Nucleus Accumbens Grey Matter Associations with Chronic Pain and Adverse Childhood Experiences

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Background & Aims

Adverse childhood experiences (ACEs) have been associated with persistent brain changes, altered behaviour and stress reactivity, and an increased risk of physical and mental health morbidities, including chronic pain and depression. However, the underlying structural brain alterations remain poorly understood. This study aimed to investigate the associations between ACEs and chronic pain. We investigated the brain's grey matter volumes among participants who had reported experiencing chronic pain and further examined the relationship between those who had reported chronic pain and ACEs in brain regions involved in pain perception and reward networks.

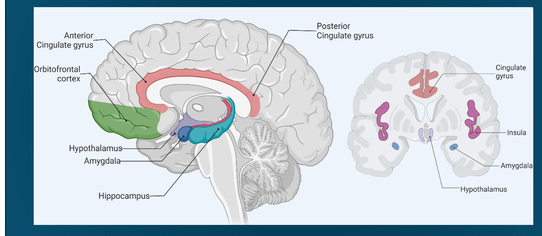

Figure 1: This figure illustrates the key brain regions used for the predefined ROI analysis [2].

Methods

The Generation Scotland Scottish Family Health Study (GS:SFHS)[1] dataset of around 24000 community-based participants contains socio-demographic and clinical data collected at study entry, including the Chronic Pain Grade (CPG) for people with pain for more than 3 months. We analysed a subset of the GS:SFHS participants who participated in the Stratifying Resilience and Depression Longitudinally (STRADL) study, including assessments of structural MRI scans. Each participant completed ratings of childhood adversity using the sort form Childhood Trauma Questionnaire (CTQ).

Voxel-based morphometry (VBM) and Region of Interest (ROI) statistical analysis were performed using CAT12, see Figure 2 for the pipeline, on brain regions associated with pain perception and the reward network, including the nucleus accumbens (Nacc), thalamus, hippocampus, amygdala, cingulate, and orbitofrontal areas (see Figure 1). ROI analysis was utilised to perform a more detailed examination of the impact and interaction between chronic pain and ACEs.

		Subgroup category	Proportion participants with CP	median	se	min	max
Age		-	-	61	0.01	26	84
Sex		F	245/525	-	-	-	-
		M	123/322	-	-	-	-
Chronic Pain	CPG	-	368/847	1	0.002	1	4
		1	220/368	-	-	-	-
		2	95/368	-	-	-	-
		3	28/368	-	-	-	-
		4	25/368	-	-	-	-
Adverse Childhood experiences (ACEs) sub-scores	Physical Abuse	-	65/112	5	0.003	5	25
	Sexual Abuse	-	43/75	5	0.004	5	25
	Emotional Abuse	-	72/119	5	0.004	5	25
	Physical Neglect	-	102/182	5	0.003	5	21
	Emotional Neglect	-	61/90	7	0.005	5	25
	Denial	-	-	1	0.001	0	3
Multiple ACEs	No ACEs	-	210/543	-	-	-	-
	One ACEs	-	71/170	-	-	-	-
	Two ACEs	-	34/57	-	-	-	-
	Three ACEs	-	22/32	-	-	-	-
	Four ACEs	-	17/27	-	-	-	-
	Five ACEs	-	14/18	-	-	-	-
Total Intracranial Volume-TIV (cm^3)		-	-	1436.5	0.163	1110	1877

Table 1: Demographic of the population

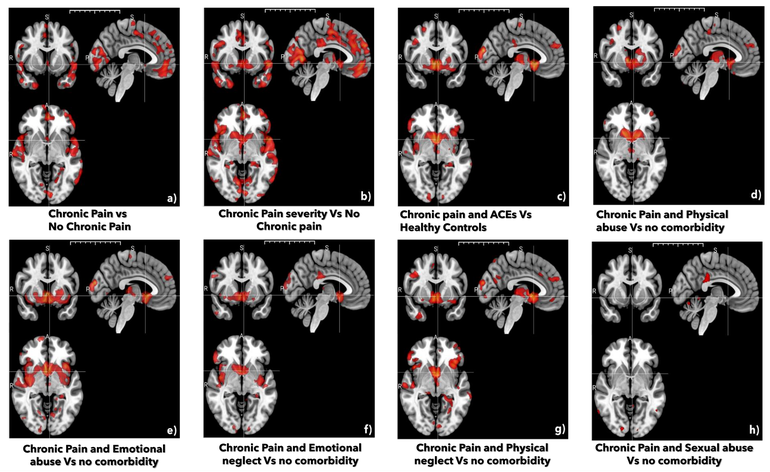

Figure 3: Brain images of negative association between grey matter with individuals who reported chronic pain and different Adverse childhood experience scores, Voxel Based Morphometry analysis

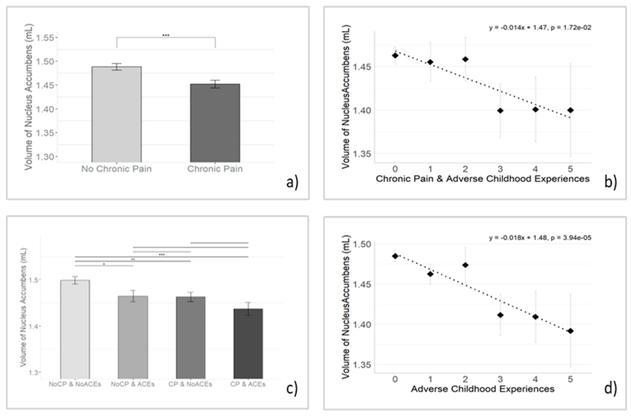

Figure 4: Regions of Interest analysis of Nucleus accumbens. a) Volume of Nucleus accumbens for individuals who reported having chronic pain compared to those who did not report chronic pain, b) Volume of Nucleus accumbens for individuals who reported having chronic pain and reported ACEs, counting ACEs c) The volume of Nucleus accumbens for individuals who did not report chronic pain and ACEs, for the individual who reported ACEs but did not report CP, for the individuals who reported chronic pain but did not report ACEs and for the individuals who reported both ACEs and CP d) Volume of Nucleus accumbens for individuals who reported ACEs.

	Nacc	SMA	Hip	PHip	Amy	Ins	Th	Put	Cau	lOrb	mOrb	ACC
Chronic Pain	**	**	*	**	*	*				**	***	**
Severity of CP (CPG)	*	.	*	*	.	*						.
CP(ACEs Vs no ACEs)												
No ACEs (CP Vs no CP)	*	*	.	**	.					*	**	.
ACEs (CP Vs no CP)		*			.						*	*
No(CP & ACEs) Vs (CP&ACEs)	**	*	*	*	**	*				**	**	**
No CP (ACEs Vs no ACEs)	.											
No CP&ACEs Vs CP&NoACEs		*									*	
CP&ACEs (0-5)	.											
ACEs (0-5)	**		*		*	.	.	.		*		
CP (PA Vs no PA)												
CP (SA Vs no SA)				.								
CP (EA Vs no EA)	.			*	.							
CP (PN Vs no PN)												
CP (EN Vs no EN)										.		
CP&PA Vs no Co-occurrence	*						.		.			
CP&SA Vs no Co-occurrence			.	*								
CP&EA Vs no Co-occurrence	**		.	*	**	*		*	.			
CP&PN Vs no Co-occurrence	*		.									.
CP&EN Vs no Co-occurrence	*						.		.			
Severity of Anxiety				*			.					
Severity of Depression			.	*						*	*	

*Table 2: Negative association between grey matter with chronic pain and Adverse childhood experience scores, Regions of Interest analysis. Significant p-values FDR corrected ***p<0.001, **p<0.01, *p<0.05, . p<0.1.*

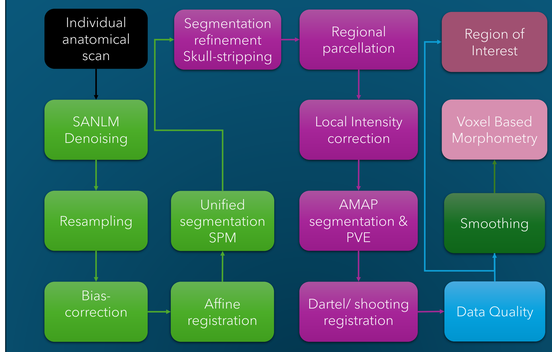

Figure 2: CAT12 pipeline for analysing the structural MRI images.

Results

The dataset included a total of 847 participants, demographic of the population can be seen in Table 1. In the VBM analysis, reduction of the grey matter of the Nacc in participants who had reported chronic pain was observed compared to those without, as well as with the severity of more severe chronic pain. Moreover, the same pattern emerged in those who had reported ACEs, as well as for the combined impact of chronic pain and ACEs sub-scores, see Figure 3. In the ROI analysis, further investigation confirmed the results from the VBM analysis. When examining chronic pain and ACEs separately, each exhibited a similar pattern: lower grey matter volume in the Nacc, see Figure 4. However, there was no noticeable difference in the effects of ACEs or Chronic pain, while when testing for the combined impact of chronic pain and ACEs, the effect appears to be synergistic, see Figure 4.

Conclusions

When considered independently, chronic pain and ACEs lead to comparable decreases in grey matter volume in the Nacc. This study provides new insights into the common neural substrates underlying chronic pain and ACEs by demonstrating significant structural alterations in brain regions associated with reward processing.

1. Habota, Tina, et al. "Cohort profile for the STratifying Resilience and Depression Longitudinally (STRADL) study: A depression-focused investigation of Generation Scotland, using detailed clinical, cognitive, and neuroimaging assessments." Wellcome open research 4 (2019).

2. Antoniou, Georgia, et al. "The effect of adverse childhood experiences on chronic pain and major depression in adulthood: a systematic review and meta-analysis." British Journal of Anaesthesia 130.6 (2023): 729-746..

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