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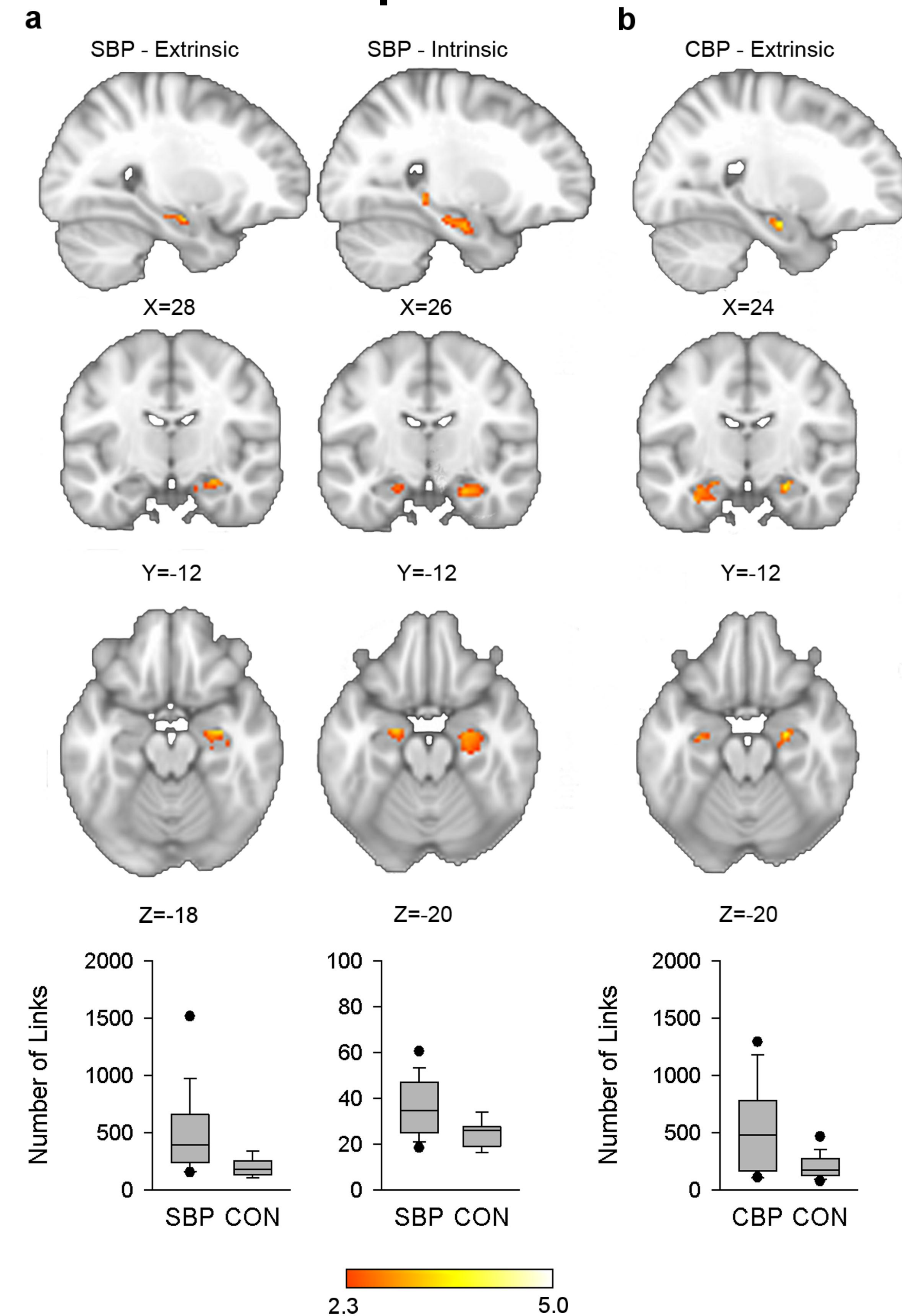
INTRODUCTION

- The hippocampus is known to undergo robust molecular and synaptic changes in animals with chronic neuropathic pain, and hippocampal volume is decreased in human chronic pain patients (Mutso et al., 2012).
- These changes complement a myriad of hippocampal-mediated behavioral changes in chronic pain patients.
- In a longitudinal brain imaging study we identified particular brain reorganization that is causally involved in pain chronification (Nac-mPFC) (Baliki et al., 2012).
- This study aims to identify properties of hippocampal functional connectivity in human back pain patients, as well as determine if hippocampal functional connectivity can differentiate patients whose pain will become chronic vs. ones who will recover.

METHODS

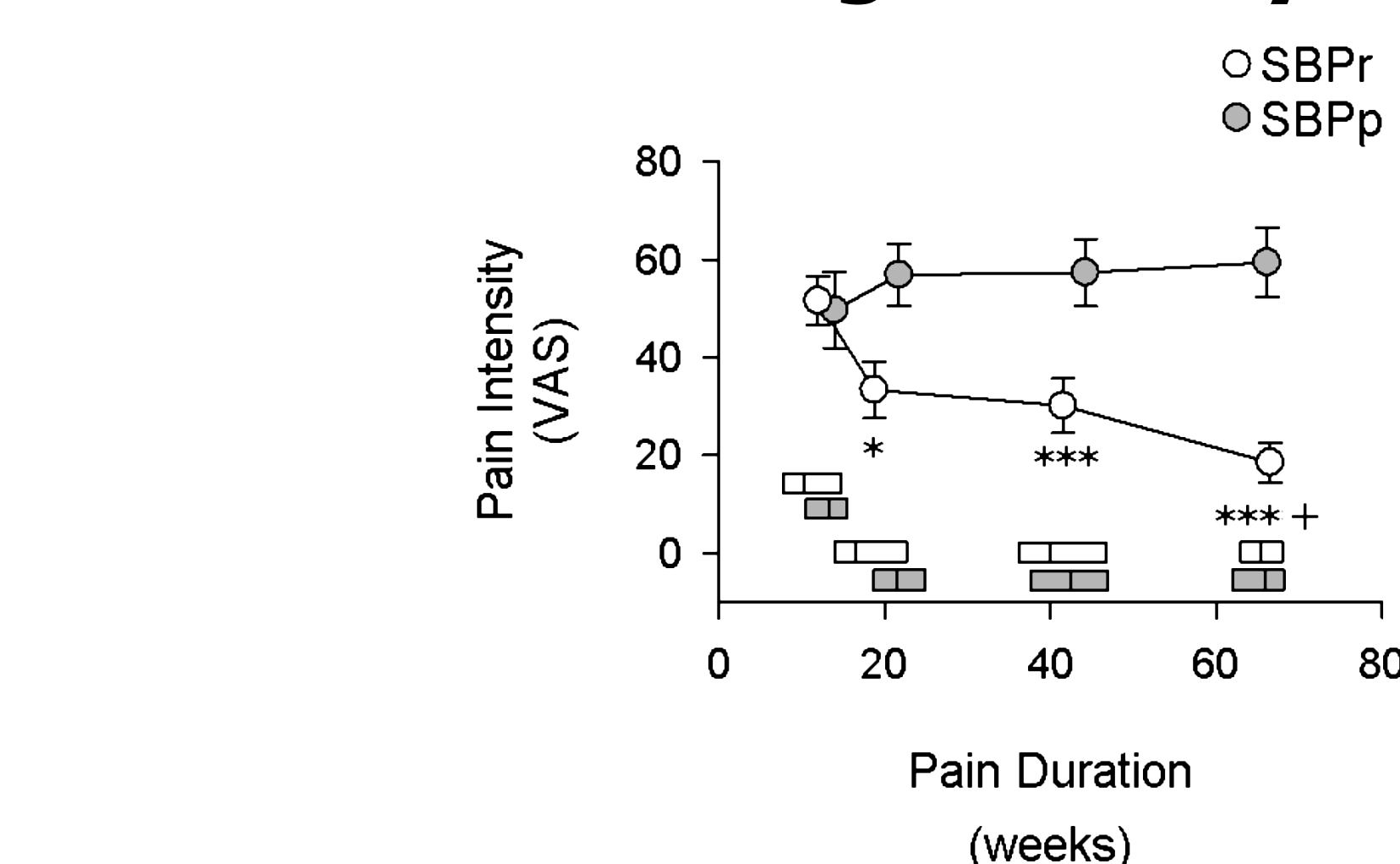
- T1 and functional MRI data was acquired with a 3T Siemens Trio on 15 healthy (CON), 17 chronic back pain (CBP, pain > 5 years) and 32 sub-acute back pain (SBP, back pain for 4-16 wks).
- Subjects performed a visual control bar-rating task with a finger span device during a 10 minute fMRI. Subjects were scanned 2 weeks after recruitment, 6 weeks, 6 months and 1 year later. Data were analyzed with FSL v4.1.8.
- SBP were subdivided into persisting (SBPp) and recovering (SBPr) groups based on whether or not pain decreased by 20% or more from recruitment.
- Hippocampus was identified in each subject's T1 using FAST. Connectivity ($r > 0.3$) of hippocampal voxels with the rest of the brain (extrinsic) and with other hippocampal voxels (intrinsic) was computed using ABLM. Group differences were identified using voxel based permutation testing.
- Analysis with FEAT examined every voxel's correlation with a parahippocampal region of interest.
- The region of interest was identified based on the conjunction of results of ABLM analyses. Post-hoc testing identified group differences in time.

1 Hippocampus has more extensive connectivity in sub-acute and chronic back pain than controls



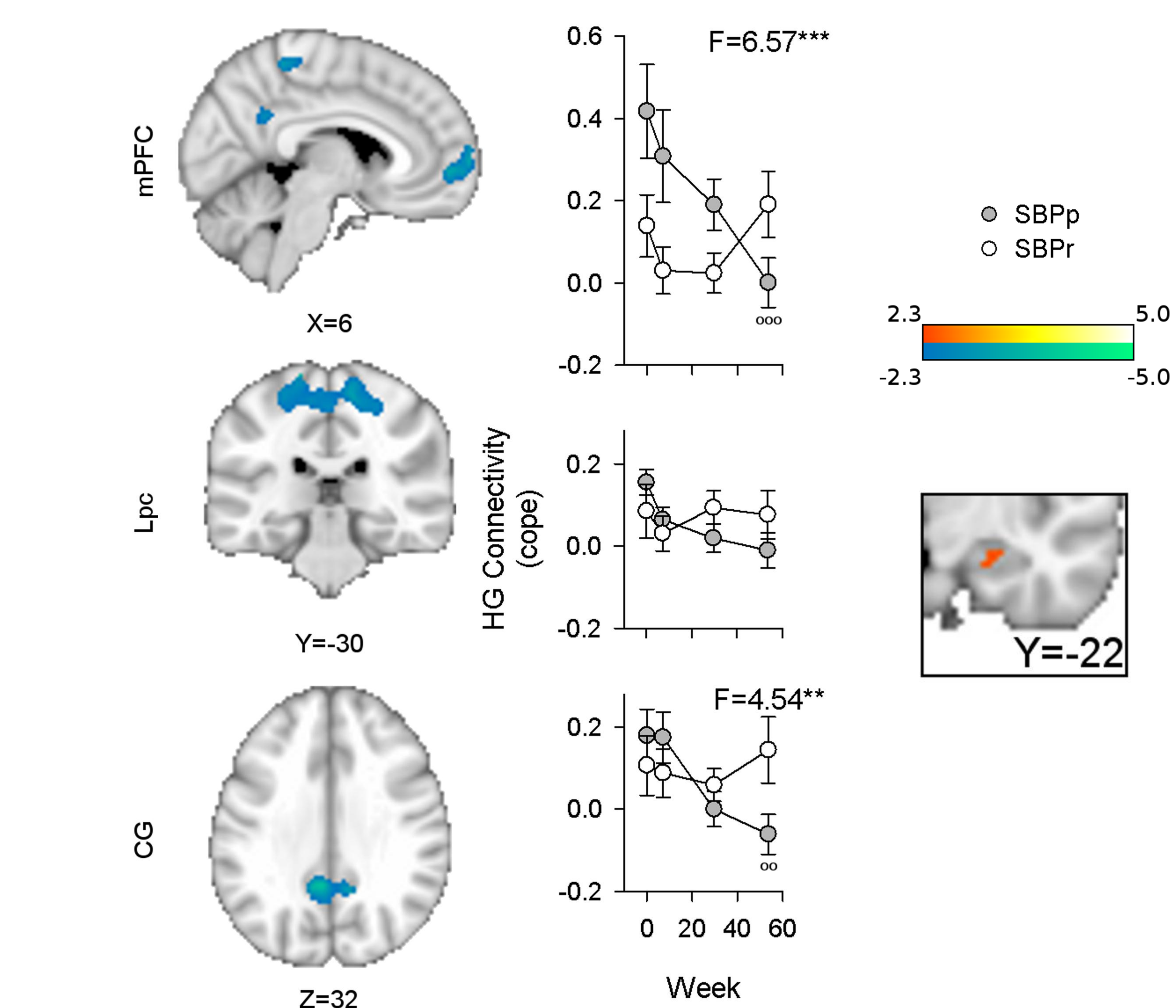
A SBP show greater extrinsic and intrinsic hippocampal connectivity at visit 1 than CON in the right hippocampus and bilaterally, resp. (Post-hoc U-test: intrinsic connectivity $p < 0.001$, extrinsic connectivity $p = 0.007$). **B** CBP show greater extrinsic hippocampal connectivity than CON bilaterally (post-hoc U-test $p = 0.007$).

2 Pain decreases in SBPr patients over the course of the study and ultimately differs significantly from SBPp



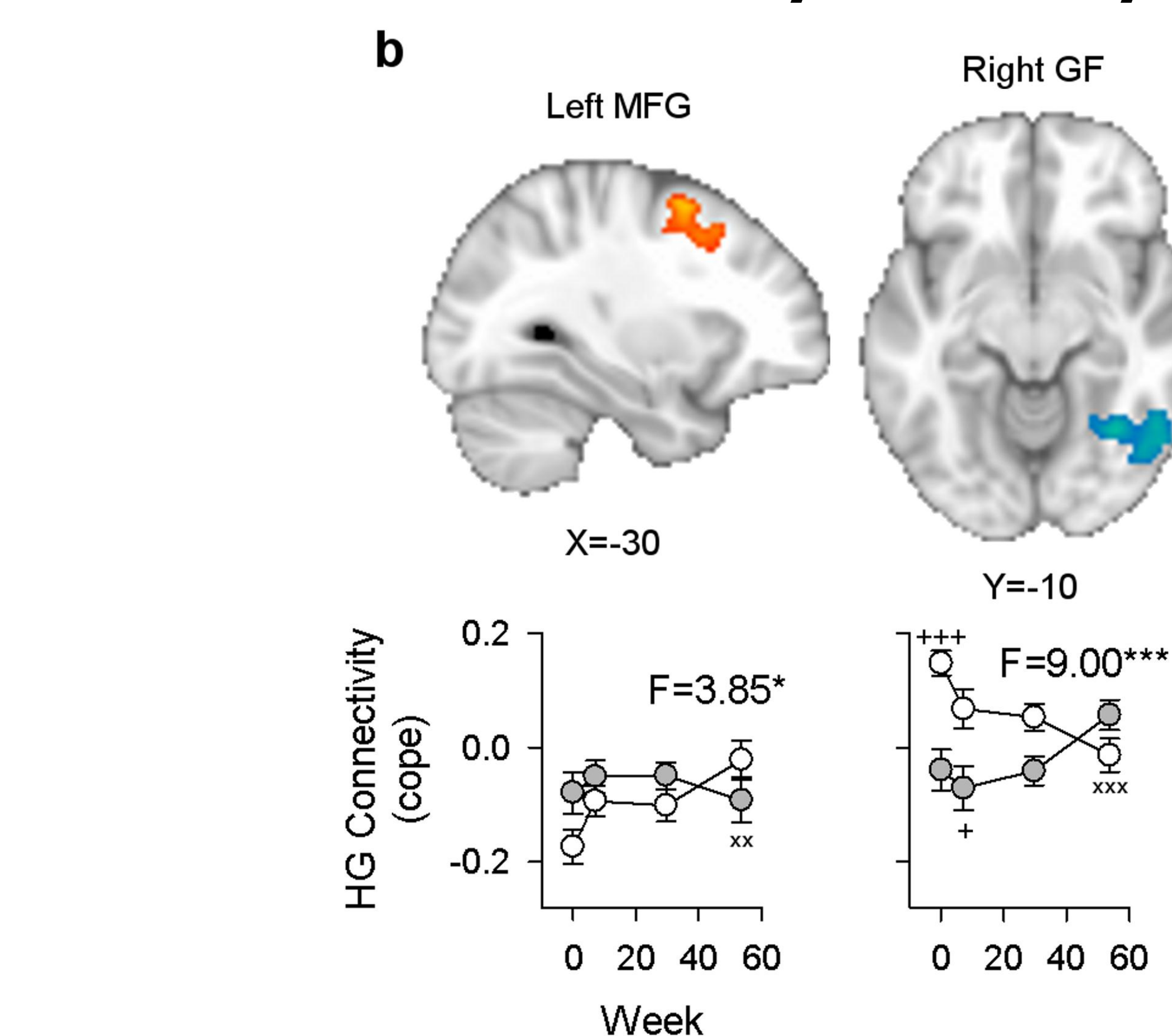
There is a significant group*time effect (rm-ANOVA, $p < 10^{-5}$). Post-hoc (Tukey) tests: $+p < 0.05$ within group comparison to visit 1; $*p < 0.05$, $***p < 0.001$ group contrast at fixed time.

3 SBPp have specific regions of decreased hippocampal functional connectivity over one year



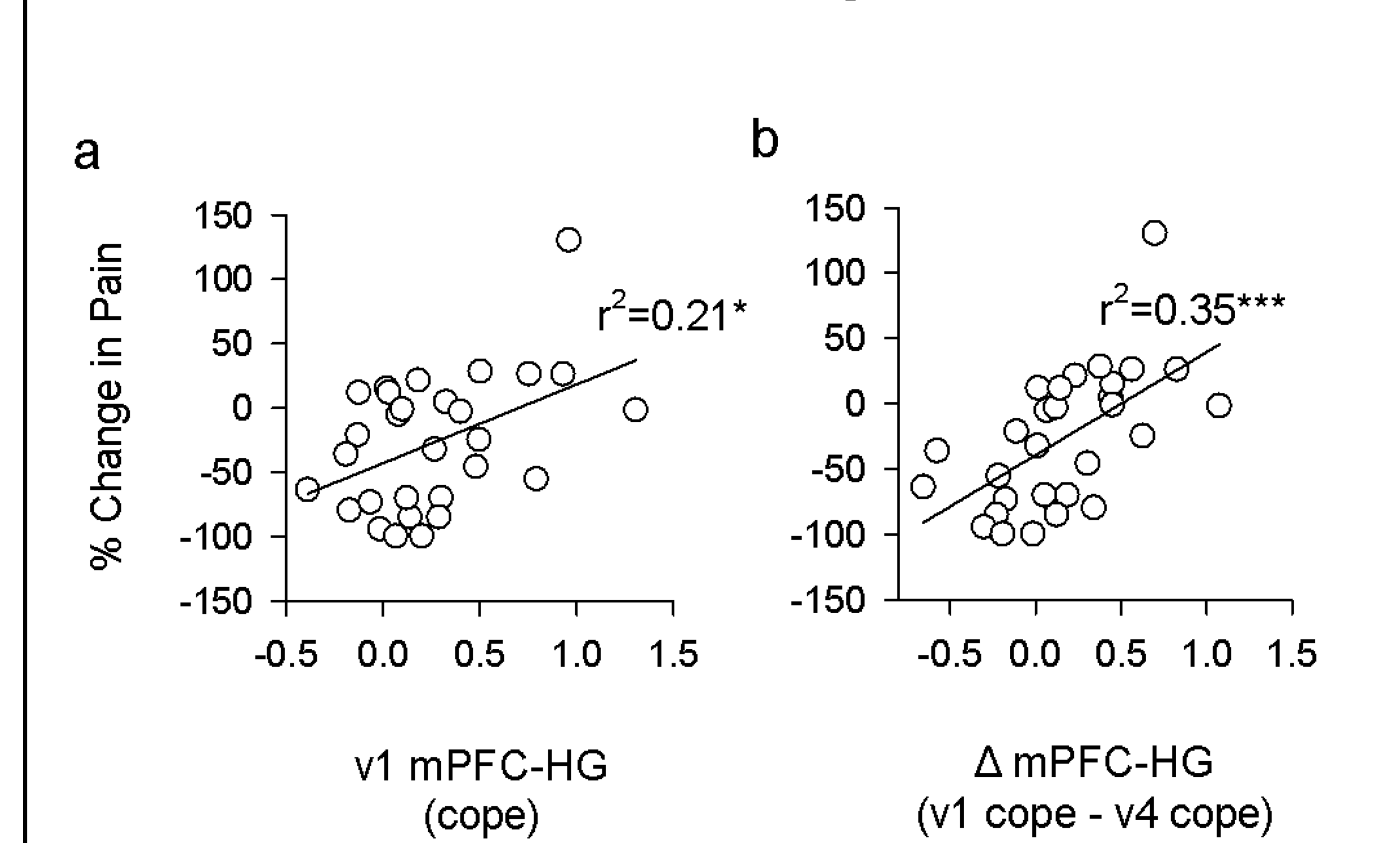
HG in SBPp subjects shows significant decreases in connectivity to mPFC, Lpc and CG over one year (paired t-test, $z > 2.3$, cluster $p < 0.05$). Time evolution of mPFC and CG connectivities differ between SBPp and SBPr (mPFC: $F_{(3,75)} = 6.57$, $p < 0.0005$; CG: $F_{(3,75)} = 4.54$, $p = 0.0056$).

4 SBPr have regions of increased and decreased hippocampal functional connectivity over one year



In SBPr, left MFG and right GF connectivities to HG change significantly over the same period (paired t-test visit 1 vs. visit 4). Across all timepoints, the time evolution of left MFG and right GF connectivities differ between groups ($F_{(3,75)} = 3.85$, $p = 0.0128$ and $F_{(3,75)} = 9.00$, $p = 4 \times 10^{-5}$, resp).

5 Parahippocampal-mPFC connectivity reflects future pain in SBP



A mPFC connectivity to HG at visit 1 correlates with amount pain changes after one year ($r^2 = 0.21$, $p = 0.013$). **B** The more mPFC connectivity to HG drops over the course of one year the more persistent the pain at visit 4 (mPFC $r^2 = 0.35$, $p = 0.0007$).

CONCLUSIONS

- The results are the first demonstration that hippocampal intrinsic, and cortical, functional connectivity is disrupted with back pain, during a simple motor-attentional task where performance is matched across groups.
- SBP patients whose pain persist vs. those patients who recover from pain over one year have specific hippocampal functional network changes over the same time period.
- Particularly of interest, SBPp patients have a decrease in HG-mPFC connectivity over one year, and HG-mPFC connectivity at visit 1 correlates with the later persistence of pain.
- This suggests there is a specific early contribution of the hippocampus in the development of chronic pain, and is consistent with evidence of disruption in the default mode network in chronic pain.
- The observed connectivity changes may contribute to the transition from subacute to chronic pain and also to common learning and emotional abnormalities in pain patients.

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