

Cumulating negative experiences induces structural changes in the DG-CA3 system and self related cortical areas

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INTEREST

In an overwhelming crisis period: coronavirus pandemia with long lasting confinements, sickness, losing acquaintances, loss of job, housing issues, separations... the majority of the population is exposed to negative life experiences. Still there is considerable individual variability in the amount and type of events we go through in life. Research on stress-related psychopathologies shows brain structural changes. But we do not know yet if these findings are merely associated to stress or if they are also related to the differences in the level of cumulated life experiences?

What if structural changes can occur due to cumulative negative life experiences per se?

In neuroimaging studies the cumulated life experiences of the individuals are not taken into account. This project aims to investigate the importance that this aspect might have for long-term memory research, specially after this crises period.

BACKGROUND

HIPPOCAMPUS & STRESS RELATED DISORDER

- Major depression related to decreased volume in left posterior hippocampus (Bergouignan et al. 2011) more precisely to DG-CA3 (pattern separation and pattern completion system).
- PTSD also related to decreased volume in DG-CA3 (Wang et al., 2010).

CORTICAL AREAS ASSOCIATED TO EPISODIC HIPPOCAMPAL SYSTEM

- Episodic Hippocampal system includes precuneus, medial prefrontal cortex (mPFC) and ACC
- mPFC is also known to be affected by stress-related disorders (Van Rooij et al., 2018)

CUMULATION OF LIFE EXPERIENCES

- Behavioral assessment on cumulated life experiences in the 70s show significant association of stress-related disorders and the accumulation of negative life experiences (Johnson, Sarason 1978; Sarason et al. 1978).
- In that period life change itself was supposed to be a stress driver and to induce behavioral outcomes such as increases in stress disorders.

INTRUSIVE MEMORIES

- Intrusive memories are spontaneous recall of striking life experiences (which would trigger spontaneously the episodic hippocampal system's activity).
- The avoidance of intrusive memories has been repetitively associated to level of depression (Williams et al 2007).

METHOD- BEHAVIOR

PARTICIPANTS

- 45 healthy participants were recruited
- 18 > Age < 45
- With no past or present neurological or psychiatric pathology.
- Exclusion criteria: BDI > 20 (which corresponds to moderate and severe depression)
- Total inclusion of 43 participants (2 participants with BDI > 12)

BEHAVIORAL ASSESSMENT

Survey on accumulation of life experiences during their lifespan (revised LES, Sarason et al. 1978).

- Outputs:
- **Negative experiences score**
 - Positive experiences score
 - Balance score
 - Quantity of negative experiences

Intrusive memories assessment: (IES-R questionnaire)

- Outputs:
- **IES global score**
 - Intrusion score
 - Avoidance score
 - Excitement score

54 ASSESSED EVENTS: examples:

- Detention in a jail or comparable institution
- Detención en una cárcel o institución similar
- Death of spouse
- Muerte de su pareja
- Marriage (formal commitment in a relationship)
- Matrimonio compromiso formal en una relación
- Foreclosure on mortgage or loan
- Juicio hipotecario o de un préstamo
- Death of a close friend
- Muerte de un amigo(a) cercano
- Outstanding personal achievement
- Logros personal sobresaliente
- Minor law violations (traffic tickets, disturbing the peace, etc.)
- Violaciones menores de la ley (multas de tránsito, disturbio público)
- Male: Wife/girlfriend's pregnancy
- Hombre: Embarazo de esposa o novia
- Female: Pregnancy
- Mujer: Embarazo
- Changed work situation (different work responsibility, major change in working conditions, working hours, etc.)
- Cambio en situación de su empleo (responsabilidades diferentes, cambio notable en las condiciones de trabajo, cambio en las horas de trabajo, etc.)
- Serious illness of a close family member
- Enfermedad grave de un familiar cercano

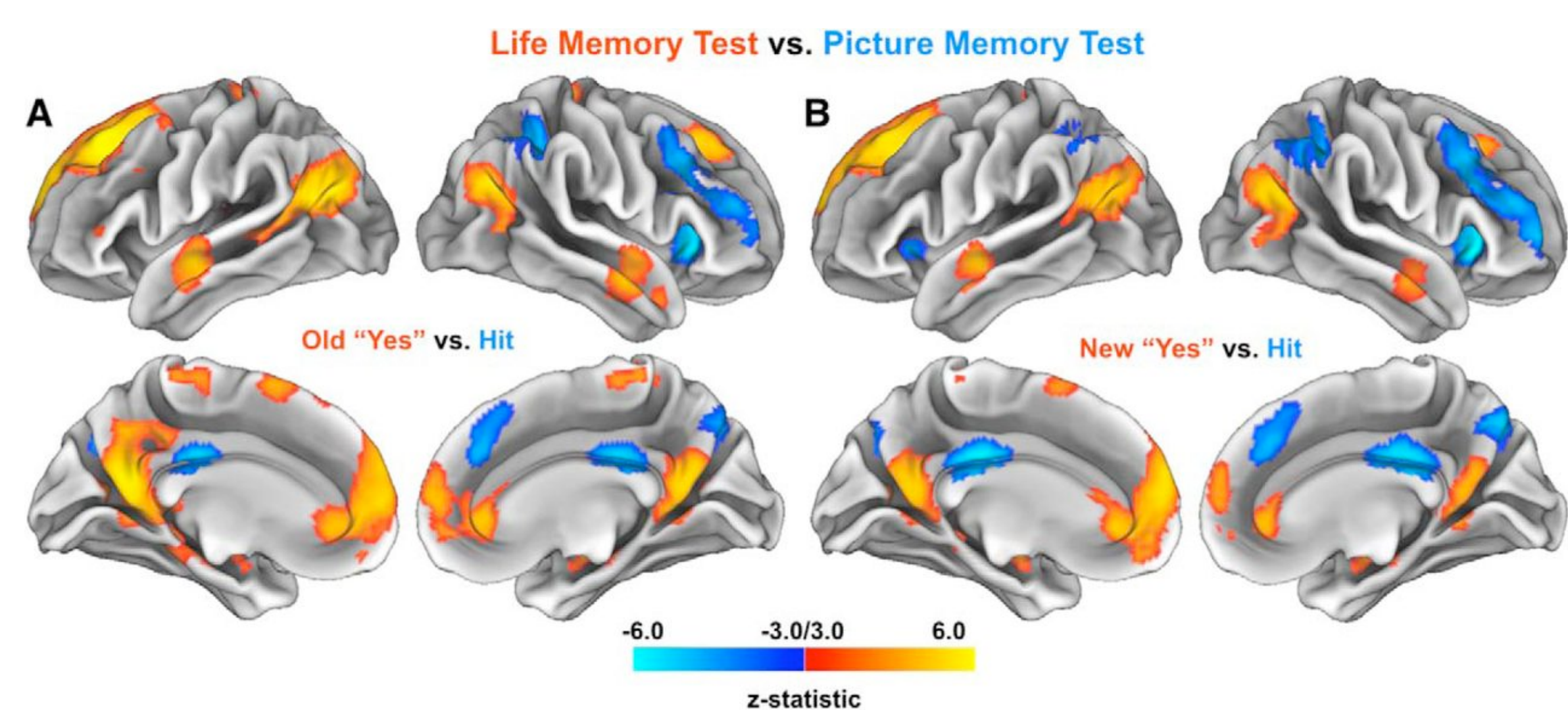


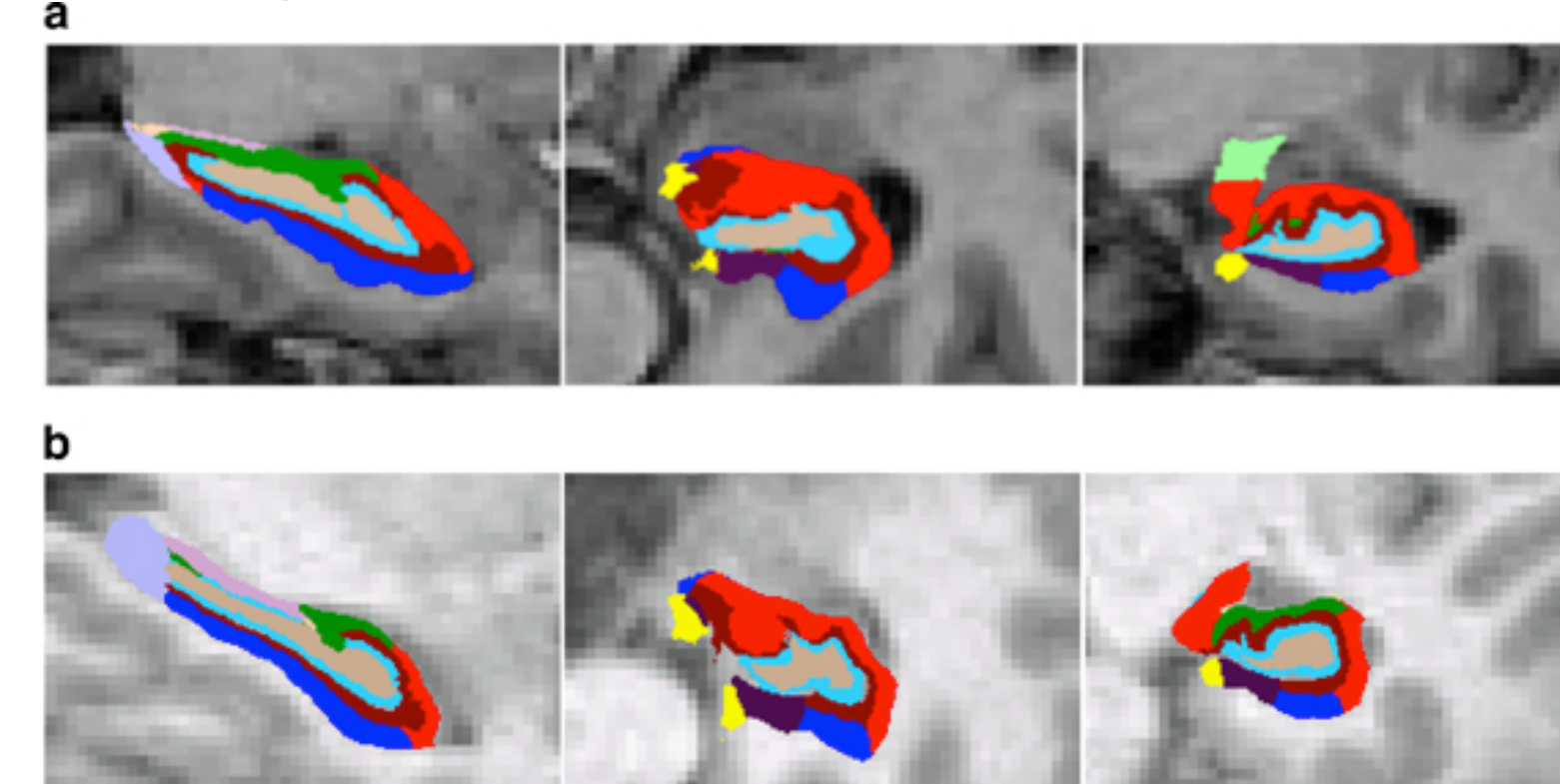
Figure 1: Both negative life experiences integration and intrusive memories are thought to activate the above network. Intrusive memories are life memories that get recalled spontaneously. It is supposed that this spontaneous recalls activate the same episodic hippocampal system as in conscious controlled recall. We here include for visual purposes the network from Chen et al. JN 2017; to underline the origin of the targeted areas and the hypothesis of the current project.

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HIPPOCAMPAL SUBFIELDS & CORTICAL AREAS

- Structural T1 high resolution acquisition in the same day as behavioral assessment.
- Automated hippocampal subfields using Freesurfer version 6.3.
- Subfields for analysis: granule cells/molecular layer/dentate gyrus (GCMLDG), CA1, CA3, whole hippocampus (Iglesias et al. 2015).
- We calculated the volume of DG-CA3 together to follow our hypothesis, and focused on the left hippocampus (see background).



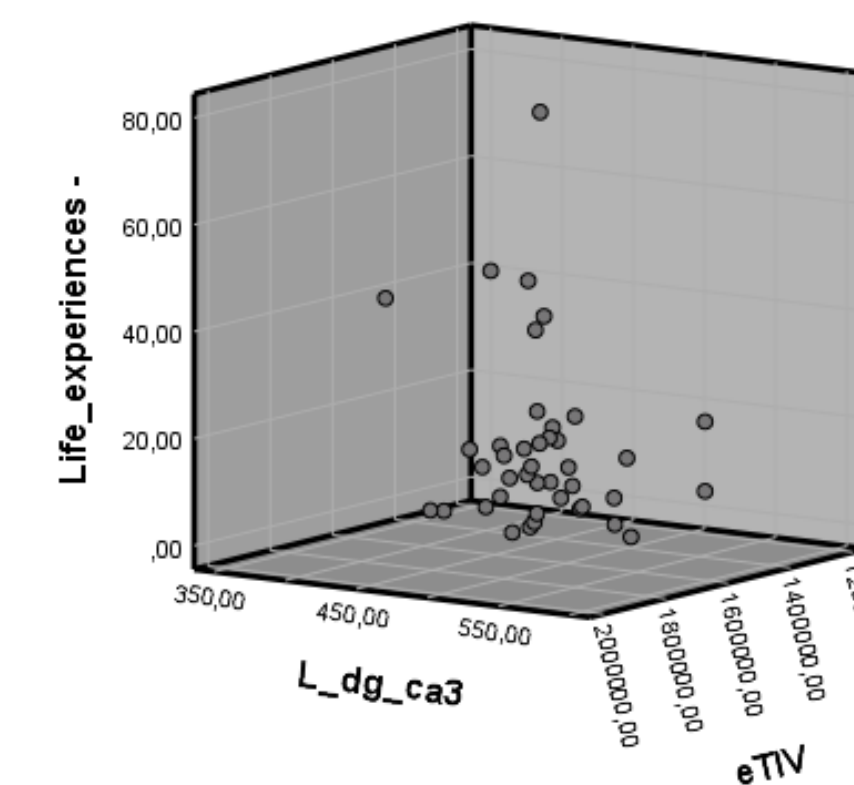
- Alveus
- Parasubiculum
- Presubiculum
- Subiculum
- CA1
- CA2/3
- CA4
- Granule cell layer (dentate gyrus)
- Hippocampus-amygdala-transition-area
- Fimbria
- Molecular Layer
- Hippocampal fissure
- Hippocampal tail

- Automated cortical areas were also assessed using the standard output of Freesurfer.
- We specifically checked the left precuneus and left Orbito-Frontal Cortex.

RESULTS

BEHAVIOR

- The older we are the more we have cumulated negative experiences ($r=0.487$, $p=0.010$).
- The more we cumulate negative life experiences the higher the level of intrusion of our worst life experience ($r=0.403$, $p=0.008$, no effect on avoidance).
- The more we cumulate negative experiences the higher the stress level (BDI, $r=0.421$, $p=0.005$). Whereas BDI is highly correlated to avoidance of the intrusion of our worst life experiences ($r=0.407$, $p=0.007$; for intrusion:



NEGATIVE LIFE EXPERIENCES AND HIPPOCAMPAL SUBFIELDS

The more participants went through negative life experiences the smaller the volume of the left DG-CA3 system (partial correlation of negative experience score with left DG-CA3 volume, controlling for eTIV ($r=-0.33$, $p=0.038$)).

NEGATIVE LIFE EXPERIENCES AND SELF-RELATED CORTICAL AREAS

In the self-related cortical areas the accumulation of negative experiences was also associated with less decreased left precuneus ($r=-0.503$, $p=0.033$), with no significant effects being found for left orbitofrontal cortex in this sample ($r=0.092$, $p=0.092$).

INTRUSIVE MEMORIES & Brain structure

For this sample we observed neither significant effect of intrusion on DG-CA3 nor on precuneus or orbito-frontal cortex ($p>0.05$)

CONCLUSIONS

The more we age the more we cumulate negative life experiences. Negative life experiences cumulation has a specific impact on brain structure. It affects preferentially the left DG-CA3 system and the left precuneus.

One could think this impact to be triggered by potential intrusions, but even though behavioral the cumulation of negative experiences is linked to our tendency of having intrusions. Whatsoever, intrusions do not show specific structural effect on the system. The only fact that we go through negative life experiences modifies our brain, without the presence of any past or present psychopathology or neurological disease.

There is a long debate on the vulnerability factors of psychopathologies, before anything one should take into account the life context of participants.

All in all, these results suggest that our brains are not only the results of pure biology without context, negative life experiences matter to our brain and more specifically the brain areas that integrate life experiences.

Future research should take into account potential changes induced by negative life experiences for the interpretation of clinical and neuroscientific findings.

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