Altered resting-state functional connectivity in women with traumatic and non-traumatic chronic neck pain compared to pain-free women: associations with pain outcomes and central sensitization?

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BACKGROUND

? **KNOWLEDGE GAP:** Research examining **functional brain alterations**, and **associations with pain outcomes and central sensitization** in patients with chronic whiplash associated disorders (CWAD) and patients with chronic idiopathic neck pain (CINP) is lacking.

CINP
Non-traumatic chronic neck pain

CWAD
Traumatic chronic neck pain

Previous research revealed

- differences in pain-related outcomes and central sensitization between patients with CINP and CWAD
- **structural brain alterations** (white matter structure and gray matter morphology) in patients with CWAD compared to CINP and healthy controls
- associations between structural brain alterations & maladaptive pain cognitions and central sensitization

AIM

- To examine **resting-state functional connectivity (rsFC) alterations** in CWAD and non-traumatic CINP patients compared to healthy pain-free controls
- To assess **associations** between **rsFC alterations** and **pain intensity, pain cognitions, disability & central sensitization** in both patient groups

METHODS

107 women:
37 CWAD, 38 CINP, 32 healthy controls
High-resolution T1-weighted structural magnetic resonance (MR) images and T2*-weighted **resting-state functional MR images** were acquired.

Pain intensity, pain cognitions (PCS, PVAQ), disability (NDI) & symptoms of central sensitization (CSI) were assessed (see Table 1).

Experimental measures of central sensitization:
Pressure hyperalgesia (pressure pain threshold, PPT) & conditioned pain modulation (CPM) efficacy were examined at the m. quadriceps.

After data pre-processing, **seed-to-seed rsFC analyses** were conducted (CONN toolbox). 17 regions of interest were selected as seed regions. These seeds are implicated in (chronic) pain and found to be structurally altered in this population. Targets were all frontal, parietal and subcortical regions, and the periaqueductal grey (PAG). All regions were extracted from the Harvard-Oxford cortical and subcortical atlas, except for the PAG (coordinate-based).

Potential rsFC group differences were examined. Within regions showing a main effect of group, associations with disability, pain intensity, pain cognitions, and measures of CS were examined.

Also, within the patient group, associations were investigated between measures of CS and rsFC between all seeds and targets.

Age was included as covariate in all analyses. For the main effect of group, a FDR correction was applied (p-FDR < .05), and a Bonferroni correction was performed for pairwise group comparisons.

RESULTS

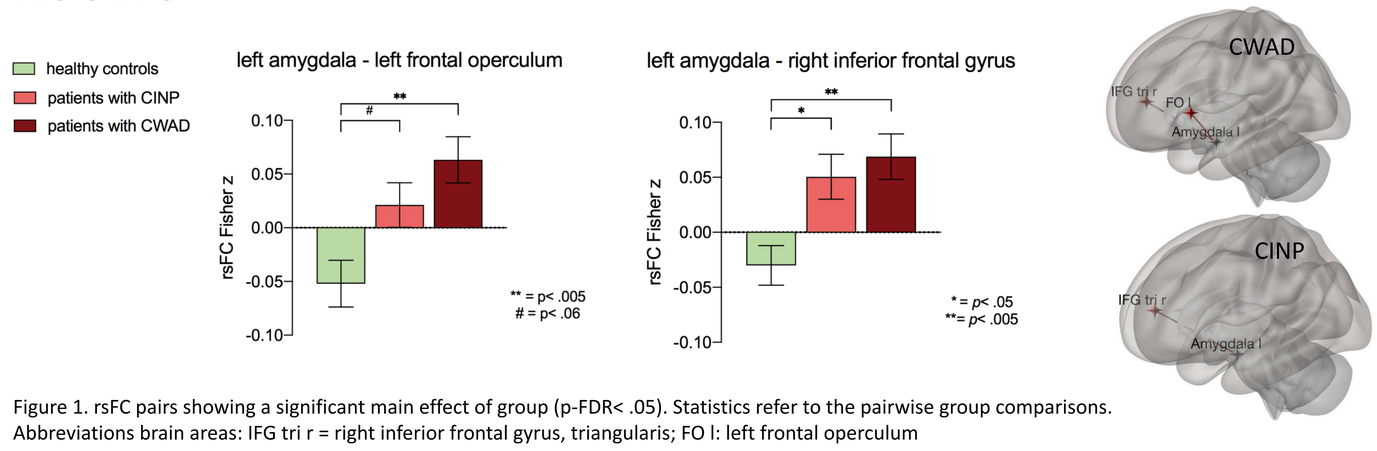

Figure 1. rsFC pairs showing a significant main effect of group (p-FDR< .05). Statistics refer to the pairwise group comparisons. Abbreviations brain areas: IFG tri r = right inferior frontal gyrus, triangularis; FO l: left frontal operculum

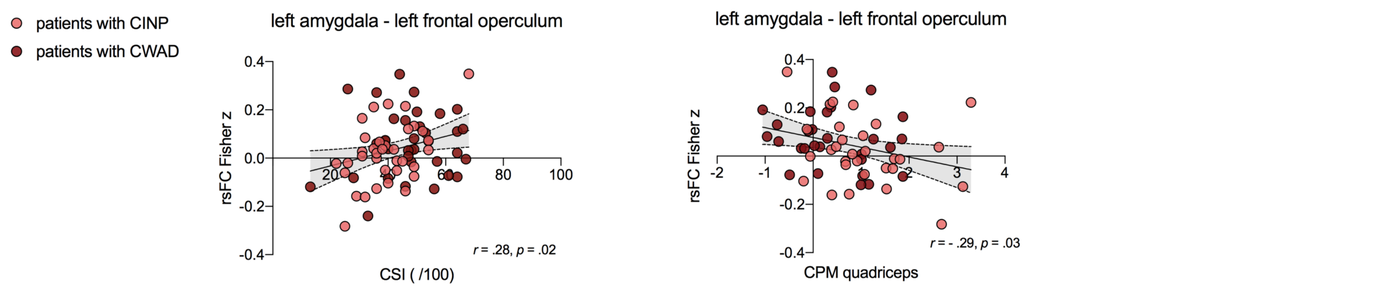

Figure 2. Scatterplots of associations between increased rsFC between left amygdala and left frontal operculum, and more central sensitization symptoms and decreased efficacy of conditioned pain modulation.

Table 1. Patient characteristics	Healthy controls Mean; median (range)	Patients with CINP Mean; median (range)	Patients with CWAD Mean; median (range)	CINP-CWAD	HCON-CINP	HCON-CWAD
Age (years)[a]	24 (18-62)	36 (18-62)	38 (21-59)	p= .966	**p= .006**	**p= .003**
Pain duration (months)[a]	NA	60 (4-288)	60 (3-444)	p= .670	NA	NA
Current pain intensity (NRS) [0-10]	0 (0-0)	3 (0-6)	6 (1-10)	**p< .001**	**p< .001**	**p< .001**
Pain disability (NDI) [0-50][a]	2 (0-6)	17 (10-27)	22 (10-37)	**p= .001**	**p< .001**	**p< .001**
Pain vigilance and awareness ($PVAQ_{total}$) [0-80][b]	31 (10-55)	37 (13-70)	38 (15-56)	p> .99	p= .065	**p= .019**
Pain catastrophizing (PCS_{total}) [0-52][a]	8 (0-30)	13 (1-26)	17 (0-37)	p= .203	p= .019	**p= .003**
Central sensitization symptoms (CSI) [0-100][a]	20 (9-35)	39 (22-68)	48 (13-67)	**p= .001**	**p< .001**	**p< .001**
Pressure pain thresholds m. quadriceps (kgf)[b]	5 (2.94-8.79)	4.30 (1.45-9.72)	3.43 (.30-7.72)	p= .154	p= .377	**p= .003**
Efficacy of conditioned pain modulation (PPT_Q during CPT minus PPT_Q before CPT)[b]	1.15 (- .14-3)	1.05 (- .54-3.29)	.43 (- 1.05-1.87)	**p= .019**	p> .99	**p= .005**

[a]Data were not normally distributed: group differences analyzed with the Kruskal-Wallis test and the Mann-Whitney U test for post hoc comparisons (p< .017 (.05/3)).
[b]Data were normally distributed: analyzed with the 1-way analysis of variance, and post hoc pairwise group comparisons were applied with the Bonferroni correction.

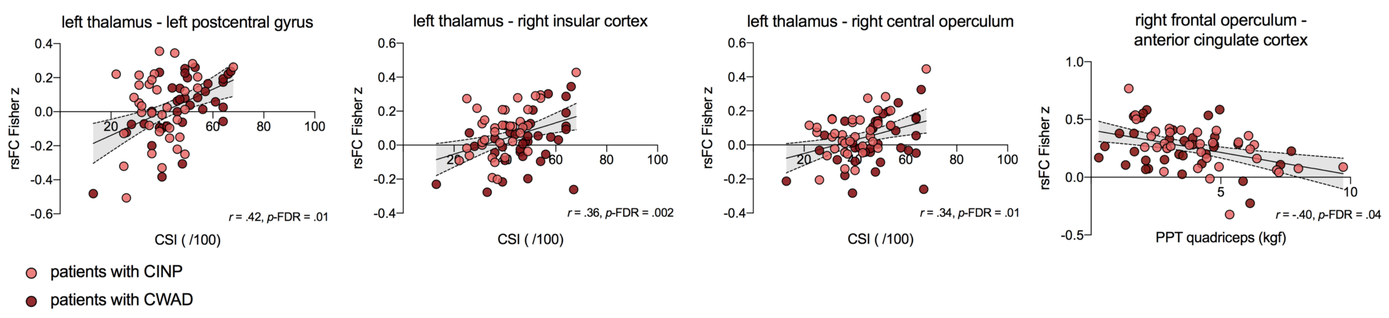

Figure 3. Scatterplots of associations between more central sensitization symptoms and higher pressure hyperalgesia, and increased rsFC between various regions of interest investigated at the whole-brain level (all selected regions).

CONCLUSIONS

- In CWAD & CINP patients compared to HCON: **increased amygdala functional coupling during rest with regions in the ventrolateral prefrontal cortex**
- No rsFC differences were observed between the traumatic and non-traumatic chronic neck pain group.
- The **increased rsFC** between the amygdala and the frontal operculum was related to **more self-reported symptoms of central sensitization** and **decreased efficacy of endogenous pain inhibition.**
- In addition, other associations between **increased rsFC** of various pain-related regions of interest and **more signs of central sensitization** were observed.
- The altered amygdala-prefrontal cortex rsFC may be involved in the pathophysiology of CWAD and CINP.
- Further prospective longitudinal studies are warranted, and future research should explore whether therapy reverses these brain alterations.

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