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CLINICAL RESEARCH ARTICLE



## Childhood maltreatment interacts with hypothalamic-pituitary-adrenal axis negative feedback and major depression: effects on cognitive performance

Neus Salvat-Pujol <sup>a,b,c</sup>, Javier Labad <sup>c,d</sup>, Mikel Urretavizcaya <sup>a,c,e</sup>, Aida de Arriba-Arnau <sup>a,c</sup>, Cinto Segalàs <sup>a,c,e</sup>, Eva Real <sup>a,c</sup>, Alex Ferrer <sup>a,b</sup>, José M. Crespo <sup>a,c,e</sup>, Susana Jiménez-Murcia <sup>a,e,f</sup>, Carles Soriano-Mas <sup>a,c,g</sup>, José M. Menchón <sup>a,c,e</sup> and Virginia Soria <sup>a,c,e</sup>

<sup>a</sup>Bellvitge University Hospital, Psychiatry Department. Bellvitge Biomedical Research Institute (IDIBELL), Neurosciences Group - Psychiatry and Mental Health, Barcelona, Spain; <sup>b</sup>Corporació Sanitària Parc Taulí, Department of Mental Health, I3PT, Sabadell, Spain; <sup>c</sup>Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Carlos III Health Institute, Madrid, Spain; <sup>d</sup>Institut d'Investigació i Innovació Parc Taulí (I3PT), Department of Mental Health, Consorci Sanitari del Maresme, Mataró, Spain; <sup>e</sup>Department of Clinical Sciences, School of Medicine, Universitat de Barcelona, Barcelona, Spain; <sup>f</sup>Centro de Investigación Biomédica en Red de Fisiopatología Obesidad y Nutrición (CIBEROBN), Carlos III Health Institute, Madrid, Spain; <sup>g</sup>Department of Psychobiology and Methodology of Health Sciences, Universitat Autònoma de Barcelona, Bellaterra, Spain

### ABSTRACT

**Background:** Childhood maltreatment (CM) is associated with impaired hypothalamic-pituitary-adrenal (HPA) axis negative feedback and cognitive dysfunction, resembling those abnormalities linked to major depressive disorder (MDD).

**Objectives:** We aimed to assess the potential modulating effects of MDD diagnosis or HPA axis function in the association between different types of CM and cognitive performance in adulthood.

**Methods:** Sixty-eight MDD patients and 87 healthy controls were recruited. CM was assessed with the Childhood Trauma Questionnaire. We obtained three latent variables for neuropsychological performance (verbal memory, visual memory and executive function/processing speed) after running a confirmatory factor analysis with cognitive tests applied. Dexamethasone suppression test ratio (DSTR) was performed using dexamethasone 0.25 mg.

**Results:** Different types of CM had different effects on cognition, modulated by MDD diagnosis and HPA axis function. Individuals with physical maltreatment and MDD presented with enhanced cognition in certain domains. The DSTR differentially modulated the association between visual memory and physical neglect or sexual abuse.

**Conclusions:** HPA axis-related neurobiological mechanisms leading to cognitive impairment might differ depending upon the type of CM. Our results suggest a need for early assessment and intervention on cognition and resilience mechanisms in individuals exposed to CM to minimize its deleterious and lasting effects.

### El maltrato infantil interactúa con la retroalimentación negativa del eje hipotalámico-hipofisario-adrenal y la depresión mayor: efectos sobre el rendimiento cognitivo.

**Antecedentes:** El maltrato infantil (MI) se asocia con una alteración en la retroalimentación negativa del eje hipotalámico-hipofisario-adrenal (HHA) y disfunción cognitiva, que se asemejan a las anomalías vinculadas al trastorno depresivo mayor (TDM).

**Objetivos:** Nuestro objetivo fue evaluar los posibles efectos moduladores del diagnóstico de TDM y de la función del eje HHA en la asociación entre diferentes tipos de MI y el rendimiento cognitivo en la edad adulta.

**Métodos:** Se reclutaron 68 pacientes con TDM y 87 controles sanos. El MI se evaluó con el Cuestionario de trauma infantil. Se obtuvieron tres variables latentes para el rendimiento neuropsicológico (memoria verbal, memoria visual y función ejecutiva/velocidad de procesamiento) tras realizar un análisis factorial confirmatorio con las pruebas cognitivas aplicadas. La ratio de supresión de cortisol en el test de supresión con dexametasona (DSTR) se realizó usando dexametasona 0,25 mg.

**Resultados:** Los diferentes tipos de MI tuvieron diferentes efectos sobre la cognición, modulados por el diagnóstico de TDM y la función del eje HHA. Los individuos con maltrato físico y TDM presentaron una cognición mejorada en ciertos dominios. El DSTR moduló diferencialmente la asociación entre memoria visual y negligencia física o abuso sexual.

**Conclusiones:** Los mecanismos neurobiológicos relacionados con el eje HHA que conducen al deterioro cognitivo pueden diferir según el tipo de MI. Nuestros resultados sugieren la necesidad de una evaluación e intervención tempranas sobre la cognición y los mecanismos de resiliencia en individuos expuestos a MI para minimizar sus efectos nocivos y duraderos.

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### KEYWORDS

Childhood abuse; childhood neglect; cortisol; HPA axis; dexamethasone suppression test; cognition; memory; major depression

### PALABRAS CLAVE

abuso infantil; negligencia infantil; cortisol; eje HHA; prueba de supresión de dexametasona; cognición; memoria; depresión mayor

### 关键词

童年期虐待; 儿童忽视; 皮质醇; HPA轴; 地塞米松抑制试验; 认知; 记忆; 重性抑郁

### HIGHLIGHTS

- We studied the effects of childhood maltreatment (CM), HPA axis feedback (DST), and depression on cognition.
- Different types of CM had a distinct impact on cognitive performance.
- MDD diagnosis and DST modulated the association between CM and cognition.

## 童年期虐待与下丘脑-垂体-肾上腺轴负反馈和重性抑郁障碍的相互作用：对认知表现的影响

**背景:** 童年期虐待 (CM) 与下丘脑-垂体-肾上腺 (HPA) 轴负反馈受损和认知功能损伤有关, 类似于重性抑郁障碍 (MDD) 相关异常。

**目的:** 我们的目的是在不同类型CM与成年认知表现之间的关联中评估MDD诊断或HPA轴功能的潜在调节作用。

**方法:** 招募了68名MDD患者和87名健康对照者。通过儿童创伤问卷评估了CM。在使用认知测试进行验证性因素分析后, 我们得到了3个神经心理学表现潜变量 (语言记忆, 视觉记忆和执行功能/处理速度)。使用0.25mg地塞米松得到地塞米松抑制试验比率 (DSTR)。

**结果:** 不同类型CM对认知的影响不同, 受到MDD诊断和HPA轴功能的调节。遭受身体虐待和MDD的个体在某些领域认知增强。DSTR有差异地调节了视觉记忆与身体忽视或性虐待之间的关联。

**结论:** 导致认知损伤的HPA轴相关神经生物学机制可能因CM类型而异。我们的结果表明需要对CM暴露个体的认知和韧性机制进行早期评估和干预, 以将其有害和持久影响最小化。

## 1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is a major physiological stress response system that regulates its own activity through a negative feedback loop exerted by cortisol. Patients with major depressive disorder (MDD) commonly show a hyperactive HPA axis (Wolkowitz, Burke, Epel, & Reus, 2009), including an altered feedback inhibition by endogenous glucocorticoids (Pariante & Miller, 2001). The feedback inhibition of the HPA axis can be assessed with the administration of dexamethasone, a synthetic glucocorticoid receptor agonist that results in the suppression of the secretion of cortisol by the adrenal gland. In patients with MDD, there is a lack of suppression of cortisol secretion after dexamethasone intake, which indicates a reduced feedback sensitivity and is considered a measure of glucocorticoid resistance (Pariante & Miller, 2001; Wolkowitz et al., 2009).

Prolonged exposure to glucocorticoids resulting from lowered negative feedback on the HPA axis in MDD has been associated with cognitive impairment (Behnken et al., 2013; Hansson, Murison, Lund, & Hammar, 2013; Zobel et al., 2004). Nevertheless, not all patients with MDD suffer such disturbances in the HPA axis feedback or in cognition, and childhood maltreatment (CM) is thought to be involved in this variability.

CM can be divided into abuse, which is an exposure to threatening behaviours, and neglect, a deprivation of cognitive and psychosocial stimulation. CM is associated with deficits in memory and executive function (Majer, Nater, Lin, Capuron, & Reeves, 2010; Nikulina & Widom, 2013), independent of psychopathology (R-Mercier, Masson, Bussi eres, & Cellard, 2018). Thus, neurobiological consequences of CM may be deemed as a potential explanation for poor cognitive functioning in MDD (Gould et al., 2012; Kaczmarczyk, Wingenfeld, Kuehl, Otte, & Hinkelmann, 2018). Additionally, CM induces

neurobiological changes that persist into adulthood and resemble the neuroendocrine features of MDD, including alteration of glucocorticoid receptor functioning and impaired HPA axis feedback (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Heim, Shugart, Craighead, & Nemeroff, 2010). Indeed, lasting HPA axis dysfunction related to CM has been found to be independent of psychopathology (Carvalho Fernando et al., 2012; Hinkelmann et al., 2013; Majer et al., 2010). Therefore, it has been hypothesized that neuroendocrine abnormalities in MDD may be partly explained by the long-lasting effects of CM on the HPA axis and might represent the vulnerability for the development of depression in response to stress rather than consequences of depression (Heim, Newport et al., 2008). Furthermore, studies have linked CM with an increased risk of MDD in adulthood, predicting early-onset, severe, chronic and treatment-resistant depression (Nelson, Klumparendt, Doebler, & Ehring, 2017).

There is evidence that HPA axis hyper- and hypoactivation emerge sequentially after CM (Bernard, Frost, Bennett, & Lindhiem, 2017). Indeed, maltreated children show hypercortisolemia resulting from sensitization of the HPA axis after stress, followed by hypocortisolemia in adulthood due to a downregulation of the HPA system in response to initially high cortisol levels (Bernard et al., 2017). Some authors have further pointed out that the basal cortisol pattern may be related to the severity and the type of maltreatment (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Specifically, they found that moderate CM was associated with morning hypercortisolemia and a steep diurnal cortisol slope, whereas severe CM was associated with hypocortisolemia and a flatter slope (van der Vegt et al., 2009). This effect on the HPA axis function was stronger for childhood abuse than neglect (van der Vegt et al., 2009).

The various types of CM have also been linked to dysfunction of the HPA axis negative feedback in adulthood (Miller, Chen, & Zhou, 2007). However, it is not clear whether this influence ultimately leads to an enhancement or a suppression of cortisol secretion. On the one hand, some studies have related emotional abuse (Carpenter et al., 2009), emotional neglect (Carvalho Fernando et al., 2012), or sexual abuse (Stein, Yehuda, Koverola, & Hanna, 1997) to hyper-suppression of the HPA axis in response to dexamethasone administration. On the other hand, increased cortisol responses to the Dex/CRH test have been reported in sexual or physical abuse (Heim, Mletzko et al., 2008). Lu, Gao, Huang, Li, and Xu (2016) found that subjects with MDD and CM showed decreased glucocorticoid feedback inhibition compared with healthy individuals without MDD or CM. Not only the type of CM but also its severity might be critical for HPA axis responsivity in the Dex/CRH test. A recent study reported that patients with a mood disorder and mild childhood emotional neglect had an enhanced HPA axis response, while patients reporting severe neglect did not differ from controls in their cortisol response (Watson et al., 2007).

The vast majority of literature reports an association of CM with poor performance in memory and executive function tasks (Dannehl, Rief, & Euteneuer, 2017; Majer et al., 2010; Saleh et al., 2017; Su, D'Arcy, Yuan, & Meng, 2019). Some works report that the nature and magnitude of cognitive deficits may vary according to the kind of trauma experienced (Dannehl et al., 2017; Gould et al., 2012; Grainger et al., 2019). In particular, it has been suggested by some authors that neglect might have more detrimental effects on cognition than abuse (Geoffroy, Pinto Pereira, Li, & Power, 2016; Gould et al., 2012; Grainger et al., 2019; Majer et al., 2010; Nikulina & Widom, 2013), independently of mental health (Geoffroy et al., 2016). Other authors have pointed out that physical abuse and neglect might have a more critical influence on memory and executive functions than emotional maltreatment (Dannehl et al., 2017). More counter-intuitive associations have been found, mostly in samples of adults over 50 years, linking different types of abuse to better cognitive performance (Dannehl et al., 2017; Feeney, Kamiya, Robertson, & Kenny, 2013; Ritchie et al., 2011). Biological mechanisms underlying these different CM effects on cognition are unknown.

Although both CM and MDD may contribute to the cognitive dysfunction, the neurobiological mechanisms underlying this relationship are not yet fully understood. The present study aimed to assess the potential modulating effects of MDD diagnosis in the association between different types of CM and

cognitive performance in adulthood. We hypothesized that HPA axis dysfunction might play an important role, as neuroendocrine abnormalities have been related to CM as well as with MDD. More specifically, we hypothesized that the relationship between CM and cognitive performance is modulated by MDD and HPA axis activity: 1) CM, and particularly neglect, is associated with poorer cognitive performance in people with MDD, and 2) failure to suppress cortisol levels after dexamethasone administration in patients with MDD and individuals exposed to CM is associated with poor cognitive performance.

## 2. Materials and methods

### 2.1. Sample

Our sample included 68 patients with MDD (67.6% females, mean age  $59.87 \pm 11.05$  years) recruited from the Psychiatry Department at Bellvitge University Hospital (Barcelona) and 87 healthy controls (HC; 66.7% females, mean age  $56.14 \pm 11.61$  years) recruited from the same geographic area.

Exclusion criteria were an age less than 18 years; a diagnosis of other psychiatric disorders (except nicotine dependence), mental retardation, neurological or severe medical conditions; pregnancy or puerperium; electroconvulsive therapy in the previous year, and corticosteroid treatment in the previous three months.

The sample partially overlaps with that used in previous studies (Labad et al., 2018; Salvat-Pujol et al., 2017), which explored different hypotheses.

The Bellvitge University Hospital Ethical Committee approved the research protocol, and all procedures complied with the Helsinki Declaration of 1975 (revised in 2013). All participants provided written informed consent after having received a full explanation of the study and acknowledged that they cannot be identified via the paper.

### 2.2. Clinical assessment

All patients were diagnosed with MDD by their treating psychiatrist and met DSM-IV-TR criteria for MDD (American Psychiatric Association, 2000). MDD diagnosis was confirmed by an experienced psychiatrist using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). HC had no history of psychiatric disorders as assessed with a semi-structured interview and a score below 7 on the 28-item Spanish adaptation of the Goldberg General Health Questionnaire (GHQ-28)

(Lobo, Perez-Echeverria, & Artal, 1986). The HDRS was also administered to HC, since it was used as a predictive variable in the multiple linear regression analysis. Although some participants suffered CM, none met DSM-IV-TR criteria for PTSD (American Psychiatric Association, 2000).

Sociodemographic and clinical variables were assessed using a semi-structured interview. Sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Weight and height were measured in all participants to calculate the body mass index (BMI) using the formula weight (kg)/height (m<sup>2</sup>).

Exposure to CM was retrospectively assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998), which is a self-report inventory with 28 items rated on a five-point Likert scale depending on their frequency of occurrence. The CTQ yields a total score and scores for five subscales corresponding to different types of maltreatment (emotional, physical, and sexual abuse, and emotional and physical neglect). Subscale scores range from 5 (no history of abuse or neglect) to 25 (history of extreme abuse or neglect). Cut-off scores for none, low, moderate, and severe exposure to maltreatment are provided for each subscale. Exposure to CM was determined when at least one CTQ subscale was rated on or above the moderate cut-off score (emotional abuse  $\geq 13$ ; physical abuse

$\geq 10$ ; sexual abuse  $\geq 8$ ; emotional neglect  $\geq 15$ ; and physical neglect  $\geq 10$ ) (Bernstein & Fink, 1998). Cases classified as negative on all subscales were considered as not exposed to CM.

### 2.3. Neuropsychological assessment

On the same day of clinical assessment, participants underwent a neuropsychological evaluation to assess verbal memory, visual memory, processing speed and executive function. Table 1 includes information on the administered tests.

### 2.4. Salivary cortisol measurements

Participants collected saliva samples at home for cortisol analyses shortly after clinical and neuropsychological assessments using Salivette® (Sarstedt AG & Co., Nümbrecht, Germany) containers and following the same process as in our previous studies (Labad et al., 2018; Salvat-Pujol et al., 2017). Eating, drinking, smoking, or brushing teeth were not allowed in the 15 minutes prior to the collection of each sample. Participants were instructed to collect six saliva samples at home over two consecutive regular days, avoiding stressful situations and intense physical activity.

For the present study, two saliva samples were considered. Patients were asked to collect a morning salivary sample at 10 a.m. (day 1), take 0.25 mg of

**Table 1.** Neuropsychological tests and cognitive domains assessed.

| Cognitive domain   | Neuropsychological test                                                  | Test description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Verbal memory      | Hopkins Verbal Learning Test Revised™ (HVLt-R)                           | Subjects are presented with 12 words and asked to recall as many as possible. This procedure is repeated three times. The outcome measure is the total number of words recalled (range 0–36).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Visual memory      | Rey Complex Figure Test (RCFT)                                           | Subjects are asked to copy a complex line drawing and reproduce it from memory after a short delay (immediate recall) and after a 20–30 minute delay (delayed recall). Each reproduction is scored taking into account the accurate position and shape of 18 design elements (total range 0–36). In our study, we considered scores in immediate and delayed recall, as they are measures of visual learning and memory.                                                                                                                                                                                                                                                                                                                                                                                               |
| Processing speed   | Trail Making Test Part A (TMT-A)                                         | Subjects need to sequentially connect 25 targets (numbers 1 to 25). The outcome measure is the number of seconds needed to perform the task.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                    | Brief Assessment of Cognition in Schizophrenia – Symbol Coding (BACS-SC) | As quickly as possible, participants write numbers 1 to 9 as matches to symbols on a response sheet for 90 seconds. The outcome measure is the total number of correct responses. This test is used not only in schizophrenia but also in affective disorders (Cholet et al., 2014).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                    | Category fluency (animal naming)                                         | Participants are given 60 seconds to name as many words as possible within the animal category. The outcome measure is the number of unique words generated.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                    | Stroop test (direct sub-scores for words)                                | Subjects are presented with a list of colour names (red, green, blue) written in black ink, and are given 45 seconds to read as many as they can (word sub-score).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Executive function | Neuropsychological Assessment Battery® Mazes – NAB-Mazes                 | There are seven mazes that become progressively more difficult. Mazes are scored based on completeness and completion time. Higher scores indicate better performance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                    | Stroop test (interference scores)                                        | After the list of colour names, a second list is presented, containing 'Xs' written with red, green, or blue ink; the subject is now asked to give the ink colour (colour sub-score). A third list contains words that name colours which are different to the ink colour in which the words themselves are written; the subject is again asked to give the ink colour (word-colour sub-score). This task requires subjects to inhibit the automatic response of reading and to name the colour the word is written in. After obtaining these sub-scores, an interference score is calculated, which is the difference between real and expected interference. Positive scores indicate adequate inhibition of automatic responses, while negative scores indicate that the subject has inhibited worse than expected. |
|                    | Corsi Block-Tapping Test (CBTT)                                          | Ten cubes arranged on a board are presented to the subject. The examiner taps pre-defined progressively longer sequences. The subject is asked to repeat the tapping sequence, forwards and backwards. The outcome measure is the total number of correct items (range 0–32).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

For all tests, higher scores reflect better cognitive performance, with the exception of TMT-A, in which higher scores reflect poorer cognitive performance.

dexamethasone at 11 p.m. on the same day (day 1) and collect another salivary sample at 10 a.m. on the day after (day 2). Another sample was taken immediately before the neuropsychological assessment, which was performed in one morning (mean [SD] starting time 10:37 [00:51] a.m.) prior to home-collection cortisol sampling.

Samples were stored in refrigerators and returned personally by each participant. After the Salivettes were received, they were stored at  $-20^{\circ}\text{C}$  and later sent to the BioBanc from the Institut d'Investigació Sanitària Pere Virgili (IISPV) for centrifugation (3000 rpm for 5 min) and aliquotation, after which they were frozen at  $-20^{\circ}\text{C}$  until analysis by enzyme-linked immunosorbent assay (IBL International, Hamburg, Germany) to determine saliva cortisol levels.

The feedback inhibition of the HPA axis was assessed with the dexamethasone suppression test (DST). The cortisol suppression ratio in the DST (DSTR) was defined as the ratio [cortisol at 10 a.m. on day 1]/[cortisol at 10 a.m. on day 2 (post dexamethasone)]. The DSTR provides information about the negative feedback system of the HPA axis. Higher DSTR values indicate greater suppression of cortisol secretion after dexamethasone administration, and a lack of suppression is considered a measure of glucocorticoid resistance.

The DSTR was assessed using a very low dose of dexamethasone (0.25 mg), much lower than the conventional 1 mg used in plasma analyses. The reasons for this decision were as follows: (1) salivary cortisol presents more profound suppression than does plasma cortisol or plasma ACTH in a dose-response pattern after different doses of dexamethasone are administered; although the reasons for the greater salivary cortisol suppression by dexamethasone are not clear, the binding of plasma cortisol by cortisol-binding globulin might limit the amount of free diffusible cortisol, so that saliva cortisol levels fall more rapidly than the total plasma cortisol concentration (Castro, Elias, Elias, & Moreira, 2003); (2) higher dexamethasone doses are expected to completely suppress the axis and are more likely to result in reproducibly undetectable cortisol levels; previous studies (Reynolds et al., 1998) using 0.25 mg doses have reported post dexamethasone cortisol levels that are well within the detection limits of cortisol assays, showing approximately 30% suppression and greater within-subject variability; (3) we were interested in exploring DST as a continuous measure (cortisol suppression ratio), and the use of more conventional dexamethasone doses would not have allowed us to detect subtle alterations in cortisol secretion regulation.

## 2.5. Statistical analyses

Data processing was performed using SPSS 21 (SPSS, IBM, USA). We normalized the data as described in previous works (Labad et al., 2018; Salvat-Pujol et al., 2017).

To reduce the number of cognitive variables and statistical models, we conducted a confirmatory factor analysis (CFA) with R (version 3.5.2 [December 2018]) using the lavaan (version 0.6-4 [July 2019]) and semPlot (version 1.1.2 [August 2019]) packages. We considered three latent variables that included information on cognitive tasks in three different domains: verbal memory, visual memory and executive function/processing speed (Figure 1). This later factor resulted from the combination of two latent variables (executive functioning and processing speed). The reason for combining both latent variables was because of the known relationship between processing speed and executive functioning (Albinet, Boucard, Bouquet, & Audiffren, 2012), and because this combination improved the fitting of the CFA model. The variances of all latent variables were set equal to one to standardize the model. Three fit indexes were considered: Chi-square ( $\chi^2$ ), Comparative Fit Index (CFI), and Standardized Root Mean Square Residual (SRMR). Ideally, for a model that fits the data, the  $\chi^2$  would not be significant ( $p > 0.05$ ) (Iacobucci, 2010). CFI values  $>0.90$  indicate a reasonably good fit of the SEM model (Hu & Bentler, 1999). SRMR represents the standardized difference between the observed correlation and the predicted correlation. A SRMR value  $<0.08$  is generally considered a good fit (Hu & Bentler, 1999). However, as these indexes, particularly  $\chi^2$ , are affected by sample size, some authors have suggested adjusting  $\chi^2$  by the degrees of freedom (df) (Iacobucci, 2010). A model demonstrates a reasonable fit if  $\chi^2/\text{df} \leq 3$ . Our CFA model showed the following fitting indexes:  $\chi^2 = 72.655$ ,  $\text{df} = 49$ ,  $p = 0.016$ ; CFI = 0.981; SRMR = 0.048, which indicate a good fit, as  $\chi^2/\text{df}$  was 1.48. Three factor scores (one for each main latent variable) were computed with the lavPredict() function.

Categorical data among groups (MDD vs. HC) were compared with Chi-square tests, and T-tests for independent samples were applied to compare continuous variables.

We performed exploratory partial correlation analyses stratified by diagnosis and adjusted by gender, age, and years of education to explore the relationship between CM (CTQ scores on emotional, physical and sexual abuse, and emotional and physical neglect), cognitive performance (latent variables extracted from the CFA) and DSTR. As these

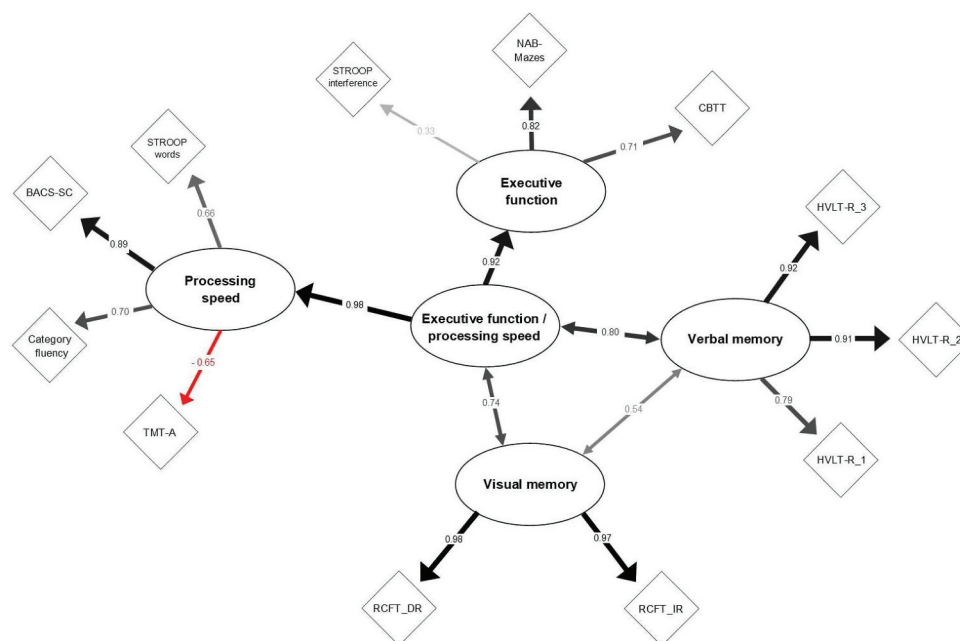


**Figure 1.** Confirmatory factor analysis of neuropsychological variables. We considered three latent variables that included information of cognitive tasks in three different domains: verbal memory, visual memory and executive function/processing speed. Our CFA model showed the following fitting indexes:  $\chi^2 = 72.655$ ,  $df = 49$ ,  $p = 0.016$ ; CFI = 0.981; SRMR = 0.048.

Abbreviations: BACS-SC: Brief Assessment of Cognition in Schizophrenia – Symbol Coding; CBT: Corsi Block-Tapping Test; HVL-R\_1, HVL-R\_2, HVL-R\_3: Hopkins Verbal Learning Test Revised<sup>TM</sup>, trials 1, 2 and 3; NAB-Mazes: Neuropsychological Assessment Battery<sup>®</sup> Mazes; RCFT\_DR: Rey Complex Figure Test, delayed recall; RCFT\_IR: Rey Complex Figure Test, immediate recall; TMT-A: Trail Making Test Part A.

analyses were exploratory in nature, we did not correct for multiple comparisons (Bender & Lange, 2001).

We performed separate multiple linear regression (MLR) analyses for each latent variable obtained in the CFA, including all participants, to explore the association of cognitive performance with different types of CM and to assess the potential modulating effects of MDD diagnosis and HPA axis negative feedback in the relationship between different types of CM and cognitive performance. We controlled for potential confounders, including gender, age, years of education, BMI, tobacco consumption, sleep quality, HDRS scores and cortisol levels at the time of neuropsychological assessment (Salvat-Pujol et al., 2017). All independent variables were entered into the equation. Interaction terms between CM, DSTR, and MDD diagnosis were tested in a final step. Only significant interaction terms were kept in the final equation. The statistical significance level was set at  $p < 0.05$  (bilateral).

### 3. Results

#### 3.1. Clinical data

The demographic and clinical variables for the two study groups are described in Table 2. MDD patients were older ( $t(153) = -2.024$ ,  $p = 0.045$ ), had a lower

educational level ( $t(153) = 4.480$ ,  $p < 0.001$ ), higher BMI ( $t(152) = -2.631$ ,  $p = 0.009$ ) and reported poorer sleep quality ( $t(139) = -5.005$ ,  $p < 0.001$ ) than HC. Total CTQ scores were higher in MDD patients than in HC ( $t(153) = -2.111$ ,  $p = 0.036$ ).

#### 3.2. HPA axis function and cognition

Cortisol and cognitive measures are described in Table 3. HPA axis measures did not differ between groups, except for cortisol salivary concentrations the morning after dexamethasone administration ( $t(153) = -2.123$ ,  $p = 0.035$ ), which were higher in MDD patients. HC performed better than MDD patients in all cognitive tasks.

#### 3.3. Partial correlation analyses

CM, cognitive and cortisol variables did not correlate with each other (see Supplementary Tables 1 and 2 online).

#### 3.4. Multiple linear regression analyses

Table 4 displays the results of the MLR analyses.

##### 3.4.1. Verbal memory

MDD diagnosis had a negative effect on verbal memory ( $\beta = -0.679$ ,  $p < 0.001$ ). However, the DSTR

**Table 2.** Demographic data and clinical variables by study groups.

|                                         | HC            |              | MDD           |               | Statistics                                                      |
|-----------------------------------------|---------------|--------------|---------------|---------------|-----------------------------------------------------------------|
|                                         | <i>n</i> = 87 |              | <i>n</i> = 68 |               | (T-test/ $\chi^2$ )                                             |
| Age (years)                             | 56.14 (11.61) |              | 59.87 (11.05) |               | <b>t(153) = -2.024, <i>p</i> = 0.045</b>                        |
| Female gender, <i>n</i> (%)             | 58 (66.7)     |              | 46 (67.6)     |               | $\chi^2 = 0.017, p = 1.000$                                     |
| Education (years)                       | 12.11 (3.95)  |              | 9.16 (4.23)   |               | <b>t(153) = 4.480, <i>p</i> &lt; 0.001</b>                      |
| BMI (kg/m <sup>2</sup> )                | 26.80 (4.90)  |              | 28.87 (4.75)  |               | <b>t(152) = -2.631, <i>p</i> = 0.009</b>                        |
| PSQI                                    | 5.26 (3.37)   |              | 8.75 (4.92)   |               | <b>t(139) = -5.005, <i>p</i> &lt; 0.001</b>                     |
| <i>Substance use</i>                    |               |              |               |               |                                                                 |
| Smoking, <i>n</i> (%)                   | 14 (16.1)     |              | 15 (22.1)     |               | $\chi^2 = 1.006, p = 0.405$                                     |
| Tobacco consumption (cigarettes/day)    | 2.15 (6.63)   |              | 3.51 (8.14)   |               | t(153) = -1.150, <i>p</i> = 0.252                               |
| Daily alcohol intake, <i>n</i> (%)      | 29 (33.3)     |              | 20 (29.4)     |               | $\chi^2 = 0.147, p = 0.729$                                     |
| Daily alcohol intake (g/day)            | 2.70 (6.36)   |              | 2.02 (4.24)   |               | t(136) = 0.710, <i>p</i> = 0.479                                |
| <i>Clinical variables of depression</i> |               |              |               |               |                                                                 |
| HDRS                                    | 0.70 (1.15)   |              | 9.56 (8.70)   |               | <b>t(153) = -9.398, <i>p</i> &lt; 0.001</b>                     |
| Suicide attempts, <i>n</i> (%)          | 0 (0.0)       |              | 14 (20.6)     |               | <b><math>\chi^2 = 19.690, p &lt; 0.001</math></b>               |
| Age at onset (years)                    | NA            |              | 42.02 (12.79) |               | NA                                                              |
| Melancholic symptoms, <i>n</i> (%)      | NA            |              | 56 (82.4)     |               | NA                                                              |
| Atypical symptoms, <i>n</i> (%)         | NA            |              | 3 (4.40)      |               | NA                                                              |
| Psychotic symptoms, <i>n</i> (%)        | NA            |              | 3 (4.40)      |               | NA                                                              |
| Number of depressive episodes           | NA            |              | 3.91 (2.73)   |               | NA                                                              |
| Number of hospitalizations              | NA            |              | 0.55 (1.54)   |               | NA                                                              |
| <i>Childhood Trauma Questionnaire</i>   |               |              |               |               |                                                                 |
|                                         | <i>n</i> (%)  | mean (SD)    | <i>n</i> (%)  | mean (SD)     |                                                                 |
| CTQ – emotional abuse                   | 7 (8.0)       | 7.11 (2.97)  | 10 (14.7)     | 8.12 (4.30)   | $\chi^2 = 1.734, p = 0.206$ ; t(153) = -1.715, <i>p</i> = 0.088 |
| CTQ – physical abuse                    | 4 (4.6)       | 5.86 (1.68)  | 8 (11.8)      | 6.40 (3.51)   | $\chi^2 = 2.745, p = 0.131$ ; t(153) = -1.252, <i>p</i> = 0.213 |
| CTQ – sexual abuse                      | 8 (9.2)       | 5.56 (1.25)  | 8 (11.8)      | 5.93 (2.94)   | $\chi^2 = 0.272, p = 0.607$ ; t(153) = -1.040, <i>p</i> = 0.300 |
| CTQ – emotional neglect                 | 8 (9.2)       | 9.13 (4.07)  | 9 (13.2)      | 10.29 (4.13)  | $\chi^2 = 0.638, p = 0.448$ ; t(153) = -1.762, <i>p</i> = 0.080 |
| CTQ – physical neglect                  | 8 (9.2)       | 6.33 (2.21)  | 10 (14.7)     | 7.00 (2.60)   | $\chi^2 = 1.129, p = 0.320$ ; t(153) = -1.722, <i>p</i> = 0.087 |
| CTQ – total score                       |               | 34.00 (8.61) |               | 37.74 (13.33) | <b>t(153) = -2.111, <i>p</i> = 0.036</b>                        |
| Exposed to CM                           | 22 (25.3)     |              | 22 (32.4)     |               | $\chi^2 = 0.937, p = 0.372$                                     |

Abbreviations: HC, healthy controls; MDD, major depressive disorder; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; HDRS, Hamilton Depression Rating Scale; CTQ, Childhood Trauma Questionnaire.

All variables presented in mean (SD) or *n* (%).

NA: non applicable.

**Table 3.** Cortisol measures and neuropsychological variables by study groups.

|                                                                | HC            | MDD           |                                                    |
|----------------------------------------------------------------|---------------|---------------|----------------------------------------------------|
|                                                                | <i>n</i> = 87 | <i>n</i> = 68 | T-test                                             |
| <i>Cortisol measures</i>                                       |               |               |                                                    |
| 10-h cortisol (nmol/L)                                         | 11.06 (9.72)  | 12.27 (8.22)  | <i>t</i> (146) = −1.011, <i>p</i> = 0.314          |
| 10-h post-DXM cortisol (nmol/L)                                | 4.55 (4.68)   | 6.50 (7.82)   | <b><i>t</i>(153) = −2.123, <i>p</i> = 0.035</b>    |
| DSTR <sup>†</sup>                                              | 9.97 (20.06)  | 5.91 (9.71)   | <i>t</i> (153) = 1.319, <i>p</i> = 0.189           |
| Cortisol at NPS (nmol/L)                                       | 10.53 (5.79)  | 13.11 (9.75)  | <i>t</i> (149) = −1.208, <i>p</i> = 0.229          |
| <i>Cognitive domains</i>                                       |               |               |                                                    |
| <b>Latent variable 1</b> (verbal memory)                       | 0.43 (1.32)   | −0.54 (1.24)  | <b><i>t</i>(153) = 4.664, <i>p</i> = &lt;0.001</b> |
| <b>Latent variable 2</b> (visual memory)                       | 2.35 (6.37)   | −3.00 (6.15)  | <b><i>t</i>(153) = 5.265, <i>p</i> = &lt;0.001</b> |
| <b>Latent variable 3</b> (executive function/processing speed) | 5.19 (11.12)  | −6.64 (13.02) | <b><i>t</i>(153) = 6.101, <i>p</i> = &lt;0.001</b> |

Abbreviations: HC, healthy controls; MDD, major depressive disorder; DXM, dexamethasone; NPS, neuropsychological assessment;

DSTR, dexamethasone suppression test ratio.

All variables presented in mean (SD).

Cortisol raw scores and untransformed DSTR are shown, outliers excluded. *P* values calculated upon transformed cortisol and DSTR values, outliers excluded.

<sup>†</sup>DSTR = 10-h cortisol/10-h post-DXM cortisol.

Latent variable 1 (verbal memory) includes the 3 subscores of the Hopkins Verbal Learning Test – Revised (HVLT-R).

Latent variable 2 (visual memory) includes scores of immediate and delayed recall of the Rey Complex Figure Test (RCFT).

Latent variable 3 (executive function/processing speed) includes scores on Neuropsychological Assessment Battery® Mazes (NAB-Mazes), STROOP interference task, and Corsi Block-Tapping Test for executive function; and category fluency, Brief Assessment of Cognition in Schizophrenia – Symbol Coding (BACS-SC), Trail Making Test part A, and STROOP word subscore for processing speed.

modulated this relationship ( $\beta = 0.182, p = 0.031$ ), reflecting that a greater suppression after dexamethasone administration in MDD patients exerted a positive effect on this cognitive domain.

Meanwhile, CTQ scores in physical abuse ( $\beta = 0.182, p = 0.017$ ) and sexual abuse ( $\beta = 0.134, p = 0.040$ ) were positively associated with verbal memory performance, but without significant interactions with DSTR or depression diagnosis.

Physical neglect negatively affected verbal memory ( $\beta = -0.409, p < 0.001$ ). Nevertheless, the interaction

between physical neglect and depression diagnosis ( $\beta = 0.621, p = 0.002$ ) suggests that higher physical neglect scores were associated with enhanced verbal memory in MDD patients.

### 3.4.2. Visual memory

Depression diagnosis ( $\beta = -0.669, p = 0.002$ ) was associated with poorer visual memory performance.

Physical abuse ( $\beta = -0.270, p = 0.045$ ) and physical neglect ( $\beta = -0.286, p = 0.007$ ) negatively affected

**Table 4.** Results of multiple linear regression analyses exploring the association between childhood maltreatment, HPA axis function, MDD diagnosis, and cognitive performance.

|                                           | Latent variable 1                  |                  | Latent variable 2                  |                  | Latent variable 3                       |                  |
|-------------------------------------------|------------------------------------|------------------|------------------------------------|------------------|-----------------------------------------|------------------|
|                                           | Verbal memory                      |                  | Visual memory                      |                  | Executive function and processing speed |                  |
|                                           | R <sup>2</sup> final model = 0.594 |                  | R <sup>2</sup> final model = 0.502 |                  | R <sup>2</sup> final model = 0.686      |                  |
|                                           | $\beta$                            | $p$              | $\beta$                            | $p$              | $\beta$                                 | $p$              |
| Gender                                    | 0.127                              | 0.057            | −0.181                             | <b>0.015</b>     | −0.059                                  | 0.305            |
| Age                                       | −0.464                             | <b>&lt;0.001</b> | −0.425                             | <b>&lt;0.001</b> | −0.447                                  | <b>&lt;0.001</b> |
| Years of education                        | 0.200                              | <b>0.007</b>     | 0.189                              | <b>0.022</b>     | 0.364                                   | <b>&lt;0.001</b> |
| BMI                                       | 0.020                              | 0.763            | 0.048                              | 0.535            | −0.034                                  | 0.561            |
| Tobacco consumption (cig/day)             | 0.026                              | 0.695            | −0.099                             | 0.180            | −0.014                                  | 0.809            |
| HDRS scores                               | −0.207                             | <b>0.028</b>     | −0.079                             | 0.450            | −0.132                                  | 0.103            |
| MDD diagnosis                             | −0.679                             | <b>0.001</b>     | −0.669                             | <b>0.002</b>     | −0.136                                  | <b>0.048</b>     |
| PSQI                                      | −0.176                             | <b>0.028</b>     | −0.075                             | 0.395            | −0.070                                  | 0.304            |
| CTQ- emotional abuse                      | −0.108                             | 0.212            | 0.052                              | 0.584            | −0.080                                  | 0.283            |
| CTQ- physical abuse                       | 0.182                              | <b>0.017</b>     | −0.270                             | <b>0.045</b>     | 0.082                                   | 0.213            |
| CTQ- sexual abuse                         | 0.134                              | <b>0.040</b>     | 0.252                              | <b>0.009</b>     | 0.157                                   | <b>0.006</b>     |
| CTQ- emotional neglect                    | 0.094                              | 0.267            | −0.101                             | 0.285            | 0.069                                   | 0.347            |
| CTQ- physical neglect                     | −0.409                             | <b>&lt;0.001</b> | −0.286                             | <b>0.007</b>     | −0.161                                  | <b>0.023</b>     |
| DSTR <sup>†</sup>                         | −0.075                             | 0.286            | 0.316                              | 0.485            | −0.023                                  | 0.657            |
| Cortisol at NPS <sup>#</sup> (T7)         | 0.007                              | 0.912            | 0.028                              | 0.690            | 0.011                                   | 0.840            |
| MDD diagnosis x CTQ- physical neglect     | 0.621                              | <b>0.002</b>     | NA                                 | NA               | NA                                      | NA               |
| MDD diagnosis x CTQ- physical abuse       | NA                                 | NA               | 0.551                              | <b>0.025</b>     | NA                                      | NA               |
| MDD diagnosis x DSTR <sup>†</sup>         | 0.182                              | <b>0.031</b>     | NA                                 | NA               | NA                                      | NA               |
| DSTR <sup>†</sup> x CTQ- physical neglect | NA                                 | NA               | 0.538                              | <b>0.018</b>     | NA                                      | NA               |
| DSTR <sup>†</sup> x CTQ- sexual abuse     | NA                                 | NA               | −0.919                             | <b>0.028</b>     | NA                                      | NA               |

Latent variable 1 (verbal memory) includes the 3 subscores of the Hopkins Verbal Learning Test – Revised (HVLT-R).

Latent variable 2 (visual memory) includes scores of immediate and delayed recall of the Rey Complex Figure Test (RCFT).

Latent variable 3 (executive function/processing speed) includes scores on Neuropsychological Assessment Battery® Mazes (NAB-Mazes), STROOP interference task, and Corsi Block-Tapping Test for executive function; and category fluency, Brief Assessment of Cognition in Schizophrenia – Symbol Coding (BACS-SC), Trail Making Test part A, and STROOP word subscore for processing speed.

Neuropsychological variables were considered as the dependent variables.

$\beta$ : standardized beta coefficient.

Abbreviations: BMI, body mass index; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; PSQI, Pittsburgh Sleep Quality Index;

CTQ, Childhood Trauma Questionnaire; DSTR, dexamethasone suppression test ratio; NPS, neuropsychological assessment; NA, not applicable.

<sup>†</sup> DSTR = 10-h cortisol/10-h post-dexamethasone cortisol.

<sup>#</sup> Transformed cortisol values.

Non-significant interaction terms were excluded in the final equation.

visual memory, but significant interactions were found with DSTR or MDD diagnosis. More specifically, physical neglect interacted with DSTR ( $\beta = 0.538$ ,  $p = 0.018$ ); participants with higher physical neglect scores and greater suppression after dexamethasone intake showed better performance in visual memory. In turn, the significant interaction between physical abuse and depression diagnosis for visual memory ( $\beta = 0.551$ ,  $p = 0.025$ ) suggested that MDD patients with higher physical abuse scores showed better performance in this cognitive domain.

Sexual abuse was positively associated with visual memory ( $\beta = 0.252$ ,  $p = 0.009$ ). However, DSTR had a modulation effect ( $\beta = -0.919$ ,  $p = 0.028$ ), suggesting poorer visual memory performance in participants with higher sexual abuse scores and greater DSTR.

### 3.4.3. Executive function/processing speed

MDD diagnosis ( $\beta = -0.136$ ,  $p = 0.048$ ) had a negative effect on executive function/processing speed.

Sexual abuse ( $\beta = 0.157$ ,  $p = 0.006$ ) and physical neglect ( $\beta = -0.161$ ,  $p = 0.023$ ) differentially affected executive function/processing speed.

No interactions between CM and DSTR or MDD diagnosis were found for these cognitive domains.

## 4. Discussion

Apart from a study reporting cognitively beneficial effects of cortisol administration in depressed women with CM (Abercrombie et al., 2018), to our knowledge, no other studies have assessed the role of MDD diagnosis or HPA axis negative feedback in the association between different types of CM and cognitive performance in adulthood.

The present study confirmed disturbed cognitive performance in depression (Rock, Roiser, Riedel, & Blackwell, 2014). Although post-dexamethasone cortisol levels were higher in patients with MDD, the ratio of cortisol suppression did not confirm an impaired feedback sensitivity (Salvat-Pujol et al., 2017). Our results are in part similar to previous findings reporting few differences in cortisol levels (Strickland, Morriss, Wearden, & Deakin, 1998) or the DSTR (Carvalho Fernando et al., 2012) between depressed and non-depressed subjects. Total CTQ scores were higher in MDD patients than in HC, in accordance with previous studies that linked depression with higher levels of CM (Chapman et al., 2004). Despite these findings, we did not find any significant differences between groups in any of the CTQ subscale scores.

Physical maltreatment and sexual abuse had different neurobiological effects on cognition, although these effects, according to our hypothesis, were modulated by HPA axis function and MDD diagnosis.

Physical neglect was associated with poorer cognitive performance, in accordance with previous literature (Dannehl et al., 2017; Geoffroy et al., 2016; Majer et al., 2010; Nikulina & Widom, 2013). Physical abuse did not show a consistent association with cognitive performance in different domains. In contrast, sexual abuse was associated with enhanced cognition. Although most studies indicate that sexual abuse decreases cognitive performance (Dannehl et al., 2017; Gould et al., 2012), others found that it did not predict poorer executive function (Nikulina & Widom, 2013) or even concluded that sexual abuse is associated with better global cognition, memory, executive function, and processing speed (Feeney et al., 2013). In the latter study, performed in adults aged 50 years and older, authors argue that other studies rely on younger participants, in whom the abuse experience is fresher and its impact greater (Feeney et al., 2013). Previous research indicates that older adults tend to be more stress-resilient than younger individuals, probably due to prior experience with stressors, more effective coping strategies, greater tolerance for negative affect, and better emotion regulation (Feeney et al., 2013; Seery, Holman, & Silver, 2010). These findings are consistent with stress inoculation and resilience theories. Early exposure to stress has been mostly related to an increased risk for the development of psychopathology after experiencing subsequent stressors in adulthood (Heim, Newport et al., 2008). This is because early life stress alters corticolimbic brain systems that regulate stress and anxiety, disrupts the acquisition of appropriate coping styles, induces alterations in baseline activity as well as stress reactivity of the HPA axis, diminishes the volumes of the hippocampus and the prefrontal cortex (Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Van Harmelen et al., 2010), and impairs cognition (Heim, Newport et al., 2008; Majer et al., 2010; McEwen, 2007; Nikulina & Widom, 2013; Pryce, Dettling, Spengler, Spaete, & Feldon, 2004; Pryce et al., 2005), independent of psychopathology (R-Mercier et al., 2018). There is evidence that prior exposure to moderate (but not minimal or substantial) stress levels, which are challenging enough to evoke acute anxiety and transiently activate the HPA axis, fosters the development of resilience to subsequent stressors encountered later in life (Parker, Buckmaster, Hyde, Schatzberg, & Lyons, 2019; Parker & Maestripieri, 2011). Thus, the relationship between early life stress exposure and subsequent resilience can be depicted as a non-linear J-shaped function (Parker et al., 2019).

Factors such as sex, predictability of the stress, degree, duration, nature, and developmental timing of the historical stress exposure can influence the shape and inflection point of the J-shaped curve (Luine, 2002; Parker & Maestripieri, 2011). Longitudinal studies of animal development support the notion that intermittent stressful experiences early in life (a laboratory manipulation called ‘stress inoculation’) enhance long-lasting adaptive functioning, diminishing neurobiological responses to moderate stress and enhancing cognitive control of behaviour (Lyons, Parker, & Schatzberg, 2010). Prefrontal corticolimbic brain circuits have been implicated in resilience, as they play a role in cognitive control and regulate the HPA axis stress response (Diorio, Viau, & Meaney, 1993; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Miller, 2000; Sullivan & Gratton, 2002). Most studies report that early life stress inoculation promotes the development of larger prefrontal cortical volumes later in life without affecting hippocampal volumes (Katz et al., 2009; Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002; Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001), which may be due to the growth and development of the prefrontal cortex extending into early adulthood, while hippocampal growth and development occurs primarily *in utero* (Giedd et al., 1999; Khazipov et al., 2001). Nevertheless, some studies suggest that stress during childhood increases hippocampal neurogenesis (Hays et al., 2012). Even though there is some controversy on whether stress inoculation affects the hippocampal structure, evidence from animal studies suggests that stress resilience may be mediated by increased hippocampal glucocorticoid receptor expression: a functional hippocampus adequately inhibits the HPA axis response to subsequent acute stressors (Kaffman & Meaney, 2007; Parker & Maestripieri, 2011). These findings suggest that stress inoculation may either directly alter the neural substrates involved in adaptive functioning and cognitive function, or indirectly influence cognitive performance by primarily changing emotion regulation (Lyons, Parker, Katz, & Schatzberg, 2009; Parker & Maestripieri, 2011). Brain changes observed after early stress constitute neuroplastic adaptive responses to facilitate survival rather than non-specific damage, reflecting stress resilience rather than stress pathology, and this stress inoculation phenotype persists into adulthood (Parker, Buckmaster, Lindley, Schatzberg, & Lyons, 2012; Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006; Teicher & Samson, 2016). Considering all these findings, and since cognitive tasks assessed in our study involve the hippocampus and the prefrontal cortex, we conclude that the speculatively resilient individuals who have suffered sexual abuse in our sample may have

a more functionally preserved hippocampus and prefrontal cortex, which would enable a greater ability to successfully adapt to stress. Thus, we could be observing a cognitive phenotype in which individuals with sexual abuse raised in an enriching environment, which has positive effects in neurodevelopment (van Praag, Kempermann, & Gage, 2000), may present with preserved cognitive performance.

According to a recent study by Trauelsen et al., (2019), and very surprisingly, performance on cold cognitive (neurocognitive) tasks might not be the only ones enhanced in individuals with sexual abuse: although in first-episode psychosis, better metacognition abilities were reported in subjects with CM, including sexual abuse (Trauelsen et al., 2019). The authors suggested that insight could play a role in this association, and recommended future studies to include hot (social cognition) and cold cognition assessment. Even though our study was performed in patients with MDD and did not take into account metacognition, it is interesting the fact that findings on the link between sexual abuse and enhanced cognition are somehow shared. Future longitudinal studies are needed to further assess and clarify the effects of sexual abuse on cognitive abilities, taking into account different types of cognition and the insight of the subject.

Cortisol suppression after dexamethasone was not related to cognitive function. Previous literature has yielded contradictory findings on this issue. Specifically, while some studies suggest that lower cortisol suppression with the Dex/CRH could be related to poorer executive functioning in recovered MDD patients (Behnken et al., 2013), others report no association between cortisol suppression and executive function (Hansson et al., 2013; Krogh et al., 2012) or visual memory (Krogh et al., 2012) using the DST with dexamethasone 1 mg.

Surprisingly, we observed a different effect of DST in its interaction with physical neglect and sexual abuse on visual memory. DST showed an association with better visual memory in physically neglected individuals, reflecting that a more preserved HPA axis function would imply a more functionally preserved hippocampus and that despite the history of neglect, individuals would be able to sustain an adequate cognitive performance. Nonetheless, the interaction of DST with sexual abuse indicates that in those participants with sexual abuse, greater suppression of the HPA axis is associated with poorer cognitive performance.

The distinct modulation of sexual abuse and physical neglect by DST reinforces the idea that these experiences have a different impact on the HPA axis and, most likely, cognition. These findings suggest that potential HPA axis-related neurobiological mechanisms leading to cognitive

impairment might differ depending upon the type of childhood trauma: a GR resistance (reduced HPA axis negative feedback) would be pathological in people with a history of physical neglect, whereas the pathological condition would be the opposite in people with a history of sexual abuse, as increased GR binding (enhanced HPA axis negative feedback) was associated with a poorer cognitive outcome. This last finding is in accordance with classical studies reporting an enhanced dexamethasone cortisol suppression in women victims of sexual abuse (Stein et al., 1997).

Depression diagnosis negatively impacted cognition, but physical maltreatment modulated this relationship. Contrary to our expectations, individuals with physical maltreatment and MDD presented with enhanced cognition in certain domains depending on whether experienced maltreatment was abuse (visual memory) or neglect (verbal memory). Again, and according to Trauelsen findings and their interpretation (Trauelsen et al., 2019), patients who recognized physical maltreatment might be endowed with higher insight and, although speculative, be more resilient. This resiliency, coupled with the fact that maltreatment itself may lead to adaptive cognitive responses, could partially explain these results. Our findings might be supported by the observation that the absence of major psychopathology does not comprise an adequate indicator of resilience (Simeon et al., 2007). Future studies are needed to address these issues.

Upon examination of the significant interaction between DST and MDD diagnosis on cognition, we found that a greater suppression after dexamethasone administration in MDD patients was associated with enhanced verbal memory. Cortisol non-suppression in response to dexamethasone, suggesting lower sensitivity of the HPA axis negative feedback, has been reported in 40–60% of depressed patients (Carroll et al., 1981). Classical studies have reported better cognitive outcomes in MDD patients with greater dexamethasone suppression (Wauthy, Ansseau, von Frenckell, Mormont, & Legros, 1991). Although it is somewhat speculative, those patients with a more preserved HPA axis function (e.g. greater cortisol suppression to dexamethasone) will most likely present with higher integrity of the hippocampus and, hence, better cognitive performance in hippocampus-dependent cognitive tasks.

#### 4.1. Limitations and methodological issues

Some limitations and methodological issues need to be considered. All patients received antidepressant treatment according to their clinical needs and there were no drug-naïve patients in our sample. We are aware that this treatment may have impacted cortisol

or cognitive measures (Jain et al., 2019; Rosenblat, Kakar, & McIntyre, 2015). However, the fact that we still found differences in cognitive performance in patients treated with antidepressants suggests that our findings in drug-naïve patients could be even stronger. Additionally, the fact that patients were in a naturalistic setting could facilitate the extrapolation of our results to clinical populations. Patients were recruited from a tertiary source, that may differ from community-based cases, thereby limiting the generalization of these results.

Although some have indicated that the CTQ and the PSQI could be influenced by recall bias or a depressive state, they are validated psychometric instruments with good internal consistency and validity and suitable for clinical and research settings (Buysse et al., 1989; Majer et al., 2010).

Cortisol measures were assessed only once. Although we did not repeat the DST on different days, this HPA axis dynamic test has shown a relatively good individual stability over time (Golden, Wand, Malhotra, Kamel, & Horton, 2011; Huizenga et al., 1998).

Finally, the cross-sectional design precludes causal inferences, and longitudinal studies are needed to address this issue. Other variables that could modulate the relationship between MDD diagnosis, CM and cognitive function should be considered in future studies, including polymorphisms of genes implicated in the HPA axis or resilience, inflammation parameters, structural and functional neuroimaging, and personality traits. The results on these issues may provide greater knowledge and a more effective clinical assessment and management of individuals with a history of CM.

## 4.2. Conclusions

As overall conclusions, physical maltreatment and sexual abuse had different neurobiological effects on cognition, with modulating effects by HPA axis function and MDD diagnosis. Meanwhile, emotional maltreatment did not have an impact on cognitive performance and it did not interact with DST or depression diagnosis. Thus, CM and its subtypes should be taken into account in studies involving cognition, HPA axis function and psychopathology.

Our results suggest a need for early assessment and intervention on cognition and resilience mechanisms in individuals exposed to CM to minimize its deleterious and lasting effects. Since CM is thought to increase the risk of MDD and influence its clinical course, our findings may add to the knowledge of the aetiology, prevention and treatment of depression.

In addition, there is increasing evidence that CM shapes biological stress response systems, including the HPA axis. Consequently, the HPA axis might

become a potential target for specific treatment interventions in patients with CM (Menke, 2019).

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## Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

## ORCID

Neus Salvat-Pujol  <http://orcid.org/0000-0001-5320-331X>  
Javier Labad  <http://orcid.org/0000-0003-2214-1886>

Mikel Urretavizcaya  <http://orcid.org/0000-0002-9746-4068>

Aida de Arriba-Arnau  <http://orcid.org/0000-0002-7877-7341>

Cinto Segalàs  <http://orcid.org/0000-0002-0959-0356>

Eva Real  <http://orcid.org/0000-0003-4523-1649>

Alex Ferrer  <http://orcid.org/0000-0002-3040-1177>

Susana Jiménez-Murcia  <http://orcid.org/0000-0002-3596-8033>

Carles Soriano-Mas  <http://orcid.org/0000-0003-4574-6597>

José M. Menchón  <http://orcid.org/0000-0002-6231-6524>  
Virginia Soria  <http://orcid.org/0000-0001-6412-6831>

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