generalization in Health and Psychopathology, University of KU Leuven, Leuven, Belgium; (9) Universitat Pompeu Fabra, Barcelona, Spain; (10) Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia; (11)Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

Background

- Conditioned fear extinction models have a central role in our understanding of anxiety disorders and their treatment. [1]
- The neural correlates of human fear extinction remain only partly understood and there has been considerable variability in the results of individual studies.

Methods

- Literature search of fMRI **whole-brain** fear extinction studies (including unpublished datasets) **in adults** conducted between 01/1998 and 07/2015. (Figure 1)
- Meta-analysis of brain activation differences between CS+ and CS- during fear extinction using **anisotropic effect-size signed differential mapping** [2] and FDR-equivalent ($P < 0.05$, minimum extent 10 contiguous voxels) whole-brain thresholds.

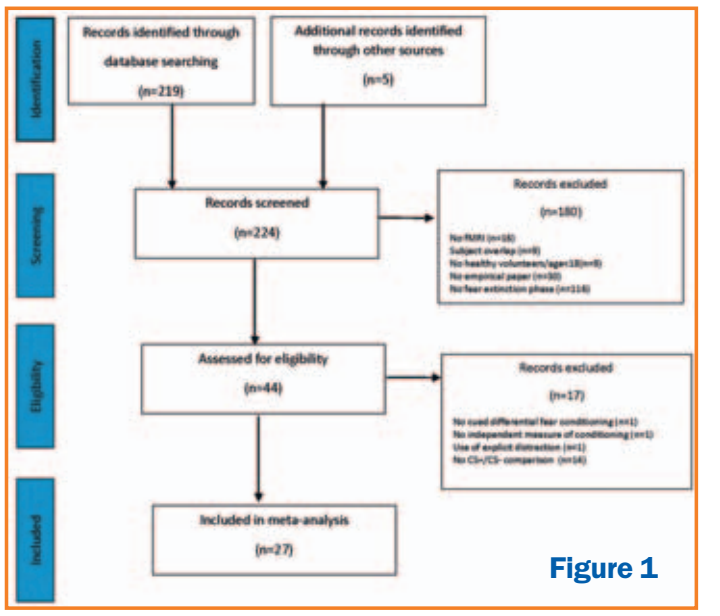
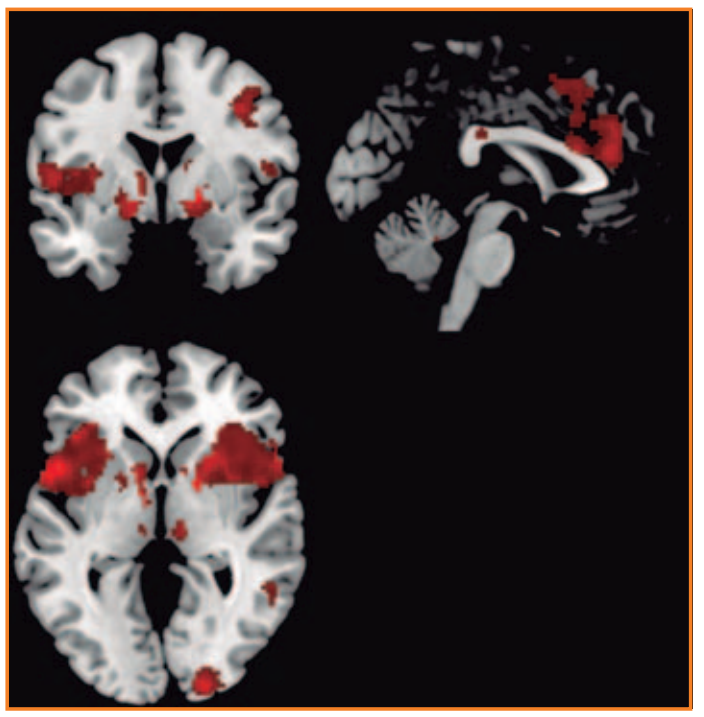


Figure 1

Results

27 datasets were included
Final sample: 1005 participants, 53% males, mean age=25.76

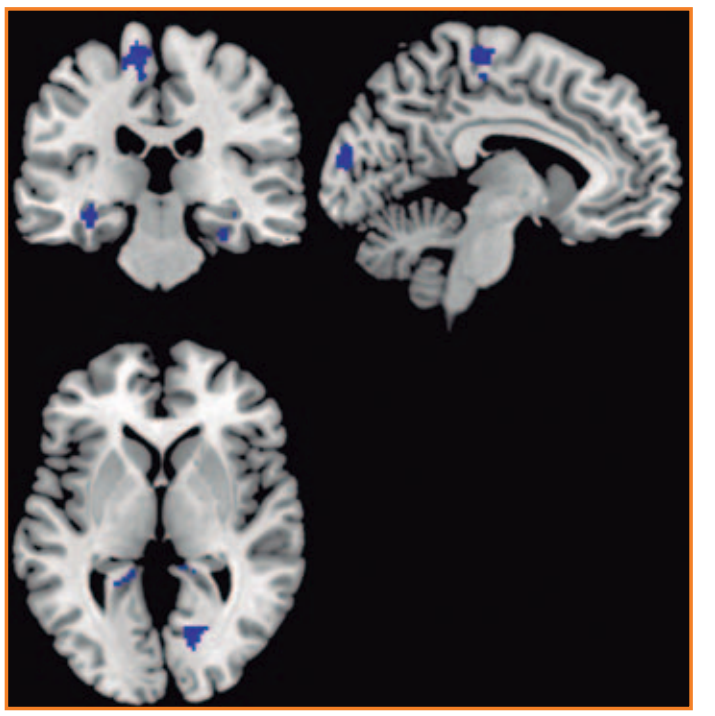
Figure 2. Significant activations (CS+>CS-) during fear extinction



Significant activations were found in:

- dorsal anterior cingulate extending to dorsomedial prefrontal cortex
- anterior insular cortex and frontal operculum
- right premotor and right dorsolateral prefrontal cortex
- primary somatosensory cortex
- ventral caudate, putamen and pallidum
- periaqueductal gray matter
- right visual association cortex.

Figure 3. Significant deactivations (CS+<CS-) during fear extinction



Significant deactivations were found in:

- posterior and retrosplenial cingulate cortex
- posterior hippocampus, primary motor cortex
- superior frontal cortex
- right orbitofrontal cortex

Conclusions

Brain responses during fear extinction broadly parallel those observed during fear conditioning (CS+ > CS-), but with an additional engagement of dorsomedial and dorsolateral prefrontal regions typically linked to **cognitive regulation**.
The absence of ventromedial prefrontal cortex differences between CS- and CS+ suggests that the extinguished CS+ is processed as a safety signal.

References

[1] Milad, M.R. & Quirk, G.J. (2012). Fear extinction as a model for translational neuroscience: ten years of progress. Annual Review of Psychology, 63, 129-151
[2] http://www.sdmproject.com/

FUNDING SUPPORT

Supported by grants from Carlos III Health Institute/FEDER to MAF (PI12/00273) and CS-M (PI13/01958).
Supported by 'Miguel Servet' contracts from the Carlos III Health Institute (Spain) to CS-M (CP10/00604) and JR (CP14/00041)

Hospital del Mar
Parc de Salut MAR Barcelona