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Ph.D. THESIS SUMMARY

CHILDHOOD ADVERSITY AND PSYCHOPATHOLOGY. THE MEDIATING ROLE OF REWARD PROCESSING

AUTHOR: Ph.D. CANDIDATE LIA-ECATERINA OLTEAN

SCIENTIFIC ADVISOR: PROFESSOR Ph.D. AURORA SZENTÁGOTAI-TĂTAR

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(a) The thesis includes the original research work of Lia-Ecaterina Oltean (author) towards the Ph.D.;

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- A software was used to check for the academic writing (see at http://www.plagiarismdetector.com/) ; the thesis has passed the critical test;
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CHAPTER I. THEORETICAL BACKGROUND

Childhood adversity (i.e., CA) consists of experiences such as neglect and/or abuse, household dysfunction, death of a parent (e.g., Euler et al., 2019; Toth et al., 2020) which challenge a child's well-being and coping ability, forcing him to undergo prolonged stress exposure (Fareri & Tottenham, 2016; Hammen, 2016; Martins-Monteverde et al., 2019; Pechtel & Pizzagalli, 2011). These experiences are highly prevalent (Kessler et al., 2010), with estimates ranging from 38% to 74% (Shi, 2013), and may be more frequent in low socioeconomic communities (McLaughlin et al., 2011). Moreover, given that more than 60% CA individuals experience multiple adversities (Kessler et al., 2010), this may indicate that these experiences greatly overlap and co-occur (Kessler et al., 2010; Gilbert et al., 2009; Smith & Pollak, 2020).

While CA has high individual, social and economic costs (Cuijpers et al., 2011; Peterson et al., 2018; Viola et al., 2015), and represents a major public health concern by itself (Cuijpers et al., 2011), it is also an important risk factor for various health problems (Anda et al., 2009; Bellis, Hughes, Leckenby, Perkins, and Lowey, 2014; Felitti et al., 1998; Norman et al., 2012). Notably, its association with multiple forms of psychopathology (Green et al., 2010; Kessler et al., 2010; for review see Cicchetti, 2016; McCrory and Viding, 2015; McLaughlin, 2016) is well-established (Li et al., 2016), and this risk, which becomes evident early during development (Bronsard et al., 2016), is maintained across life stages (Cicchetti & Banny, 2014; Forbes et al., 2016; Rapsey et al., 2019).

Given that, across disorders, CA predicts more persistent, recurrent and severe mental health problems, the scientific community has been interested in investigating underlying mechanisms that may explain this association (McLaughlin, 2016). Still, while advances in this area could contribute to increasing the specificity of psychological interventions (McLaughlin, 2019) and improving treatment response (Nanni, Uher, and Danese, 2012), such mechanisms remain insufficiently studied (Kessler et al., 2010). Recently, reward processing, a multidimensional construct consisting of three distinct dimensions (i.e., reward responsiveness, reward learning, and reward valuation; Carcone and Ruocco, 2017; NIMH, 2016; Olino, 2016) has been increasingly gaining attention (e.g., see Gerin et al., 2019 for a review) as one of the most promising candidates (e.g., Herzberg & Gunnar, 2020; Novick et al., 2018). Yet, to date, existing support for this hypothesis is indirect and stems from two separate lines of research.

On the one hand, several studies indicate an association between CA and reward processing (e.g Boecker et al., 2014; Dillon et al., 2009; Marusak et al., 2015), suggesting that it may potentially explain the transdiagnostic nature of the mental health vulnerability that characterizes individuals with CA (McLaughlin, 2016; Nusslock and Miller, 2016; Watt, Weber, Davies, and Forster, 2017). However, given that these studies report heterogeneous results (for review see Gerin, Hanson, Viding, and McCrory, 2019; Ironside, Kumar, Kang, and Pizzagalli, 2018; Kujawa et al., 2020; Novick et al., 2018), a meta-analysis aiming to clarify the direction and magnitude of this association, is warranted. Likewise, identifying potential factors that may impact on this association is equally important.

On the other hand, several studies support reward processing's involvement in psychopathology (Carcone and Ruocco, 2017; NIMH, 2016), documenting its impairments in various mental disorders. Still, findings from this line of research parallel those on CA and reward processing and are heterogeneous. While interpreting these findings is difficult, it is plausible that such impairments may vary by disorder and reward processing dimension.

Considering that specific patterns of reward processing impairments following CA and varying by dimension may emerge in distinct disorders and, considering high comorbidity rates among disorders (e.g., Groen et al., 2020; Kessler et al., 2010; Scott et al., 2007), existing data justify investigating this transdiagnostic mechanisms and suggest that it could be targeted through interventions (e.g., McLaughlin et al., 2019). Capitalizing on these data, recent studies (Craske et al., 2016; Kelley et al., 2019) have started to investigate interventions aiming to target reward processing and, although scarce, existing data suggest that they may be effective (e.g., Positive Affect Treatment; PAT; Craske et al., 2019). However, given that these interventions consist of various strategies, disentangling their active ingredients is germane. In addition, further research aimed at investigating the proposed mechanism of change is needed, considering that existing findings do did not test this hypothesis. Moreover, several potential variables that may influence treatment outcomes (e.g., CA), as well as the proposed mechanisms, should be considered.

Relevance and Impact of the Research Topic

The aim of this thesis was to investigate the associations between CA, reward processing and psychopathology, as well as other important associations with socioeconomic status and proximal stress. Specifically, we sought to investigate the potential mediating role of reward processing in the association between CA and psychopathology. In addition, we sought to investigate the efficacy of several interventions aiming to address reward processing. Finally, we aimed to clarify the impact of CA on the efficacy of these interventions. Thus, the thesis has several important theoretical and clinical implications that are outlined below.

An important first step in clarifying the potential mediating role of reward processing in the association between CA and psychopathology is investigating the association between CA and reward processing and delineating potential factors that may impact on it. If reward processing dimensions moderated these associations, this would justify investigating these constructs and their implications for psychopathology separately. If the type of measure and sample characteristics moderated these associations, this would inform on general conclusions that may be drawn from existing studies and guide future research. If, in turn, these factors didn't have a significant impact, this would mean that their relevance for these associations is limited.

A second important step in clarifying the potential mediating role of reward processing in the association between CA and psychopathology is investigating associations between these constructs, that would clarify the potential predictive role of CA and reward processing for different symptoms. If CA and/or reward processing were linked with specific symptoms, this would justify further investigation of these potential constructs together. In addition, if distinct reward processing dimensions mediated the association between CA and specific symptoms, this would offer a coherent theoretical explanatory model for their etiopathogenesis. Given that existing interventions aiming to target reward processing are limited to depressive and anxiety symptoms (Craske et al., 2019), these findings would be particularly important and would justify developing new intervention protocols in other pathologies. Finally, given that CAs are associated with low socioeconomic status, exploring alternative models would further clarify the interplay between these variables and their unique relevance for psychopathology.

Reward processing impairments are well documented in depression and may be an underlying mechanism explaining its link with CA (McLaughlin et al., 2019). An important step towards understanding the potential mediating role of reward processing in depression is examining distinct reward processing dimensions separately. If one or all reward processing dimensions mediated the association between CA and depression, this would favor including them in an explanatory model of depression. Consistent with the diathesis-stress hypothesis (Admon et al., 2013), accounting for the potential psychological impact of stress in this model

is germane. Finally, another important step that would increase the specificity of the proposed explanatory model is testing alternative models in which low socioeconomic status is also examined.

Depressive symptoms are highly comorbid with anxiety symptoms and other health problems (Mrazek et al., 2014), suggesting common risk factors. Given that reward processing is a potential mediator in the association between CA and depression, replicating the model in anxiety and physical symptoms would add support to the aforementioned hypothesis and justify the need for a transdiagnostic approach. If the proposed model for depression could be extended to anxiety disorders, this would justify developing protocols that target reward processing in both conditions.

Existing psychological interventions aiming to alleviate depressive and anxiety symptoms through reward processing show promising results (Craske et al., 2019), but do not test the proposed mechanism of change. Thus, examining this hypothesis is important. In addition, existing interventions use multiple strategies aiming to target reward processing, but active ingredients are unclear. Therefore, examining these strategies separately would expand current knowledge both on their effectiveness and on the proposed mechanism of change. In addition, if standalone strategies were effective, this would potentially reduce treatment costs. Investigating other potentially relevant variables that may impact on these interventions is equally important and may inform clinicians in designing treatment. While CA has been singled out as an important risk factor for psychopathology, it also impacts on treatment response (Toth et al., 2020) and may be associated with the proposed mechanism of change. Thus, CA may be one relevant candidate that impact on treatment response, adherence and dropout.

CHAPTER II. OBJECTIVES AND GENERAL METHODOLOGY

The thesis sought to investigate several theoretical, methodological and clinical aspects related to the association between CA and psychopathology, as well as reward processing, one of the potential mechanisms that may explain this association (Nusslock & Miller, 2016). Building on important research questions, we designed studies that addressed them through the general and specific goals outlined below.

The first questions are related to the association between CA and reward processing: Is CA associated with impaired reward processing and, if they are associated, what are some of the potential factors impacting on this association? In order to address these questions, we formulated the following objectives: to systematically review and synthesize the available data on the association between CA and reward processing, and to investigate potential sources of between-study heterogeneity. Thus, we conducted a meta-analysis (**Study 1**; see Figure 1) in which we investigated several theoretical and methodological potential moderators.

The second set of questions pertains to the potential mediating role of reward processing in the association between CA and psychopathology: If CA predicts impaired reward processing and psychopathology, could reward processing mediate the relationship between CA and psychopathology? Are all reward processing dimensions equally relevant? Aiming to address these questions, we derived two objectives: to investigate the association between CA, reward processing and psychopathology and to investigate the potential mediating role of reward processing in the association between CA and psychopathology. Thus, we conducted a large correlational study (**Study 2a**; see Figure 1) on young adults (18-35) and collected self-report data on CA, reward processing and its dimensions, as well as several symptoms (i.e., depressive, manic symptoms, alcohol abuse, emotional eating, borderline personality traits) that have been previously linked with both CA and reward processing. In addition, we investigated socio-economic status and its link with these variables. Likewise, given that reward processing impairments on all three dimensions have been documented in depression (Eshel & Roisier, 2010; Fischer et al., 2018; Luking et al., 2016; Proudfit, 2015), but no previous study investigated these dimensions together, we conducted a correlational study on a sample of clinically depressed patients (**Study 2b**; see Figure 1).

CA increases the risk for pathology, including mental (Cicchetti, 2016) and physical problems (Janson, 2018). Building on data indicating that these conditions are highly comorbid (James et al., 2018), hinting common mechanisms, several other questions emerged: if reward processing may partially explain the association between CA and psychopathology, could this model be extended to other health related problems? May other variables, such as psychological impact of recent stressful events, influence the model? We sought to answer these questions through the following objective: to investigate the association between CA, psychological impact of recent stressful events, reward processing, and health (i.e., depressive and anxiety symptoms, physical health). In order to address this objective, we conducted a correlational study on a community sample (**Study 2c**; see Figure 1).

The last set of questions is related to reward processing's potential clinical implications: do existing strategies target reward processing and are these strategies effective? If these strategies are effective, is reward processing the mechanism of change? Do CA and other factors impact on the effectiveness of these strategies? We sought to address these questions through the following objectives: to investigate the effectiveness of existing reward processing interventions in reducing depressive and anxiety symptoms and negative affect and increasing positive affect; to investigate reward processing and its dimensions as potential mechanisms of change; to investigate other potential moderators for these interventions' effectiveness. In order to address these objectives, we conducted two experimental studies (**Study 3a** and **Study 3b**; see Figure 1). We conducted a randomized controlled trial (**Study 3a)** on an analogue sample

(i.e., participants exhibited above DASS-21R (Lovibond & Lovibond, 1995) cut-off scores for depressive and anxiety symptoms). The study had three experimental groups: the behavioral, the cognitive training and the control group, and lasted 4 weeks. Pre-post data was collected on primary and secondary outcomes through self-report measures. Given that recent data suggests gratitude interventions target reward processing (Craske et al., 2019), we sought to test this hypothesis and furtherly clarify the effectiveness of these interventions. Thus, we conducted a randomized controlled trial (**Study 3b**) in which we recruited a community sample and randomly allocated participants in one of the two groups: the gratitude intervention and the control group. We collected data on primary and secondary outcomes before and after the intervention.

The thesis is the first investigation of reward processing dimensions and their distinct associations with CA and psychopathology that also took into consideration several other important variables, such as socio-economic status and psychological impact of stressful events. Thus, some of the aforementioned objectives were followed up by exploratory analyses. All studies were conducted following international ethical guidelines, as well as the guidelines of Babes-Bolyai University's Institutional Review Board.

Providing answers to the aforementioned questions has important theoretical, methodological and clinical implications. First, the thesis attempted to clarify distinct associations between CA, reward processing and psychopathology, providing a comprehensive framework for these interrelated constructs. Second, in order to address the aforementioned research questions, we used various methodological approaches. Study 1 was the first quantitative review to systematically investigate the association between CA and impaired reward processing. Study 2a and Study 2b used a cross-sectional design to investigate the indirect effect of CA on psychopathology, through different reward processing dimensions, both in a community sample and a sample of clinically depressed patients. Using a similar cross-sectional design, in Study 2c, we extended the model to other health related problems. We used moderated-mediation analyses in order to investigate the potential moderating role of psychological impact of stressful events on the mediating role of reward processing in the association between CA and health. Moreover, we used experimental designs and conducted two randomized clinical trials (Study 3a and Study 3b). These designs allowed the investigation of causal relationships between variables. Finally, the thesis extends the existing literature and provides useful guidelines for clinicians working with individuals reporting past CA.

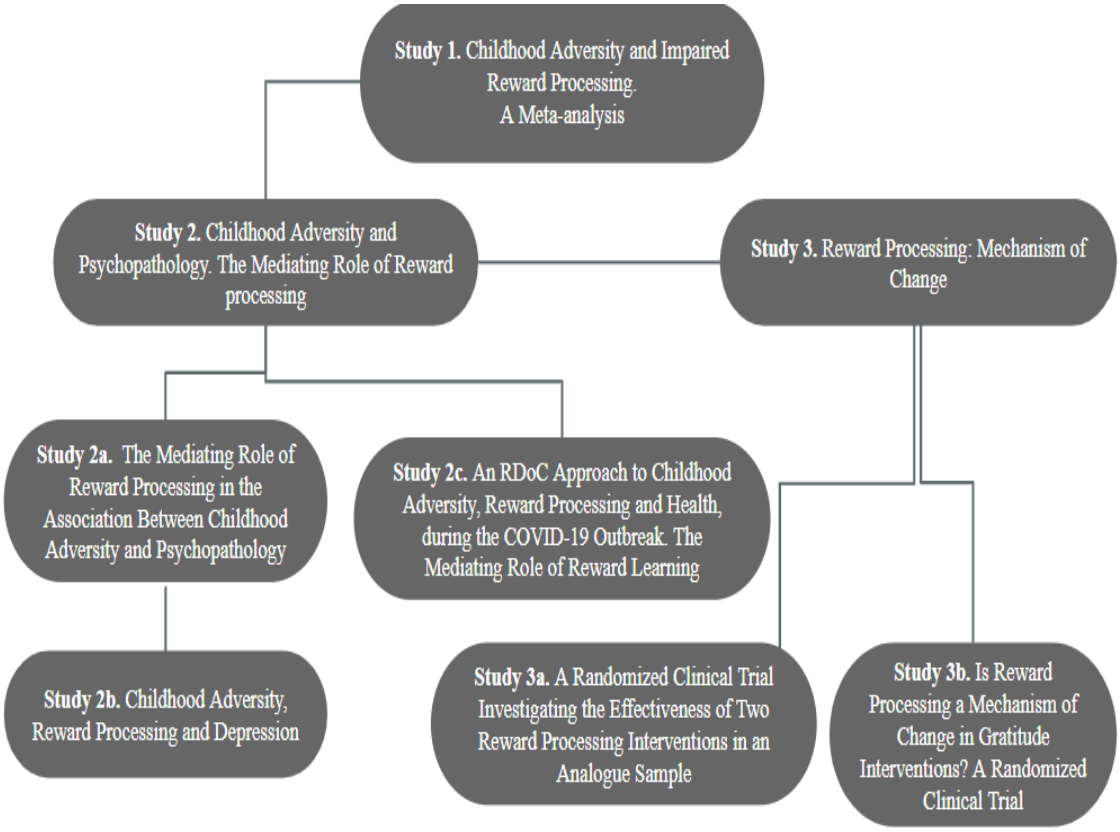

Figure 1. The Schematic Structure of the Thesis

CHAPTER III. ORIGINAL RESEARCH

3.1. Study 1. Childhood adversity and impaired reward processing. A meta-analysis[1]

3.1.1. Introduction

Childhood adversity (CA) is associated with a lifelong risk for multiple forms of psychopathology (Green et al., 2010; Kessler et al., 2010; for review see Cicchetti, 2016; McCrory and Viding, 2015; McLaughlin, 2016) and advances pertaining to underlying mechanisms (McLaughlin, 2016) could contribute to increasing the specificity of psychological interventions (McLaughlin, 2019) and improving treatment response (Nanni, Uher, and Danese, 2012). Reward processing has been proposed as a potential mechanism, but available evidence on its association with CA is heterogeneous (for review see Gerin, Hanson, Viding, and McCrory, 2019; Ironside, Kumar, Kang, and Pizzagalli, 2018; Kujawa et al., 2020; Novick et al., 2018), and a meta-analysis is warranted.

Previous studies support an association between the two, but the effects vary in direction and magnitude. Provided that this apparent heterogeneity is substantiated in meta-analysis, it could be explained by between-study differences in the conceptualization and assessment of both reward processing and CA, as well as in sample characteristics related to developmental stage, sex distribution, and clinical status.

Reward processing is a multidimensional construct which includes three distinct processes: reward responsiveness, reward learning, and reward valuation (Carcone and Ruocco, 2017; NIMH, 2016; Olino, 2016). We hypothesized that CA may differentially impact these reward processing dimensions, explaining some of the between-study heterogeneity in previous studies.

Another potential moderator is the type of instrument used to assess reward processing. Both cognitive tasks and questionnaires have been employed in studies investigating reward processing (Novick et al., 2018). Medium to non-significant correlations have been reported between cognitive tasks and self-report measures of reward processing (e.g., Herman, Critchley, and Duka, 2018; Suhr and Tsanadis, 2007), which suggests that they do not overlap.

Similarly, the type of CA measure could moderate the association between CA and reward processing. Multiple distinctions among these instruments have been proposed, but one that is particularly relevant is that between non-retrospective and retrospective measures. There is evidence that CA is underreported in retrospective assessments, with rates dropping to as low as 16% in adult men with official records of sexual abuse, for instance (Widom and Morris, 1997).

Other variables could also impact the association between CA and reward processing. Age at the time of assessment may be a moderator of this association. Reward responsiveness is higher in women compared to men (Urošević et al., 2012), which suggests that sex distribution could also explain some of the heterogeneity in previous studies on CA. Clinical status is another potential moderator of the effects of CA in light of the reward valuation deficits that have been found in patients with depression compared to healthy controls (Pulcu et al.,

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[1] This study has been accepted for publication.
Oltean, L.E., Șoflău R., Miu, A.C., Szentágotai-Tătar, A. (in press). Childhood adversity and impaired reward processing: A meta-analysis. *Child Abuse & Neglect.*

The authors contributed to the article as follows: Oltean, L.E.: study design, writing the protocol, literature search and summary, data analysis, writing the manuscript; Șoflău, R.: literature search and summary, writing the manuscript; Miu, A.C.: study design, writing the protocol, data analysis, writing the manuscript; Szentágotai-Tătar, A.: study design, writing the protocol, data analysis, writing the manuscript.

2014). Finally, sample size could contribute to the between-study heterogeneity considering that sample sizes varied by almost tenfold, and some, which have included as little as twenty participants, may have been underpowered.

The present meta-analysis pooled the available data on the relation between CA and reward processing, and investigated potential sources of between-study heterogeneity. We expected larger effect sizes in: (1) studies on reward learning and responsiveness compared to reward valuation; (2) studies that assessed reward processing using cognitive tasks, compared to self-report; and (3) studies in which CA assessments were non-retrospective rather than retrospective. In addition, we expected larger effect sizes of the relation between CA and reward processing in studies conducted in adolescents compared to adults, in predominantly female samples, clinical samples, and studies with larger sample sizes.

3.1.2. Methods

Literature search

We conducted a systematic search in the Cochrane Central, PsychInfo, PubMed, Science Direct, Scopus, and Web of Science bibliographic databases. The search was conducted in March 2018 and updated in May 2020, using keywords (including truncated terms) related to CA (["childhood" OR "early"] AND ["adversity", "maltreatment", "abuse", "neglect", "stress" OR "trauma"]) and reward processing ("reward", "reinforcement" OR "behavioral approach system").

Study selection

As indicated in the PRISMA flowchart (Fig. 1), the database search yielded 1784 records, with 1007 left after duplicate removal. Based on information in abstracts, 120 potentially relevant records were identified and their full-text was read. Eligible studies had to meet the following criteria: (a) work was conducted in human subjects; (b) empirical data were reported; (c) both CA (i.e., stressful events before age 18) and RP were measured; and (d) RP was assessed using cognitive tasks and self-report measures. Case studies and qualitative analyses were excluded. Thirty-four studies met the inclusion criteria. There were insufficient data to calculate the effect sizes in 15 of these studies, but, after contacting the authors, data were obtained from 8 of these studies. Therefore, 27 studies were included in the present meta-analysis.

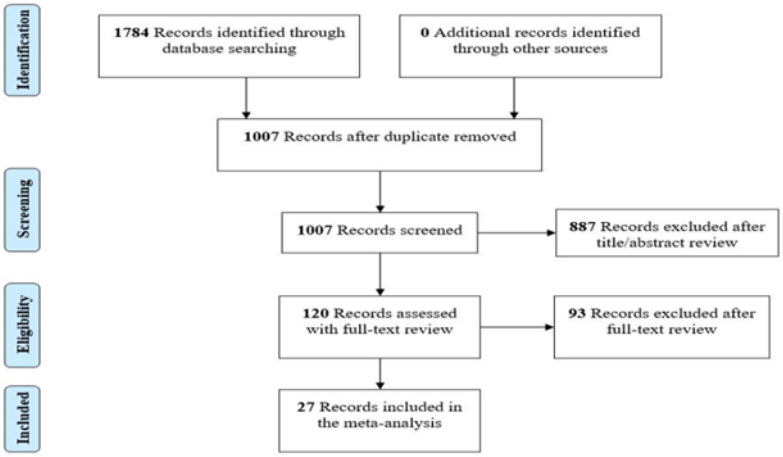

Figure 1. PRISMA flowchart describing the selection of studies.

Procedure

Study characteristics were extracted by two coders (94.15% inter-rater agreement), and all disagreements were resolved through discussion. Pearson's r was used as effect size coefficient, estimated using the random effects model (Borenstein, Hedges, Higgins, and

Rothstein, 2011; Lipsey and Wilson, 2001). Heterogeneity of effect sizes was assessed using the Q-statistic, and the proportion of observed variability that was due to heterogeneity rather than chance was estimated based on the I^2 coefficient (Borenstein et al., 2011; Lipsey and Wilson, 2001).

In line with the assumption of effect independence, a single mean effect size from studies that reported data on multiple outcomes was included in the pooled and subgroup analyses. In studies that reported data for multiple categories of the moderator variables (RP dimensions; type of CA measure), we initially used the effect size that was based on more multiple measures and was thus likely to provide a more reliable estimation. Follow-up sensitivity analyses were subsequently run, in which the initially selected effect size was switched with the other effect size.

Subgroup analyses examined the potential moderator role of multiple study differences. First, subgroups of studies were distinguished based on the RP dimensions: reward learning; reward valuation; and reward responsiveness. Second, subgroups of studies were compared based on the type of instrument used to assess RP: cognitive task vs. self-report. Third, studies were grouped based on the type of instrument used to assess CA: official records vs. subjective (i.e., self- and other-) reports. Several studies used multiple instruments to document CA, including official records, and were coded in the former category. Fourth, studies were grouped based on the age category at the time of assessment: adolescents aged 11-19 vs. adults over age 19 (there was only one study in children aged 5-10, which was discarded from this subgroup analysis considering the developmental differences in RP between children and both adolescents and adults; see Urošević et al., 2012).

Study quality was evaluated mostly based on previously developed criteria (Thornberry, Knight, and Lovegrove, 2012). Four criteria were added: two related to the clinical status and two related to measures. In line with common practice, a minimum of three studies in each subgroup was considered necessary for the reliable estimation of effect size in each subgroup.

Meta-regression analyses were also used to investigate the potential moderator role of age (i.e., mean age in the sample) at the time of the study, and sample sex distribution (i.e., % women).

Potential publication bias was examined through multiple methods, including inspection of the funnel plot and Egger's test of funnel asymmetry (Egger, Smith, Schneider, & Minder, 1997). The trim-and-fill procedure (Duval & Tweedie, 2000) was also used to determine how many studies would need to be imputed to render the funnel plot symmetrical, and estimate an adjusted effect size. All analyses were conducted in Comprehensive Meta-Analyses 2.2.064 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

3.1.3. Results

Pooled effects

By pooling the effect sizes from all 27 studies (total $N = 6801$), we found a statistically significant, small-sized association between CA and RP ($r = 0.12$, 95% CI [0.07, 0.16], $p < 0.001$). A sensitivity analysis, including only reward-related outcomes adjusted for individual differences in neutral trials, replicated the initial result. Heterogeneity was significant and medium-sized ($Q(26) = 69.19$, $p < 0.001$; $I^2 = 62.43$).

Subgroup analyses

Subgroups of studies were compared based on the RP dimension (learning vs. responsiveness vs. valuation), the type of RP assessment (cognitive task vs. self-report), type of CA assessment (official records vs. subjective report), and age category at the time of study (adolescents vs. adults) (Table 1). There was a significant difference between studies on different RP dimensions, with a medium-sized association between CA and reward learning,

and small-sized associations between CA and both reward valuation, and reward responsiveness. Switching effect sizes in studies that assessed multiple dimensions of RP (k = 8) replicated these differences ($Q_{between}$ = 6.91, p = 0.032). The effect size was also larger in studies using cognitive tasks to assess RP, compared to self-report. One study used both task and self-report measures of RP, but the difference remained significant irrespective of which effect size was used in the analysis ($Q_{between}$ = 5.45, p = 0.020). Studies in which CA was assessed using official records also reported significantly larger effect sizes (medium-sized) compared to studies using subjective reports (small-sized). Finally, the effect size was not significantly different between studies in adolescents and adults.

Table 1
Results of subgroup analyses on RP dimension, type of RP measure, type of childhood adversity measure, and age group

Moderator	Categories	*k*	*r*	*p*	*CI*	*Qw*	*p*	*Qb*	*p*
RP dimension	Reward learning	7	0.26	< 0.001	0.14; 0.36	9.06	0.170	7.04	0.030
	Reward valuation	10	0.11	< 0.001	0.05; 0.17	23.90	0.004		
	Reward responsiveness	10	0.07	0.071	-0.01; 0.15	23.17	0.006		
Type of RP measure	Task	14	0.20	< 0.001	0.12; 0.27	26.08	0.017	6.73	0.009
	Questionnaire	13	0.08	0.006	0.02; 0.13	32.51	0.001		
Type of childhood adversity measure	Including official records	8	0.27	< 0.001	0.16; 0.37	12.52	0.085	9.25	0.002
	Subjective	19	0.07	< 0.001	0.04; 0.13	40.81	0.002		
Age group	Adolescents	12	0.06	0.082	-0.01; 0.13	20.33	0.041	2.54	0.111
	Adults	14	0.13	< 0.001	0.08; 0.19	32.75	0.002		

Meta-regression analyses

There was a tendency for an association between effect size and mean age (B = 0.003, Qmodel = 3.81, p = 0.051). The relation between effect size and percentage of female participants was not significant (B = -0.0005, Qmodel = 0.20, p = 0.658).

Publication bias

The funnel plot (Fig. 2) showed that studies tended to cluster at the top, and suggested that studies in smaller sample sizes may have remained unpublished. In addition, the distribution was slightly skewed to the right. Publication bias was corroborated by Egger's test, which indicated a significant funnel plot asymmetry ($B0$ = 1.24, 95% CI [0.24; 2.25], p = 0.009). Duval and Tweedie's trim-and-fill procedure also detected some degree of asymmetry and suggested that imputing 8 studies on the left side of the distribution would decrease the effect size (r = 0.06, 95% CI [0.01; 0.11], which would nonetheless remain significant.

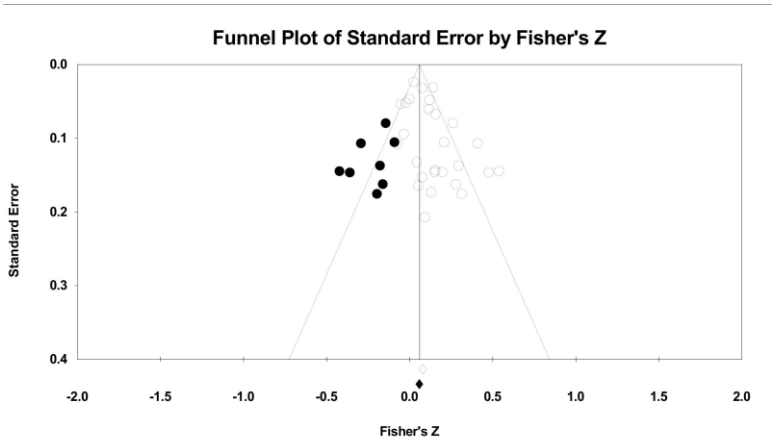

Figure 2. Funnel Plot of the Observed (Open Circles) and Imputed (Filled Circles) Effect Sizes.

Study quality evaluation

No study employed a representative sample. Non-clinical participants, including community dwellers and students, took part in most studies (96.3%), but the absence of psychopathology was confirmed in a minority of these studies (29.6%). All studies included participants with and without CA, but the absence of CA was not documented in several studies (11.1%) that compared between exposed and non-exposed participants. CA assessments employed multiple informants in a minority of studies (29.6%). Most studies (70.3%) used dichotomous measures of CA, where participants were either classified as CA or non-CA based on specific criteria (e.g., checklist answers; continuous ratings dichotomized based on a threshold; official records of CA, coded dichotomously; institutionalization). Most, but not all studies (88.9%) employed validated measures of CA. One study used an RP measure for which validity information could not be found.

3.1.4. Conclusions

We found a consistent association between CA and impaired RP which mirrored the RP alteration in major depressive disorder (Pizzagalli, 2014). Together, these findings lend support to the involvement of RP in the pathway from CA to psychopathology, and suggest it may be an important intervention target.

While the overall effect was small, it was larger and in the medium range in studies that assessed reward learning rather than reward valuation and reward responsiveness. This difference is in line with the pattern of findings in anhedonia, which is characterized by impaired RP in reinforcement learning and decision making rather than hedonic reactivity (Pizzagalli, 2014; Treadway & Zald, 2013).

Other sources of heterogeneity were related to the type of instruments used to assess RP and CA. The effect size was larger in studies that used cognitive tasks rather than self-report measures of RP. The effect size was also larger in studies that relied on objective CA records rather than subjective reports. We also hypothesized that developmental stage at the time of study may influence the effect size, but failed to find a difference when studies were contrasted based on age categories roughly corresponding to adolescence and adulthood.

The assessment of study quality indicated that the use of non-representative samples, failure to support the absence of psychopathology in putatively non-clinical participants and the absence of CA in putatively non-exposed participants, as well as the use of unstandardized measures of CA and RP may have contributed to risk of bias in the previous literature. In addition, the limited use of multiple informants and the predominance of dichotomous measures of CA may have also biased effect sizes. Using continuous rather than dichotomous measures would allow for the assessment of the level of CA exposure, and would also be

instrumental in investigating the potential moderator role of multiple CA features such as chronicity and developmental stage (Smith & Pollak, 2020). While still in its early stages, current work offers consistent evidence for the relation between CA and impaired RP as indexed by self-report and behavioral outcomes.

Study 2. Childhood Adversity and Psychopathology. The Mediating Role of Reward Processing

3.2. Study 2a. The Mediating Role of Reward Processing in the Association Between Childhood Adversity and Psychopathology

3.2.1. Introduction

Mental disorders are one of the leading causes of nonfatal burden of disease and are associated with enormous costs (Whiteford et al., 2013). They are highly prevalent (Rehm & Shield, 2019) and have become a major public health concern (Patel et al., 2007; Ustün, 1999). These conditions have high comorbidity rates (Kessler et al., 2011), and may have common underlying risk factors. Investigating such risk factors may have important implications in mental disorders' prevention (Ebert & Cuijpers, 2018) and treatment regimens (Danese, 2020) and may decrease associated costs (Demyttenaere et al., 2004).

One of the most prevalent risk factors for mental disorders (e.g., Bellis et al., 2014; Schlossberg et al., 2010) is CA (e.g., Cicchetti & Toth, 2005). It is associated with various mental disorders (Kessler et al., 2010; for detailed reviews see Cicchetti, 2016; McCrory, & Viding, 2015; McLaughlin et al., 2010), including depressive disorders (Li et al., 2016; Nelson et al., 2017), addictions (Cicchetti & Handley, 2019; Halpern et al., 2018), eating disorders (Molendijk et al., 2017; Monteleone et al., 2017; Monteleone et al., 2019), personality disorders (Battle et al., 2004; Cohen et al., 2005; Hock et al., 2018), as well as highly heritable disorders, such as bipolar disorders (Aas et al., 2020; Hosang et al., 2018). Still, CA tends to be more frequent in low socioeconomic communities (McLaughlin et al., 2011) and low childhood socioeconomic status (SES) has also been associated with mental disorders (McLaughlin et al., 2011; Romens et al., 2015). Thus, clarifying these associations and identifying mechanisms involved in the association between CA and mental disorders is warranted. While such mechanisms remain largely unknown, recent data hint that reward processing is a promising candidate (e.g., Gerin et al., 2019).

Evidence for this hypothesis stem from studies investigating CA and reward processing (e.g Boecker et al., 2014; Dillon et al., 2009) indicating that distinct reward processing dimensions have distinct associations with CA. A distinct line of research investigates reward processing and mental disorders (e.g., Anderson, 2021; Berry et al., 2019; Eshel & Roiser, 2010; Treadway & Zald, 2013; Whitton et al., 2015) and, mirroring associations between CA and reward processing dimensions, suggests that impairments within these dimensions may vary by mental disorder. Evidence supporting this hypothesis is highlighted below.

Reward processing impairments are well documented in depression (for a review, see Halahakoon et al., 2020; see also Keren et al., 2018) and tend to vary by reward processing dimension (Borsini et al., 2020). In line with this view, most data suggest decreased reward responsiveness (Keren et al., 2018) and learning (Borsini et al., 2020), while the association with reward valuation is less clear. Likewise, while reward processing impairments are well established in bipolar disorders (for a review, see Alloy et al., 2016), they contrast those documented in depression. Bipolar patients exhibit increased reward responsiveness (Alloy et al., 2016), learning (Whitton et al., 2015) and valuation (Nusslock et al., 2014).

Similar patterns of reward processing impairments have been documented in addictions (for a review, see Luijten et al., 2017; see also Owens et al., 2019) and are characterized by

positively biased valuation, especially in addiction-related cues (Diekhof et al., 2008), and learning impairments (Baskin-Sommers & Foti, 2015). Findings on reward responsiveness in addictions are less consistent. Reward processing impairments documented in eating disorders resemble those reported in addictions (Joranby et al., 2005): increased reward valuation (Steward et al., 2017) coupled with decreased learning (Neuser et al., 2020) have been reported in these conditions, while reward responsiveness impairments are unclear (Olsavsky et al., 2019). Finally, recent data suggest such impairments may emerge in personality disorders as well (e.g., Berenson et al., 2020), especially in borderline personality disorder (e.g., Fulford et al., 2015). Reward valuation impairments mirroring those documented in bipolar disorders (Nusslock et al., 2014), addictions (Diekhof et al., 2008) and eating disorders (Steward et al., 2017), are best documented in borderline patients (Paret et al., 2017).

In this study, we aimed to investigate associations between CA, reward processing dimensions, and psychopathology (i.e., depressive symptoms, manic symptoms, alcohol abuse symptoms, emotional eating, borderline personality traits). Moreover, we aimed to investigate childhood SES and its link with these variables. Finally, we aimed to test the potential mediating role of distinct reward processing dimensions in the association between CA and psychopathology.

3.2.2. Methods

Sample

The sample consisted of 1048 adults (*m* = 25.24; *SD* = 5.34, 84,4% female participants). Eligible participants were aged between 18 and 35 and were recruited online.

Measures

Sociodemographic Variables

We collected data on sociodemographic variables, including age, gender and education. Consistent with recent guidelines (McLaughlin et al., 2011; Pollak & Wolfe, 2020), we constructed a SES scale and computed an overall childhood SES score.

Childhood Adversity

We assessed CA using The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997). In line with recent data that indicate CA experiences generally co-occur (Smith & Pollak, 2020), we computed an overall CA score.

Depressive symptoms

We assessed depressive symptoms using a self-report screening measure: The Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001).

Manic Symptoms

We evaluated lifetime manic symptoms using the 7 Up subscale of the 7 Up 7 Down Inventory (Youngstrom et al., 2013).

Alcohol Abuse Symptoms

We chose to evaluate alcohol abuse symptoms, given that it is among the most prevalent addictions (Bahji et al., 2019), and we utilized the Alcohol Dependence Scale (ADS; Skinner & Allen, 1982).

Emotional Eating

Emotional eating is associated with eating disorders (Lindeman & Stark, 2001) and may precede these conditions (Turton et al., 2017). We evaluated it using the subscale of the 18-item revised version of the Three Factor Eating Questionnaire (TFEQ-R18; Karlsson et al., 2000).

Borderline Personality Traits

We evaluated borderline personality disorder symptoms using the McLean screening instrument for Borderline Personality Disorder (MSI-BPD; Zanarini et al., 2003).

Reward Processing

Given that reward learning, responsiveness and valuation have been conceptualized as distinct dimensions of reward processing, we evaluated these constructs separately. We assessed reward responsiveness using The Reward Responsiveness subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS; Carver & White, 2004) and reward learning using The Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; Ball & Zuckerman, 1990; NIMH, 2016). We evaluated reward valuation using The Drive Subscale of the BIS/BAS (Carver & White, 2004) and The Monetary Choice Questionnaire (MCQ; Kirby et al., 1999).

3.2.3. Results

Descriptive Statistics and Associations Between Variables of Interest

Table 1 indicates descriptive statistics for all variables of interest. On average, participants were above the cut-off score for moderate depression (Kroenke, Spitzer, & Williams, 2001).

Table 1. *Correlation matrix and descriptive statistics*

	ch-SES	CTQ	BAS rew	Grapes	BAS drive	MCQ	PHQ-9	7 Up	ADS	TFEQ	*m*	*SD*
ch-SES	1										12.357	2.241
CTQ	-.248**	1									42.517	15.818
BAS rew	.003	-.152**	1								17.856	2.104
Grapes	.035	-.125**	.236**	1							7.313	3.162
BAS drive	-.012	-.096**	.410**	.413**	1						11.443	2.324
MCQ	-.084**	-.033	.053	.048	.110**	1					0.054	0.076
PHQ-9	-.086**	.307**	-.111**	-.332**	-.118**	.035	1				10.378	6.325
7 Up	-.008	.016	.207**	.328**	.241**	.121**	.155**	1			8.723	4.536
ADS	.033	.174**	-.017	-.042	.018	.010	.288**	.176**	1		4.049	4.777
TFEQ	.030	.096**	.041	-.068*	-.139**	-.029	.252**	.124**	.139**	1	6.187	2.692
MSI-BPD	-.130**	.368**	-.061*	-.254**	-.040	.054	.666**	.198**	.361**	.255**	4.531	2.721

Note: ** $p < 0.01$ (2-tailed); * $p < 0.05$ (2-tailed)
SES-ch = Socio-economic status during childhood (based on McLaughlin et al.. 2011; Pollak & Wolfe. 2020); CTQ = Childhood Trauma Questionnaire (Bernstein et al.. 1997); BAS rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; Grapes = Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman. 1990); BAS drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; MCQ = The Monetary Choice Questionnaire (Kirby et al.. 1999); PHQ-9 = The Patient Health Questionnaire-9 (Kroenke et al.. 2001); 7 Up = the 7 Up subscale of the 7 Up 7 Down Inventory (Youngstrom et al.. 2013); ADS = Alcohol Dependence Scale (Skinner & Allen. 1982); TFEQ = Three Factor Eating Questionnaire (Karlsson et al.. 2000); MSI-BPD = McLean screening instrument for Borderline Personality Disorder (Zanarini et al.. 2003).

The mediating role of reward processing in the associations between CA and psychopathology

We tested mediation models for measures of CA, reward processing and psychopathology that exhibited significant association (see Table 1; see Table 2).

Table 2. *The mediating role of reward processing in the associations between CA and psychopathology*

	Variables	Paths	*b*	*SE*	*LLCI*	*ULCI*	*t*	*F*model	R^2
Y =	PHQ-9	a	-.020	.004	-.028	-.012	-4.963	24.636	.023
X =	CTQ	b	-.198	.089	-.374	-.023	-2.221	57.148	.099
M =	BAS rew	c	.123	.112	.099	.146	10.438	108.956	.094
		c'	.119	.012	.095	.142	10.000		
		IE	**.004**	**.002**	**.0002**	**.008**			
Y =	PHQ-9	a	-.025	.006	-.037	-.012	-4.070	16.565	.016
X =	CTQ	b	-.596	.056	-.707	-.485	-10.564	116.032	.182
M =	Grapes	c	.123	.012	.099	.146	10.438	108.956	.094
		c'	.108	.011	.086	.130	9.571		
		IE	**.015**	**.004**	**.007**	**.023**			
Y =	PHQ-9	a	-.014	.005	-.023	-.005	-3.130	9.794	0.009
X =	CTQ	b	-.244	.080	-.401	-.087	-3.043	59.538	.102
M =	BAS drive	c	.123	.012	.099	.146	10.438	108.956	.094
		c'	.119	.012	.096	.143	10.137		
		IE	**.004**	**.002**	**.001**	**.008**			
Y =	TFEQ	a	-.025	.007	-.038	-.012	-3.842	9.523	.016
X =	CTQ	b	-.048	.028	-.104	.007	-1.705	5.645	.012
M =	Grapes	c	.016	.006	.005	.027	2.892	8.363	.009
		c'	.015	.006	.004	.026	2.655		
		IE	**.001**	**.001**	**-.0003**	**.003**			
Y =	TFEQ	a	-.016	.005	-.026	-.007	-3.357	11.268	.012
X =	CTQ	b	-.151	.038	-.226	-.075	-3.2917	11.921	.026
M =	BAS drive	c	.016	.006	.005	.027	2.892	8.363	.009
		c'	.014	.006	.003	.025	2.892		
		IE	**.002**	**.001**	**.001**	**.005**			
Y =	MSI-BPD	a	-.020	.004	-.028	-.012	-4.963	24.636	.023
X =	CTQ	b	-.007	.038	-.081	.067	-0.191	81.744	.135
M =	BAS rew	c	.063	.005	.053	.073	12.608	163.604	.135
		c'	.063	.005	.053	.073	12.608		
		IE	**.0001**	**.0008**	**-.001**	**.002**			
Y =	MSI-BPD	a	-.025	.006	-.037	-.012	-4.070	16.565	.016
X =	CTQ	b	-.182	.024	-.229	-.134	-7.476	111.044	.179
M =	Grapes	c	.063	.005	.053	.073	12.791	163.604	.135
		c'	.058	.005	.049	.068	12.086		
		IE	**.005**	**.001**	**.002**	**.007**			

Note: CTQ = Childhood Trauma Questionnaire (Bernstein et al.. 1997); BAS rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; Grapes = Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman. 1990); BAS drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; PHQ-9 = The Patient Health Questionnaire-9 (Kroenke et al.. 2001); TFEQ = Three Factor Eating Questionnaire (Karlsson et al.. 2000); MSI-BPD = McLean screening instrument for Borderline Personality Disorder (Zanarini et al.. 2003).

3.2.4. Conclusion

CA is one of the most important risk factors for psychopathology (e.g., Bellis et al., 2014; Schlossberg et al., 2010), but other variables, such as childhood SES (McLaughlin et al., 2011), may also be associated with the two. Moreover, mechanisms linking CA and psychopathology are largely unknown. Yet, recent data suggest reward processing may be a promising transdiagnostic mechanism linking CA with psychopathology (e.g., Gerin et al., 2019). Given that this is the first empirical research aiming to simultaneously probe for specific pathways linking CA and psychopathology through distinct reward processing dimensions, while they do build on existing literature, study results are novel and have important theoretical and clinical implications, as highlighted below.

We found that CA is associated with increased depressive symptoms, alcohol abuse symptoms, as well as emotional eating and borderline personality traits, adding support for CA being a transdiagnostic risk factor for psychopathology (e.g., Bellis et al., 2014; Schlossberg et al., 2010), while we did not find an association between CA and manic symptoms.

Consistent with earlier work (McLaughlin et al., 2011), we found that low CA was associated with higher childhood SES, suggesting that adverse experiences tend to be less frequent in high SES environments. In addition, it has been argued childhood SES may be associated with psychopathology (McLaughlin et al., 2011). In this study, we only found partial support for this hypothesis, with childhood SES being associated with depressive symptoms and borderline personality traits, but not with manic symptoms, alcohol abuse symptoms or emotional eating.

Consistent with our meta-analytical findings, we found that while CA was associated with reward processing, associations varied by reward processing dimension. While we found associations between CA and all three reward processing dimensions, associations were stronger for reward responsiveness and learning. In addition, when measured with the MCQ (Kirby et al., 1999), the association between CA and reward valuation did not reach significance. It is possible that the type of reward (i.e., non-monetary vs. monetary) may have influenced these associations (e.g., Estle et al., 2007).

In addition, an opposite trend emerged for associations between childhood SES and reward processing: the association between these variables reached significance only for reward valuation as measured with the MCQ (Kirby et al., 1999). We cautiously suggest that it is possible that the type of reward (i.e., non-monetary vs. monetary) or the reward processing dimension, including specific processes underlying it (e.g., effort vs. delay), may have impacted on these associations. Finally, while changes within the reward processing may follow low childhood SES (Romens et al., 2015), it has been argued that CA, including stress, may explain these changes (Ursache & Noble, 2016). Given that while CA is associated with all three reward processing dimensions, childhood SES is not, we suggest that our findings are in line with this view.

Furthermore, several patterns of associations between reward processing and psychopathology emerged. Adding support for reward processing impairments in depression (Halahakoon et al., 2020), we found associations between all three reward processing dimensions (except for reward valuation as measured with the MCQ; Kirby et al., 1999) and depressive symptoms. Furthermore, we found associations between all three reward processing dimensions and manic symptoms, supporting existing work indicating that increased reward responsiveness (Alloy et al., 2016), learning (Whitton et al., 2015) and valuation (Alloy et al., 2008) predict symptom severity of manic and hypomanic episodes (Alloy et al., 2008).

Contrasting prior work (Luijten et al., 2017; Owens et al., 2019, we did not find any associations between alcohol abuse symptoms and reward processing. Reward processing impairments are most evident in addiction related-stimuli (Diekhof et al., 2008), but we focused on general stimuli. This methdological choice may explain our findings. Moreover, extending

previous work (Neuser et al., 2020; Olsavsky et al., 2019), we found associations between emotional eating and reward learning and valuation (except for reward valuation as measured with the MCQ; Kirby et al., 1999), but not responsiveness. Finally, adding support for reward responsiveness and learning impairments in borderline personality traits (e.g., Vega et al., 2013), we found associations between borderline personality traits and these dimensions, but not reward valuation.

One of the most important findings of this study pertains to the potential mediating role of reward processing in the association between CA and psychopathology. We found that all three reward processing dimensions mediated the association between CA and depressive symptoms, but not manic symptoms. In addition, while we did not find support for reward processing mediating the association between CA and alcohol-abuse symptoms, we suggest that future research using addiction-related cues may clarify this hypothesis. Furthermore, we found that reward valuation, but not responsiveness, nor learning, mediated the association between CA and emotional eating. Finally, we found that reward learning, but not reward responsiveness, nor valuation, mediated the association between CA and borderline personality traits. This hypothesis has been seldom studied, given that existing data on reward processing impairments, especially in processes involved in reward responsiveness and learning (Paret et al., 2017) and borderline personality is scarce. Thus, our findings are novel.

While these findings are unique and may inform treatment, they should be considered in the light of several study limitations. First, considering the cross-sectional design, temporal precedence cannot be established and using longitudinal designs in future studies would be useful. Second, given that we measured CA retrospectively and used only self-report measures for all variables of interest, it may be useful to investigate these associations using multiple types of measures. Finally, given that our sample consisted of mainly women, generalizing results may be difficult and future studies should be conducted in other populations.

Nonetheless, the study has relevant theoretical and clinical implications. Our findings indicate that CA is an important risk factor for psychopathology, and help clarify the association between CA and childhood SES, childhood SES and psychopathology, as well as associations between these variables and reward processing. Moreover, they add to existing efforts aimed at identifying underlying mechanisms for CA and psychopathology singling out reward processing.

3.3. Study 2b. Childhood Adversity, Reward Processing and Depression

3.3.1. Introduction

Depression is one of the most common mental health conditions (Ebert & Cuijpers, 2018; Liu et al., 2019; Richards, 2011) and is associated with tremendous social and individual costs (Biesheuvel-Leliefeld et al., 2016), which are exacerbated by symptom severity (Richards, 2011). Thus, the scientific community has been keen on investigating potential risk factors that may be implicated in its etiology.

One of the most important environmental risk factors for depression is childhood adversity (i.e., CA; Schlossberg et al., 2010; Nelson et al., 2017; Humphreys et al., 2020), which predicts illness course (Li et al., 2016; Nanni et al., 2012), symptom onset and severity (Hovens et al., 2012), as well as treatment response (Nanni et al., 2012; Toth et al., 2020). While identifying potential mechanisms underlying the association between CA and depression may have important implications for treatment (Danese, 2020), these mechanisms remain largely unknown (Gerin et al., 2019). Reward processing is one such mechanism (Harms et al., 2019), despite apparently inconsistent findings reported across studies (e.g., Goff et al., 2013; Hanson et al., 2015). Likewise, threat processing (Gerin et al., 2019), the ability to detect and respond to negative stimuli (i.e., punishment; Gerin et al., 2019), may be another promising

candidate, but its potential implications have been seldom studied (Craske, 2012; Dillon et al., 2014).

Yet, considering that distinct features of depression may be related to different reward and/or threat processing impairments (Medeiros et al., 2020), investigating these potential mechanisms is important. Furthermore, other variables, such as childhood socioeconomic status (SES) may impact on these associations (Gerin et al., 2019).

Building on these, we aimed to investigate the association between CA, reward processing, threat processing, and depressive symptoms among clinically depressed individuals. Also, we aimed to investigate the potential mediating role of both reward and threat processing in the association between CA and depressive symptoms. Finally, we aimed to explore the aforementioned associations while controlling for childhood SES.

3.3.2. Methods

Sample

We recruited a sample ($N = 33$) of inpatients (over 18; $m = 48.36$; $SD = 11.76$) with a formal diagnosis of major depressive disorder (i.e., MDD).

Measures

Sociodemographic Variables

We collected data on sociodemographic variables, including age and gender. Also, we constructed a childhood SES scale with acceptable internal consistency (Cronbach's $\alpha = .67$).

Childhood Adversity

We used a 28 items self-report measure of CA, The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997). The CTQ exhibits good psychometric properties (Bernstein et al., 1997) and displayed good internal consistency in our study (Cronbach's $\alpha = .93$).

Depression

We used both objective (formal diagnosis) and subjective measures of depression (a self-report measure, the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001). The PHQ-9, exhibits good reliability and validity (Levis et al., 2019; Sun et al., 2020), has been previously used in clinically depressed inpatients (Sun et al., 2020) and had adequate internal consistency in our study (Cronbach's $\alpha = .64$).

Reward Processing

We assessed reward processing using the Behavioural Activation System Subscale of the Behavioral Inhibition System and Behavioural Activation System Scales (BIS/BAS; Carver & White, 2004), which exhibited good internal consistency in our sample (Cronbach's $\alpha = .84$).

Reward Responsiveness

We used The Reward Responsiveness subscale of the BIS/BAS (Carver & White, 2004) to evaluate reward responsiveness. The subscale displayed acceptable internal consistency (Cronbach's $\alpha = .65$).

Reward Learning

We evaluated reward learning using The Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; Ball & Zuckerman, 1990; NIMH, 2016). In this study, the subscale had adequate internal consistency (Cronbach's $\alpha = .79$).

Reward Valuation

We used The Drive Subscale of the BIS/BAS (Carver & White, 2004) to evaluate reward valuation, which exhibited acceptable internal consistency on this sample (Cronbach's $\alpha = .66$).

Threat Processing

We evaluated threat processing using two distinct measures: the Behavioral Inhibition System subscale of the BIS/BAS (Carver & White, 2004) and the Punishment Expectancy

subscale of the GRAPES (Ball & Zuckerman, 1990). While the BIS had somewhat acceptable internal consistency in this study (Cronbach's α = .51), the Punishment Expectancy subscale displayed unacceptable internal consistency (Cronbach's α = .35).

3.3.3. Results

Descriptive Statistics

Table 1 indicates descriptive statistics for all variables. Notably, the mean score for depressive symptoms was above the cut-off score for severe depression (Kroenke et al., 2001). Moreover, in this sample, the mean score for CA was above the 95th percentile (Scher et al., 2001).

Table 1. *Descriptive statistics*

	Minimum	Maximum	Mean	SD
PHQ	10.00	26.00	20.58	3.79
CTQ	25.00	97.00	58.27	22.63
BAS	17.00	48.00	34.37	8.51
BAS-drive	5.00	16.00	10.57	3.09
BAS-rew	5.00	20.00	13.50	3.77
Grapes-rew	0.00	12.00	4.16	3.18
BIS	15.00	28.00	24.43	3.07
SES-ch	7.00	16.00	11.45	2.06
Age	26	79	48.36	11.76

Note: CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); PHQ = Patient Health Questionnaire (Kroenke et al., 2001); BAS = Behavioural Activation System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BIS = Behavioural Inhibition System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); SES-ch = Socioeconomic Status during childhood

Associations Between Variables of Interest

Associations between variables of interest are presented in Table 2, with associations controlling for childhood SES being presented in Table 3.

Table 2. *Correlation matrix*

	PHQ	BAS	BAS-drive	BAS-rew	Grapes-rew	BIS	SES-ch
CTQ	.436*	.156	.061	.095	-.013	.462*	.065
PHQ	1	.142	.184	-.106	.033	.412*	.234
BAS		1	.871**	.881**	.450*	.081	.300
BAS-drive			1	.653**	.434*	-.027	.298
BAS-rew				1	.252	.010	.174
Grapes-rew					1	-.099	.629**
BIS						1	-.112

Note: ** $p < 0.01$ (2-tailed); * $p < 0.05$ (2-tailed)
CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); PHQ = Patient Health Questionnaire (Kroenke et al., 2001); BAS = Behavioural Activation System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-drive = Reward Drive subscale of The

Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BIS = Behavioural Inhibition System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); SES-ch = Socioeconomic Status during childhood.

Table 3. *Partial correlations – controlling for childhood SES*

	PHQ	BAS	BAS-drive	BAS-rew	Grapes-rew	BIS
CTQ	.396*	.116	-.008	.043	-.070	.441*
PHQ	-	.007	.041	-.252	-.204	.422*
BAS		-	.854**	.873**	.310	.069
BAS-drive			-	.615**	.272	-.062
BAS-rew				-	.117	-.033
Grapes-rew					-	-.105

Note: ** $p < 0.01$ (2-tailed); * $p < 0.05$ (2-tailed)
CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); PHQ = Patient Health Questionnaire (Kroenke et al., 2001); BAS = Behavioural Activation System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BIS = Behavioural Inhibition System subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994)

The Mediating Role of Reward Processing in the Association Between CA and Depression

We found no evidence that reward processing may partially explain the links between CA and depression.

The Mediating Role of Threat Processing in the Association Between CA and Depression

The regression analysis testing the potential mediating role of threat processing in the association between CA and depressive symptoms indicated that there is total effect of CA on depressive symptoms ($b = 0.07$, $SE = 0.03$, CI [0.02; 0.13]). We did not find a significant indirect effect ($b = 0.02$, $SE = 0.01$, CI [-0.02; 0.08]) and the direct effect remained significant ($b = 0.06$, $SE = 0.03$, CI [0.004; 0.12]).

3.3.4. Conclusions

Replicating previous findings indicating CA is associated with depression (e.g., Humphreys et al., 2020; Nelson et al., 2017; Schlossberg et al., 2010), we found a significant association between these variables. Contrary to our expectations, we did not find any significant associations between CA and reward processing, nor between CA and distinct reward processing dimensions. Possible explanations include relying on self-report measures, sample characteristics (symptom severity) and sample size (i.e., the study may be underpowered). Likewise, no associations between reward processing, its dimensions and depression emerged. While methodological choices (i.e., relying on self-report measures) may explain our findings, an alternative explanation is that sample characteristics (i.e., mixed symptoms; Cheng et al., 2007) may have impacted on them, considering that distinct symptoms displayed by depressive inpatients may have specific patterns of associations with reward and threat alterations (Medeiros et al., 2020).

Adding indirect support for this view, we found an association between CA and threat processing. This finding is consistent with work suggesting threat processing impairments follow CA (Hein & Monk, 2017; Kim et al., 2018; Lange et al., 2019) and it indicates CA is associated with enhanced threat reactivity. Furthermore, adding support for the role of threat alterations in major depression (Hevey et al., 2017; Y. Li et al., 2015; Medeiros et al., 2020; Sportel et al., 2011; Woody & Gibb, 2015), we found a significant association between threat processing and depressive symptoms.

While it has been argued childhood SES may be a confound variable (Gerin et al., 2019) influencing these associations, we did not find support for this view. Instead, when controlling for childhood SES, all significant associations remained stable, and no other significant associations emerged.

In addition, prior findings hint that reward processing may mediate the association between CA and depression (Hanson et al., 2015; Harms et al., 2019), but we did not find support for this claim. Likewise, we did not find support for the potential mediating role of threat processing either.

This study has several limitations pertaining to its cross-sectional design, sample size and characteristics (i.e., mostly women, poor childhood SES), measures. Therefore, we suggest that future research would benefit from investigating these hypothesis using longitudinal designs, larger samples and other populations. Moreover, it would be useful if both subjective and objective measures may be used, given that they are only modestly correlated with each other (e.g., reward processing; Kujawa & Burkhouse, 2017).

Nonetheless, the study has several important theoretical and clinical contributions, as it adds to existing work on CA and depression, as well as mechanisms underlying this association. We did not find support for reward processing, nor threat processing mediating this association. Still, our results are novel and partially support the view that distinct depressive symptoms may be differentially associated with reward and threat processing impairments (Medeiros et al., 2020). Finally, they provide preliminary support for investigating threat processing in this population, given that it is associated with both CA and depressive symptoms.

3.4. Study 2c. An RDoC Approach to Childhood Adversity, Reward Processing and Health, during the COVID-19 Outbreak. The Mediating Role of Reward Learning[2]

3.4.1. Introduction

Childhood adversity (CA) is a lifelong risk factor for various health problems (Anda et al., 2009; Bellis et al., 2014; Felitti et al., 1998; Norman et al., 2012) pertaining to mental problems and physical health problems (Janson, 2018; Sethi et al., 2018). While these conditions have high comorbidity rates (Groen et al., 2020; Kessler et al., 2010; Scott et al., 2007), suggesting common underlying mechanisms (Fisher et al., 2015), such mechanisms are largely unknown. Yet, reward processing may be an important one, given that it appears to have implications in physical health problems (Dutcher & Creswell, 2018; Nusslock & Miller, 2016), in addition to mental health problems (Rizvi et al., 2021).

[2] This study has been published.
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Reward processing impairments following CA have been documented in our meta-analysis. Likewise, such impairments are documented in depressive (Eshel & Roiser, 2010; Fischer et al., 2019; Luking et al., 2016; Proudfit, 2015) and anxiety disorders (Dillon et al., 2014; Hu, 2018), but existing data is heterogeneous and the potential link with physical health is insufficiently studied (Nusslock & Miller, 2016). Still, these associations may vary by reward processing dimension, in line with our previous findings (see Study 2a). Yet, another explanation is that other variables, such as recent stressful events and their psychological impact (Hanson et al., 2017), may impact on these associations.

Consistent with these data, we aimed to investigate associations between CA, RP dimensions, psychological impact of COVID-19 and health (i.e., mental and physical health). Given that depression and anxiety have high prevalence (Bandelow &Michaelis, 2015; Lim et al., 2018) and comorbidity rates (Groen et al., 2020) and appear to be common responses during the COVID-19 outbreak (Rajkumar, 2020), we focused on these symptoms as mental health indicators. We sought to investigate the potential mediating role of distinct RP dimensions in the association between CA and distinct health indicators, and to probe the potential moderating role of the psychological impact of COVID-19 for the mediating role of RP. Finally, we aimed to test the moderating role of CA in the relationship between the psychological impact of COVID-19 and health.

3.4.2. Methods

Sample

A community sample (N = 419) was recruited through online announcements. Most participants were females (88.1%), had at least some high school education (98.81%) and resided in urban areas (80.67%) in Romania (91.89%). Only 1 person reported being sick, while 1.43% reported knowing someone infected with COVID-19. The study began on March 16 2020, the release date of the Decree declaring a state of emergency in Romania. The state of emergency remained active throughout the data collection process that ended on May 5 2020.

Measures

Sociodemographic Variables. Sociodemographic data were collected on age, gender, education, residential location, COVID-19 status. We have also assessed physical health status and asked participants to rate it on a 1 (“poor”) to 5 (“excellent”) Likert point scale.

Childhood Adversity. We assessed CA using The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997). In line with a general approach to CA, we computed a total score for main analyses and performed additional exploratory analyses within alternative approaches (both specific and dimensional approaches).

Reward Processing. In line with recent data distinguishing between reward learning, responsiveness and valuation as different RP dimensions, we evaluated these constructs separately. ***Reward Learning.*** The 15 items Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; Ball & Zuckerman, 1990) was used to assess reward learning (NIMH, 2016). ***Reward Responsiveness.*** The Reward Responsiveness subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS; Carver & White, 1994) was used to evaluate reward responsiveness. ***Reward Valuation.*** The Drive Subscale of the BIS/BAS was used to assess reward valuation (Carver & White, 1994).

Mental Health Status: Depressive and Anxiety Symptoms. The depression and anxiety subscales of the Depression Anxiety Stress Scales-21 (DASS-21; Lovibond & Lovibond, 1995) were used to assess mental health status. DASS-21 has good internal consistency (Antony et al., 1998), and has been previously used in research investigating mental health status during the COVID-19 pandemic outbreak (Wang et al., 2020).

Psychological Impact of COVID-19. The Impact of Event Scale-Revised (IES-R; Christianson & Marren, 2012) was used to assess the psychological impact of COVID-19. Given that we were interested in the overall subjective distress of COVID-19, we tailored the scale and calculated a total score for its psychological impact.

3.4.3. Results

Descriptive Statistics

Table 1 indicates descriptive statistics and internal consistency for all variables.

Table 1 *Descriptive Statistics* (*N* = 419)

Variables	Minimum	Maximum	*m*	*SD*	Cronbach's α
Age	18	61	27.32	8.98	
CTQ	25	109	43.68	16.61	.85
BAS-rew	5	20	16.92	2.72	.73
Grapes-rew	0	15	7.23	3.12	.70
BAS-drive	4	16	11.10	2.48	.71
IES-R	0	3.73	1.60	0.71	.90
DASS-D	0	42	14.22	10.19	.84
DASS-A	0	42	12.70	9.68	.82
Physical health	1	5	4.33	0.73	

Note: CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BAS-drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; IES-R = The Impact of Event Scale-Revised adapted for COVID-19 (Weiss & Marmar, 1996); DASS-D = Depression Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS-A = Anxiety Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995).

Associations Between Variables of Interest

Associations between variables of interest are presented in Table 2.

Table 2 *Correlations Between Study Variables*

	CTQ	BAS-rew	Grapes-rew	BAS-drive	IES-R	DASS-D	DASS-A
BAS-rew	-.155**	1					
Grapes-rew	-.109*	.228**	1				
BAS-drive	-.004	.501**	.377**	1			
IES-R	.087	-.053	-.113*	.019	1		
DASS-D	.196**	-.129**	-.155**	-.003	.723**	1	
DASS-A	.186**	-.092	-.170**	.001	.687**	.888**	1
Physical health	-.155**	.156**	.147**	.073	-.247**	-.292**	-.296**

Note: ** $p < 0.01$ (2-tailed); * $p < 0.05$ (2-tailed); CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BAS-drive = Reward Drive subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; IES-R = The Impact of Event Scale-Revised adapted for COVID-19 (Weiss & Marmar, 1996); DASS-D = Depression Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS-A = Anxiety Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995).

The Mediating Role of RP on CA and Health Outcomes

We found that reward learning mediated the associations between CA and depressive symptoms, CA and anxiety symptoms, and CA and physical health. The associations between CA and health outcomes were partially explained by deficits in reward learning and the direct effect of CA remained significant in all models (see Table 3). Reward responsiveness mediated the association between CA and physical health only, while reward valuation did not significantly mediate any association.

Table 3 *The Mediating Role of RP in the Associations Between Childhood Adversity (CA) and Health Outcomes*

Variables		Paths	*b*	*SE*	*LLCI*	*ULCI*	*t*	*F*model	R^2
Y =	DASS-A	a	-.020	.009	-.038	-.002	-2.232	4.985	.011
X =	CTQ	c	.108	.028	.053	.163	3.858	14.885	.034
M =	Grapes-rew	b	-.472	.149	-.765	-.179	-3.172	12.637	.057
		c'	.098	.027	.043	.153	3.531		
		IE	**.016**	**.009**	**.0006**	**.037**			
Y =	DASS-A	a	-.025	.007	-.040	-.009	-3.208	10.292	.024
X =	CTQ	c	.108	.028	.053	.163	3.858	14.885	.034
M =	BAS-rew	b	-.231	.173	-.572	.109	-1.334	8.347	.038
		c'	.102	.028	.046	.158	3.607		
		IE	**.010**	**.010**	**-.005**	**.033**			
Y =	DASS-D	a	-.020	.009	-.038	-.002	-2.232	4.985	0.011
X =	CTQ	c	.120	.029	.062	.178	4.087	16.703	.038
M =	Grapes-rew	b	-.440	.156	-.748	-.132	-2.813	12.447	.056
		c'	.111	.029	.053	.169	3.790		
		IE	**.014**	**.008**	**.0007**	**.034**			
Y =	DASS-D	a	-.025	.007	-.040	-.009	-3.208	10.292	.024
X =	CTQ	c	.120	.029	.062	.178	4.087	16.703	.038
M =	BAS-rew	b	-.377	.181	-.734	-.020	-2.079	10.581	.048
		c'	.110	.029	.052	.169	3.730		
		IE	**.015**	**.010**	**-.0007**	**.040**			
Y =	Physical health	a	-.020	.009	-.038	-.002	-2.232	4.985	0.011
X =	CTQ	c	-.006	.002	-.011	-.002	-3.211	10.314	.024
M =	Grapes-rew	b	.030	.011	.008	.053	2.727	8.956	.041
		c'	-.006	.002	-.010	-.002	-2.920		
		IE	**-.014**	**.009**	**-.034**	**-.0005**			
Y =	Physical health	a	-.025	.007	-.040	-.009	-3.208	10.292	.024
X =	CTQ	c	-.006	.002	-.011	-.002	-3.211	10.314	.024
M =	BAS-rew	b	.036	.013	.010	.062	2.789	9.131	.042
		c'	-.005	.002	-.010	-.001	-2.765		
		IE	**-.021**	**.012**	**-.049**	**-.002**			

Note. Paths: a = effect of X on M; b = effect of M on Y; c = total effect of X on Y; c' = direct effect of X on Y; IE = indirect effect; LLCI and ULCI define 95% Confidence Interval (CI)
DASS-D = Depression Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS-A = Anxiety Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997); Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; Ball & Zuckerman, 1990)

Moderated Mediation Models

We investigated moderated mediation models only for RP dimensions that were significantly associated with CA. No significant moderated mediations emerged (see Table 4).

Table 4. *The Moderating Role of the Psychological Impact of COVID-19 for the Mediation Effect of RP in the Association Between CA and Health Outcomes*

Outcome	**Mediator**	***Index***	***SE***	***95% CI***

				LLCI	*ULCI*
DASS-A	Grapes-rew	0.007	0.005	-0.0002	0.02
	BAS-rew	0.002	0.004	-0.005	0.011
DASS-D	Grapes-rew	0.005	0.004	-0.0003	0.016
	BAS-rew	0.001	0.003	-0.006	0.009
Physical health	Grapes-rew	-0.0002	0.0004	-0.001	0.0005
	BAS-rew	-0.0003	0.0006	-0.001	0.0006

Note: Index = Index of moderated mediation; DASS-A = Anxiety Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS-D = Depression Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); BAS-rew = Reward Responsiveness Subscale of The Behavioural Inhibition System and Behavioural Activation System Scales; Grapes-rew: Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; Ball & Zuckerman, 1990).

The Moderating Role of CA on Psychological Impact of COVID-19 and Health Outcomes

Results indicate that CA did not moderate the association between the psychological impact of COVID-19 and depressive symptoms (see Table 5). Similarly, CA did not moderate the association between the psychological impact of COVID-19 and anxiety symptoms. In contrast, CA significantly moderated the association between the psychological impact of COVID-19 and physical health.

Table 5 *The Moderating Role of CA in the Associations Between Psychological Impact of COVID-19, Anxiety, Depression and Perceived Physical Health*

Outcome	**Model**	***b***	***SE***	***t***	***LLCI***	***ULCI***
DASS-A	Constant	-1.993	2182	-0.913	-6.283	2.295
	IES-R	7.242	1.204	6.014	4.875	9.609
	CTQ	0.005	0.044	0.130	-0.081	0.093
	CTQ*IES-R	0.040	0.023	1.728	-0.005	0.086
DASS-D	Constant	-3.415	2.178	-1.567	-7.698	0.866
	IES-R	8.830	1.202	7.345	6.467	11.194
	CTQ	0.036	0.044	0.810	-0.051	0.123
	CTQ*IES-R	0.027	0.023	1.180	-0.018	0.073
Physical health	Constant	4.561	0.220	20.729	4.128	4.993
	IES-R	0.008	0.121	0.069	-0.230	0.247
	CTQ	0.003	0.004	0.661	-0.005	0.111
	CTQ*IES-R	-0.005	0.002	-2.234	-0.009	-0.0006

Note: DASS-D = Depression Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS-A = Anxiety Subscale of Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); IES-R = The Impact of Event Scale-Revised adapted for COVID-19 (Weiss & Marmar, 1996); CTQ = Childhood Trauma Questionnaire (Bernstein et al., 1997)

3.4.4. Conclusion

In line with previous research (Anda et al., 2009; Cicchetti, 2016; Felitti et al., 1998; Janson, 2018), we found associations between CA and all health indicators. Also, replicating our meta-analytical results, we found associations between CA and RP that varied by RP dimension (learning and responsiveness, but not valuation). We found a similar pattern of results for the association between RP dimensions and health indicators. Our findings mirror prior work suggesting decreased reward responsiveness (Goldstein et al., 2020) and learning (Vrieze et al., 2013) in depression and indicate an inverse association between these RP dimensions and depressive symptoms. Extending limited evidence on reward processing in

anxiety, we found an association between reward learning and anxiety symptoms, but no association between anxiety symptoms and reward responsiveness or valuation. Likewise, we lend support for reward learning and responsiveness in physical health.

To our knowledge, this is the first empirical research to investigate the potential mediating role of reward processing accounting for its dimensions in both mental and physical health. Consistent with previous work (McLaughlin et al., 2019), we found that reward learning mediated the association between CA and depressive symptoms. Similarly, we found that reward learning mediated the link between CA and anxiety symptoms and physical health. Together, these findings suggest that reward learning is a potential transdiagnostic mechanism implicated in these conditions.

Although previous data has suggested reward responsiveness may be a potential mechanism linking CA and health indicators (for review see McCrory & Viding, 2015; Nusslock & Alloy, 2017; Nusslock & Miller, 2016), we did not find a significant indirect effect of reward responsiveness on these associations except for physical health. One possible explanation for these findings is that while most previous studies have used neural measures of reward responsiveness (e.g., Dennison et al., 2017), we used a self-report measure. Furthermore, we did not find support for reward valuation as a potential mechanism, suggesting that its relevance to depressive and anxiety symptoms, and physical health may be limited.

We also investigated whether the psychological impact of COVID-19 moderated any indirect effect of CA on health through RP and found that reward learning remained a significant mediator of the associations between CA and health outcomes irrespective of psychological impact of COVID-19. Reward responsiveness and valuation did not mediate these associations at various levels of COVID-19 related psychological impact.

Finally, we investigated the moderating role of CA between the psychological impact of COVID-19 and health indicators. The results suggest that the associations between the psychological impact of COVID-19 and depressive and anxiety symptoms did not vary based on CA levels. In contrast, the association between the psychological impact of COVID-19 and physical health was more pronounced at high levels of CA. Given that emotional and physical health problems increased following the outbreak (Ran et al., 2020), our results suggest that CA may be an underlying risk factor among individuals experiencing a higher psychological impact of COVID-19 for developing physical health issues but not for anxiety and depressive symptoms.

The study has several limitations which should be considered: 1) its cross-sectional nature, 2) its measures (e.g., relying on self-report measures exclusively and measuring physical health through a single item) and 3) sample characteristics. We suggest that future studies would benefit from investigating this model in longitudinal designs, combining multiple measures and recruiting more gender balanced samples.

While preliminary, these results are promising and have important theoretical and clinical implications. They justify research aiming to design and test interventions targeting reward processing, in reducing depressive and anxiety symptoms (Craske et al., 2016; Young & Craske, 2018) and add to existing work suggesting reward learning impairments may be particularly relevant among individuals with a history of CA (McLaughlin et al., 2019).

Study 3. Reward processing. Mechanism of change

3.5. Study 3a. A randomized clinical trial investigating the effectiveness of two reward processing interventions in an analogue sample

3.5.1. Introduction

Depression and anxiety disorders are the most common mental disorders (Bandelow & Michaelis, 2015; Lim et al., 2018) and are highly comorbid (Groen et al., 2020; Mrazek et al., 2014). Although various effective treatments for these conditions exist, response rates vary and around 50% patients receiving treatment remaining symptomatic (Casey et al., 2013; Loerinc et al., 2015). Targeting underlying mechanisms, such as reward processing, may increase treatment specificity.

Building on these, a few studies have started to investigate interventions aiming to target reward processing and show encouraging results (e.g., Positive Affect Treatment; Craske et al., 2016), as they increase positive affect and decrease negative affect, depressive and anxiety symptoms. Yet, such interventions include numerous strategies (e.g., behavioral and cognitive) and do not test the proposed mechanism of change, nor changes in it following intervention. Therefore, both active ingredients and the potential mediating role of reward processing remain unclear. Moreover, CA may influence treatment outcomes, as well as the proposed mechanism.

Building on these data, we aimed to investigate the effectiveness of two interventions aiming to target reward processing (i.e., behavioral activation and cognitive training) in increasing positive affect and satisfaction with life and reducing negative affect, depressive and anxiety symptoms. Furthermore, we aimed to test changes in reward processing following intervention and to investigate its potential mediating role for these interventions. Finally, we aimed to investigate the potential moderating role of CA for these interventions.

3.5.2. Methods

Sample

The sample (*N*=147) consisted of mostly females (85.7%), residing in urban areas (80.3%) in Romania (94%), with no current or past formal psychiatric diagnosis (76.9%).

Measures

Sociodemographic Variables

We collected sociodemographic data on age, gender, psychiatric status, education, residential location and current occupation.

Childhood Adversity

We evaluated CA using the Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 1997) which exhibited good internal consistency (Cronbach's $\alpha = .92$).

Reward Processing

Reward Learning

We assessed reward learning using The Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (GRAPES; (Ball & Zuckerman, 1990), in line with RDoC guidelines (NIMH, 2016). The scale displayed adequate internal consistency in this study pre (Cronbach's $\alpha = .62$) and post intervention (Cronbach's $\alpha = .67$).

Reward Responsiveness

We evaluated reward responsiveness using The Reward Responsiveness subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS; (Carver & White, 1994). The scale had adequate internal consistency for the Reward

Responsiveness subscale in our sample pre (Cronbach's α = .74) and post intervention (Cronbach's α = .63).

Reward Valuation

We evaluated reward valuation using The Drive Subscale of the BIS/BAS (Carver & White, 1994). The subscale exhibited adequate internal consistency in this study pre (Cronbach's α = .70) and post intervention (Cronbach's α = .73).

Depressive and Anxiety Symptoms

We assessed depressive and anxiety symptoms using The depression and anxiety subscales of the Depression Anxiety Stress Scales-21 (DASS-21; Lovibond & Lovibond, 1995). In our sample, both subscales displayed good internal consistency (Cronbach's α = .82 and Cronbach's α = .81 for the depression subscale; Cronbach's α = .72 and Cronbach's α = .81 for the anxiety subscale).

Affect

We evaluated affect using the Positive and Negative Affect Scale (PANAS; Watson et al., 1998). The scale exhibited good internal consistency at baseline (Cronbach's α = .84 for Positive Affect and Cronbach's α = .90 for Negative Affect) and posttest (Cronbach's α = .82 for Positive Affect and Cronbach's α = .93 for Negative Affect).

Satisfaction with Life

We used a brief self-report measure of satisfaction with life: The Satisfaction with Life Scale (SWLS; Diener et al., 1985), which displayed good internal consistency pre (Cronbach's α = .88) and post intervention (Cronbach's α = .86).

Procedure

300 potentially eligible participants were recruited from the community through online announcements. These respondents provided consent and completed an initial online screening survey. Out of them, 147 met the eligibility (i.e., being aged between 18 and 65 and scoring above cut-off scores on the depression and/or anxiety subscale of the Depression, Anxiety and Stress Scales - 21; DASS-21; Lovibond & Lovibond, 1994) and were randomly allocated in one of the three intervention groups: the behavioral activation group (N =50), the cognitive training group (N =49), and the placebo group (N =48). All interventions were delivered online and lasted 4 weeks (8 modules including written and audio content which participants had to fill in, as a measure of treatment adherence). Following intervention, participants completed questionnaires evaluating variables of interest and received written and audio self-help material developed by the research team and/or course credit.

Behavioral Activation Group

The schematic structure of behavioral activation intervention is outlined in Figure 1.

Figure 1. The Schematic Structure of the Behavioral Activation Modules

Cognitive Training Group

Participants allocated in the cognitive training group were administered the active intervention outline below (see Figure 2).

Figure 2. The Schematic Structure of the Cognitive Training Modules

Placebo

We compared the active interventions (i.e., behavioral activation, cognitive training) against an active placebo group (i.e., listing daily events, Emmons & McCullough, 2003; see Figure 3).

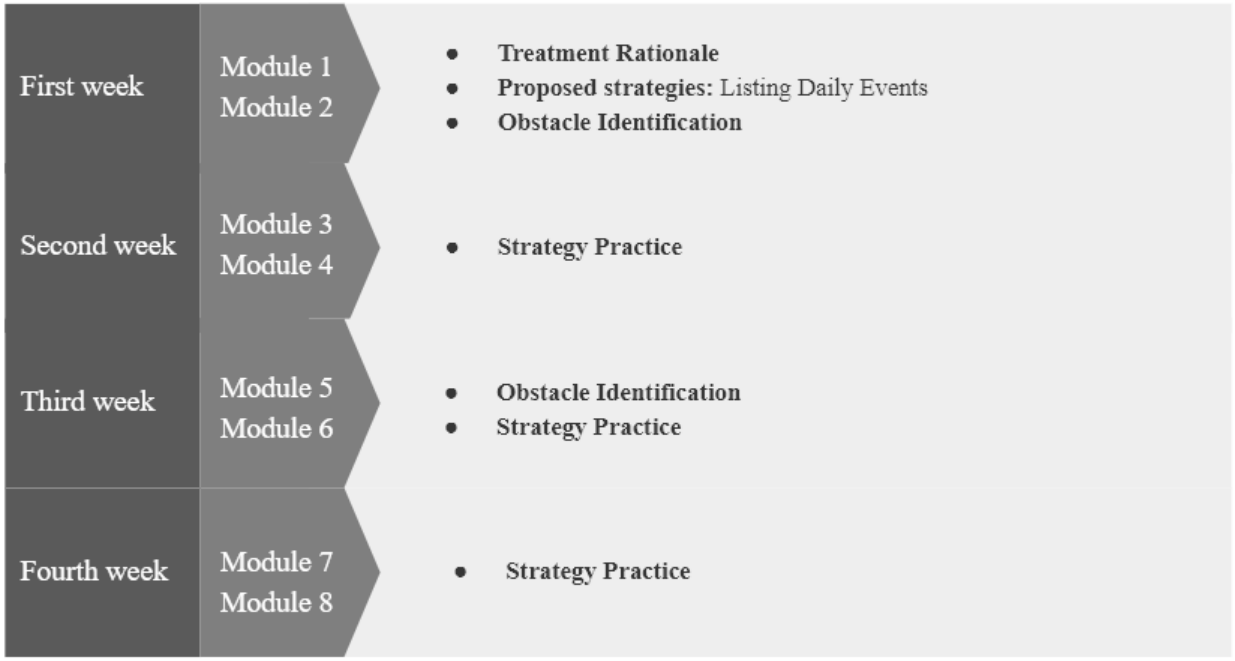

Figure 3. The Schematic Structure of the Placebo Modules

3.5.3. Results

At baseline, there were no statistically significant differences between any of the three groups (see Table 1).

Table 1. Participant demographic and clinical features

	Behavioral activation (*N*=50)		Cognitive training (*N*=49)		Placebo (*N*=48)	
Baseline variables	*m*	*SD*	*m*	*SD*	*m*	*SD*
Age	27,62	10,41	28,33	10,30	26,23	8,01
CTQ	48,60	17,06	50,88	17,65	47,31	16,84
Grapes reward	6,42	2,78	5,82	3,20	7,02	3,26
BAS reward	17,22	2,44	16,29	2,74	16,60	3,65
BAS drive	10,70	2,83	10,65	2,50	11,27	2,77
DASS depression	22,44	10,80	22,69	11,43	22,92	10,64
DASS anxiety	21,08	9,48	21,47	9,90	20,42	9,18
PANAS positive	28,86	7,26	28,67	8,09	30,23	8,04
PANAS negative	28,28	9,86	28,29	9,54	27,23	10,41
SWLS	19,22	6,96	20,31	6,94	21,27	7,61

Note: CTQ - Childhood Trauma Questionnaire (Bernstein et al., 1997); Grapes reward - The Reward Expectancy subscale of The Generalized Reward and Punishment Expectancy Scales (Ball & Zuckerman, 1990); BAS reward - The Reward Responsiveness subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS drive - The Drive Subscale of the Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); DASS depression - The depression subscale of the Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); DASS anxiety - The anxiety subscale of the Depression Anxiety Stress Scales-21 (Lovibond & Lovibond, 1995); PANAS positive - The Positive Affect score of the Positive and Negative Affect Scale (PANAS; Watson et al., 1998); PANAS negative - The Negative Affect score of the Positive and Negative Affect Scale (PANAS; Watson et al., 1998); SWLS - The Satisfaction with Life Scale (Diener et al., 1985)

Main outcomes

ITT (Table 2) and PP analyses yielded similar patterns of results.

Table 2. *The effectiveness of the interventions and moderating role of CA (ITT)*

Outcome	Predictor	Sum of squares	*df*	Mean square	*F*	*p*
Depression	time	298,42	1	298,42	18,86	0,000
	time*group	19,40	2	9,70	0,61	0,543
	time*CA	5,20	1	5,20	0,33	0,567
	time*group*CA	14,48	2	7,24	0,46	0,634
	Error	2231,25	141	15,82		
Anxiety	time	444,89	1	444,89	30,43	0,000
	time*group	19,35	2	9,68	0,66	0,517
	time*CA	9,26	1	9,26	0,63	0,428
	time*group*CA	10,43	2	5,22	0,36	0,701
	Error	2061,40	141	14,62		
Positive affect	time	84,59	1	84,59	8,45	0,004
	time*group	19,96	2	9,98	1,00	0,372
	time*CA	1,58	1	1,58	0,16	0,692
	time*group*CA	4,66	2	2,33	0,23	0,793
	Error	1412,35	141	10,02		
Negative affect	time	95,02	1	95,02	7,58	0,007
	time*group	5,79	2	2,90	0,23	0,794
	time*CA	0,26	1	0,26	0,02	0,887
	time*group*CA	11,74	2	5,87	0,47	0,627
	Error	1766,46	141	12,53		
Satisfaction with life	time	63,90	1	63,90	15,94	0,000
	time*group	13,24	2	6,62	1,65	0,196
	time*CA	6,37	1	6,37	1,59	0,210
	time*group*CA	2,08	2	1,04	0,26	0,772
	Error	565,37	141	4,01		
Reward learning	time	3,87	1	3,87	3,02	0,084
	time*group	4,07	2	2,03	1,59	0,208
	time*CA	1,72	1	1,72	1,34	0,248
	time*group*CA	0,07	2	0,03	0,03	0,974
	Error	180,39	141	1,28		
Reward responsiveness	time	1,50	1	1,50	0,76	0,386
	time*group	0,18	2	0,09	0,05	0,956
	time*CA	0,11	1	0,11	0,06	0,812
	time*group*CA	5,11	2	2,56	1,29	0,278
	Error	279,24	141	1,98		
Reward valuation	time	0,22	1	0,22	0,24	0,625
	time*group	2,43	2	1,22	1,35	0,263
	time*CA	0,37	1	0,37	0,41	0,525
	time*group*CA	1,91	2	0,95	1,06	0,350

Error	127,16	141	0,90

PP

At sample level, positive affect increased over time ($F(1,58) = 12.32$, $p < .001$), but all groups evolved similarly ($F(2,58) = 1.815$, $p = .172$). Similarly, regardless of group ($F(2, 58) = 1.000$, $p = .374$), participants reported an increase in satisfaction with life over time ($F(1, 58) = 17.264$, $p < .001$). Moreover, following intervention, participants reported lower depressive ($F(1, 58) = 19{,}687$, $p < .001$) and anxiety symptoms ($F(1,58) = 39.750$, $p < .001$), but the time*group interaction effect did not indicate any statistically significant differences between the groups on any of these outcomes ($F(2,58) = .564$, $p = .572$ for depressive symptoms; $F(2,58) = 1.539$, $p = .223$ for anxiety symptoms). Finally, we did not find a significant effect of time for negative affect ($F(1,58) = 0.54$, $p = .462$), we did not find a time*group interaction ($F(2,58) = .549$, $p = .581$).

Secondary outcomes

PP

We did not find a significant effect of time for reward responsiveness ($F(1, 58) = 1.025$, $p = .316$), reward learning ($F(1, 58) = 3.99$, $p = .050$) and reward valuation ($F(1, 58) = .184$, $p = .669$). Moreover, we did not find a significant time*group interaction for these secondary outcomes ($F(2, 58) = .056$, $p = .945$ for reward responsiveness; $F(2, 58) = 1.067$, $p = .351$ for reward learning; $F(2, 58) = 1.311$, $p = .278$ for reward valuation).

Mechanism of change

We did not find evidence for reward processing as a potential mechanism of change that may explain the effectiveness of the intervention.

Effect modifiers

Childhood Adversity

Main outcomes

PP

CA did not moderate the effectiveness of the three interventions on any of the main outcomes: positive affect ($F(2,55) = .571$, $p = .568$), satisfaction with life ($F(2,55) = .288$, $p = .751$). negative affect $F(2,55) = .504$, $p = .607$), depressive ($F(2,55) = .04$, $p = .95$) and anxiety symptoms ($F(2,55) = .129$, $p = .879$).

Secondary outcomes

PP

CA did not moderate the effectiveness of these interventions on any of the secondary outcomes: reward responsiveness ($F(2,55) = 1.848$, $p = .167$), reward learning ($F(2,55) = 1.057$, $p = .354$), reward valuation ($F(2,55) = .861$, $p = .428$).

3.5.4. Conclusions

We found that the three groups evolved similarly. A possible explanation for these findings is the nature of the placebo group. Previous meta-analytical data (Gould & Clum, 1993) indicate smaller effect sizes in studies comparing self-help interventions against active placebos. Also, given that all interventions have been administered online, this may influenced our findings. Support for this view stems from work suggesting that unassisted self-help is perceived as less acceptable (e.g., Hanson et al., 2015).

In addition, reward processing remained stable, apparently contrasting previous studies (e.g., Nagy et al., 2020; for a review see Staudinger et al., 2009) reporting changes following cognitive and behavioural strategies. One possible explanation is the type of measure used to evaluate reward processing. Most previous studies (e.g., for a review see Staudinger et al., 2009) employed neural measures of reward processing, but recent critiques suggest that neural

changes may not translate into behavioural changes (Nielson et al., 2021). Thus, we used self-report measures and this methodological choice may explain our findings.

Finally, we investigated the potential moderating role of CA for these interventions, but did not find evidence for this hypothesis. While our findings are different from previous research, one possible explanation is that CA features such as chronicity and intensity may differentially impact on their consequences (Smith & Pollak, 2020). Given that we evaluated experiences of CA and their frequency (i.e., chronicity), but did not measure the perceived intensity of such events it is possible that this may have influenced our findings.

The study has several limitations pertaining to 1) sample characteristics (i.e., analogue sample consisting of mostly women), 2) measures (self-report measures), 3) intervention delivery (unassisted self-help). Future research may investigate these hypotheses on other samples, including clinical ones, and through the use of multiple measures (e.g., behavioral) and delivery methods (e.g., guided support; psychotherapy).

Nonetheless, the study has several relevant contributions too. Although current results indicate that both behavioral and cognitive strategies appear to increase positive affect and satisfaction with life, while decreasing depressive and anxiety symptoms, similar effects may be attributed to an active placebo. Our findings extend previous research investigating these strategies that did not probe for changes in reward processing following intervention, nor test this mechanism of change (Craske et al., 2019). In addition, they account for the potential impact of CA on these interventions.

3.6. Study 3b. Is Reward processing a mechanism of change in gratitude interventions? A randomized control trial[3]

3.6.1. Introduction

Gratitude interventions have promising results, as they appear to reduce depressive symptoms (Dickens, 2017) and negative affect (Jans-Beken et al., 2020) and increase positive affect (Dickens, 2017). While, mechanisms of change for these interventions are largely unknown (Alkozei et al., 2018), it has been argued reward processing may be a promising candidate (Watkins, 2004). Indirect evidence supports this hypothesis: (1) gratitude elicits changes within the reward processing system (DeSteno et al., 2014), (2) interventions aiming to target reward processing which include gratitude show encouraging results (Craske et al., 2016), and (3) positive affect regulation strategies, including gratitude, may impact on the well-established association between reward processing and depressive symptoms (Irvin et al., 2020). Therefore, this hypothesis requires further investigation.

Likewise, although gratitude interventions show promising results, these results are somewhat inconsistent (Davis et al., 2016; Dickens, 2017), indicating that potential moderators may impact on them. One such potential moderator is CA (Toth et al., 2020), which has been documented to impact on treatment response, (Lippard & Nemeroff, 2020; Nanni et al., 2012; Nelson et al., 2017), adherence and drop-out (e.g., Lecomte et al., 2008). While these

[3] This study has been accepted for publication.
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implications for treatment may vary by CA severity and/or chronicity (Smith & Pollak, 2020), this hypothesis has not been investigated yet. Moreover, another potential moderator is trait gratitude (Dickens, 2019). According to the conductance hypothesis (McCullough et al., 2004), gratitude interventions may be more easily administered in high trait gratitude individuals, but this hypothesis requires further investigation too.

Building on these, we aimed to: (1) investigate the effectiveness of a gratitude intervention in reducing depressive symptoms and negative affect and increasing positive affect, (2) assess the impact of the gratitude intervention on reward processing, (3) investigate reward processing as a potential mechanism of change for these interventions, (4) explore differences in adherence and drop-out between these interventions, and (5) investigate the moderating role of two theoretically relevant variables: CA and trait gratitude.

3.6.2. Methods

Sample

Participants (N = 237, M = 27.22, SD = 8.758) were mostly young (M = 27.22, SD = 8.758) women (83.5%) with no current or past formal psychiatric diagnosis (89%) that resided in urban areas (71.8%) in Romania (91.6%).

Measures

Sociodemographic Variables

Sociodemographic data on age, gender, psychiatric status, education, residential location and current occupation were collected for all participants.

Childhood Adversity

We evaluated CA using the Maltreatment Abuse and Exposure Scale (MAES; Teicher & Parigger, 2015), because it evaluates both CA severity (i.e., perceived intensity of adverse events) and multiplicity (i.e., number of distinct adverse events), as opposed to other existing measures that do not allow scoring these two dimensions simultaneously (Teicher & Parigger, 2015).

Reward Processing

We evaluated reward processing using the BAS subscale of The Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS; Carver & White, 1994), which exhibited good internal consistency in our sample (Cronbach's α = .74 – baseline; Cronbach's α = .73 post-test).

Trait Gratitude

We measured trait gratitude using The Gratitude Questionnaire-Six Item Form (GQ-6; McCullough et al., 2004), a brief self-report scale which has exhibited good internal consistency in prior studies (McCullough et al., 2004) and in our sample (Cronbach's α = .83).

Depressive Symptoms

We evaluated depressive symptoms using the Patient Health Questionnaire (PHQ-9; Löwe et al., 2004), which exhibited good internal consistency in our study (Cronbach's α = .87 at baseline; Cronbach's α = .88 posttest).

Affect

We evaluated affect with the Positive and Negative Affect Scales (PANAS; (Watson et al., 1998), which exhibited good internal consistency at baseline (Cronbach's α = .78 for Positive Affect and Cronbach's α = .89 for Negative Affect) and posttest (Cronbach's α = .78 for Positive Affect and Cronbach's α = .92 for Negative Affect).

Procedure

Out of 278 respondents that completed an online consent and initial assessment measures, 237 were allocated in one of the two intervention groups (see Figure 1). Participants allocated in the gratitude intervention group were asked to submit daily journal entries

consisting of three things they were grateful for, while participants allocated in the control condition were asked to submit daily journal entries consisting of three things that happened over the day. For 14 days, irrespective of their experimental condition, all participants received daily email reminders and submitted their journal entries using an online form (as an objective measure of adherence/ drop-out). Following intervention, participants completed an online survey and received compensation.

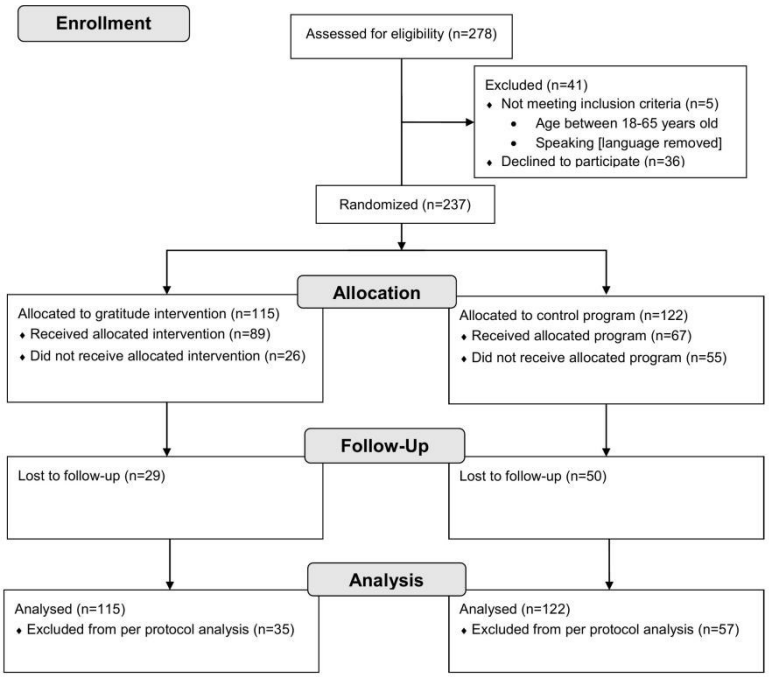

Figure 1. Participant flow (CONSORT)

3.6.3. Results

No statistically significant differences emerged between the two groups concerning baseline characteristics (see Table 1). One hundred and fifty-six of the 237 randomized participants received the intended intervention (i.e., submitted at least 7 journal entries; see Figure 1).

Table 1. *Baseline sociodemographic and clinical characteristics for each group*

Study variables	Gratitude (N = 115)	Control (N = 122)	t test / $\chi 2$	p
Age	26.65 (8.10)	27.76 (9.33)	t = -0.98	.330
Female, % (n)	87.80 (101)	79.5 (97)	$\chi 2$ = 2.98	.084
Residence, % (n)			$\chi 2$ = 0.31	.579
Rural	23.5 (27)	20.5 (25)		
Urban	76.5 (88)	79.5 (97)		
Education, % (n)			$\chi 2$ = 1.28	.527
High school or less	47.0 (50)	48.4 (59)		
Bachelor degree	35.7 (41)	39.3 (48)		
Postgraduate degree	17.4 (20)	12.3 (15)		
Psychiatric diagnosis			$\chi 2$ = 10.19	.006
History	2.6 (3)	8.2 (10)		
Current	9.6 (11)	1.6 (2)		
No diagnosis	87.8 (101)	90.2 (110)		
GQ	32.99 (5.95)	33.10 (6.60)	t = -0.14	.888
PANAS-p	31.93 (6.30)	33.36 (6.39)	t = -1.73	.085
PANAS-n	23.13 (9.60)	22.46 (8.76)	t = 0.56	.579

PHQ9	10.37 (6.77)	8.99 (6.17)	$t = 1.64$	.102
BAS	37.69 (5.70)	38.53 (5.36)	$t = -1.16$	.246
MACE mult	10.09 (11.93)	12.49 (15.31)	$t = -1.29$	.199
MACE sum	17.37 (17.71)	16.10 (15.85)	$t = 0.56$	.577

Note: MACE mult – multiplicity of CA; MACE sum – severity of CA; Group – dummy coded (1 = gratitude); GQ – trait gratitude; PANAS-p – Positive affect; PANAS-n – Negative affect; PHQ9 – depressive symptoms; BAS - reward processing;

Main outcomes

ITT

ITT analyses indicated a statistically significant overall effect of time ($F(1,235) = 6.35$, $p = .009$), but no significant time*group interaction for depressive symptoms ($F(1,235) = 3.55$, $p = .060$). Similarly, participants from both groups reported lower levels of negative affect following program ($F(1,235) = 30.05$, $p < .001$), but the time*group interaction revealed no significant improvements in the gratitude intervention group as compared to control ($F(1,235) = 0.48$, $p = .488$). No significant effect of time ($F(1,235) = 1.147$, $p = .285$) or time*group interaction ($F(1,235) = 2.97$, $p = .086$) was found for positive affect.

PP

PP analyses replicated ITT analyses results for these outcomes. Although depressive symptoms decreased over time at sample level ($F(1,143) = 8.16$, $p = .005$), there were no statistically significant differences between the gratitude intervention and the control group ($F(1,143) = 1.81$, $p = .180$). Similarly, even though participants from both groups reported lower levels of negative affect following program ($F(1,143) = 35.63$, $p < .001$), the time*group interaction did not reveal any statistically significant differences between the groups ($F(1,143) = 0.01$, $p = .973$). No significant effect of time ($F(1,143) = 0.54$, $p = .462$) or time*group interaction ($F(1,143) = 1.98$, $p = .161$) was found for positive affect.

Secondary Outcomes

ITT

Mixed model ANOVAs showed an overall increase in reward processing at the end of the program, as indicated by an increase in scores relative to baseline on BAS ($F(1,235) = 3.99$, $p = .047$). However, time*group interactions suggested that this increase in reward processing over time did not vary by group ($F(1,235) = 0.43$, $p = .510$).

PP

PP analyses replicated previous results of ITT analyses. Reward processing improved over time ($F(1,143) = 4.41$, $p = .037$), but the interaction effect did not suggest a significant benefit for the gratitude intervention over control ($F(1,143) = 1.15$, $p = .284$).

Protocol Adherence and Drop-Out

One way ANOVA indicated that participants from the gratitude condition submitted significantly more journal entries than those from the control condition ($F(1,235) = 15.03$, $p < .001$). There was a significant difference in drop-out between the two programs ($\chi^2 = 13.29$, $p < .001$). Eighty-nine (77.4%) participants allocated in the gratitude intervention completed at least 50% of the protocol, as compared to sixty-seven (54.9%) in the control group.

Mechanism of change

We did not find evidence for reward processing as a potential mechanism of change that may explain the effectiveness of the intervention.

Effect modifiers for main outcomes

CA severity

ITT

CA severity moderated the effectiveness of the two interventions on depressive symptoms (see Table 2). The gratitude intervention was more effective for participants

reporting lower CA severity. The interaction was probed by testing the conditional effects of intervention at three levels of CA severity and the results indicated that the gratitude intervention was more effective than control for participants who reported lower levels of CA severity (*b* = -2.27; 95% *CI* [-4.47;-0.06]), but less effective for those reporting severe CA (*b* = 2.62; 95% *CI* [0.04; 0.24]). No differences in depression scores were found between the two interventions for participants reporting intermediate levels of CA (*b* = -0.80; 95% *CI* [-2.48; 0.88]).

CA severity moderated the effectiveness of these interventions on negative affect. Relative to control, the gratitude intervention had a significantly greater impact on negative affect for participants with low CA severity (*b* = -3.40; 95% *CI* [-6.55; -0.25]), but similar effects for individuals with intermediate (*b* = -1.39; 95% *CI* [-3.79; 1.01]) and high levels of CA severity (*b* = 3.30; 95% *CI* [-0.22; 6.82]).

Table 2. *The moderating role of CA and trait gratitude (ITT analyses)*

Outcome	Model	Predictor	*b*	95% CI	
PHQ9	1	Constant	8.66	7.04	10.27
		Group*	-2.41	-4.68	-0.14
		MACE sum	0.02	-0.06	0.09
		Group x MACE sum*	0.14	0.04	0.27
	2	Constant	8.39	6.86	9.92
		Group	0.45	-1.74	2.64
		MACE mult	0.04	-0.04	0.12
		Group x MACE mult	-0.03	-0.16	0.10
	3	Constant	19.121	3.78	24.46
		Group*	8.91	0.84	16.99
		GQ*	-0.31	-0.47	-0.15
		Group x GQ*	-0.26	-0.50	-0.02
PANAS-n	1	Constant	21.05	18.75	2336
		Group*	-3.59	-6.84	-0.34
		MACE sum	-0.03	-0.13	0.07
		Group x MACE sum*	0.19	0.05	0.33
	2	Constant	19.92	17.78	22.06
		Group	0.61	-2.45	3.68
		MACE mult	0.05	-0.06	0.16
		Group x MACE mult	-0.08	-0.26	0.10
	3	Constant	36.22	28.72	43.71
		Group	1.34	-9.99	12.68
		GQ*	-0.48	-0.69	-0.25
		Group x GQ	-0.04	-0.38	0.30
PANAS-p	1	Constant	31.83	30.07	33.601
		Group	1.88	-0.60	4.37
		MACE sum	0.03	-0.05	0.11
		Group x MACE sum*	-0.11	-0.21	-0.01
	2	Constant	32.09	30.48	33.72
		Group	0.48	-1.82	2.79
		MACE mult	0.02	-0.06	0.10
		Group x MACE mult	-0.04	-0.17	0.10
	3	Constant	21.66	15.83	27.49
		Group	0.23	-8.59	9.06
		GQ*	0.33	0.15	0.50
		Group x GQ	-0.16	-0.28	0.25

Note: *$p \leq .05$

MACE mult –multiplicity of CA; MACE sum –severity of CA; Group – dummy coded (1 = gratitude intervention); PHQ9 – depressive symptoms; PANAS-p – Positive affect; PANAS-n – Negative affect

CA severity moderated the effectiveness of these interventions on positive affect. However, conditional effects did not reveal any significant difference between the two

conditions on positive affect for individuals with either low (*b* = 1.78; 95% *CI* [-0.63; 4.19]), intermediate (*b* = 0.66; 95% *CI* [-1.19; 2.50]) or severe CA (*b* = -1.96; 95% *CI* [-4.65; 0.74]).

PP

PP analyses indicated that CA severity did not significantly moderate the effectiveness of the interventions on depressive symptoms, negative affect, and positive affect (see Table 3).

Table 3. *The moderating role of CA and trait gratitude (PP analyses)*

Outcome	Model	Predictor	*b*	95% CI	
PHQ9	1	Constant	7.05	4.90	9.21
		Group	-1.14	-3.90	1.61
		MACE sum	0.03	-0.06	0.12
		Group x MACE sum	0.06	-0.05	0.17
	2	Constant	6.81	4.87	8.76
		Group	0.18	-2.38	2.74
		MACE mult	0.07	-0.04	0.17
		Group x MACE mult	-0.03	-0.17	0.12
	3	Constant	14.10	6.87	21.33
		Group	9.29	-0.81	19.39
		GQ	-0.18	-0.39	0.03
		Group x GQ*	-0.30	-0.59	-0.01
PANAS-n	1	Constant	18.17	15.20	21.14
		Group	-1.09	-4.89	2.71
		MACE sum	-0.02	-0.14	0.27
		Group x MACE sum	0.12	-0.04	0.27
	2	Constant	16.91	14.25	19.58
		Group	1.57	-1.94	5.08
		MACE mult	0.07	-0.07	0.21
		Group x MACE mult	-0.05	-0.25	0.14
	3	Constant	24.08	14.29	33.88
		Group	12.17	-1.51	25.85
		GQ	-0.18	-0.46	0.10
		Group x GQ	-0.35	-0.75	0.05
PANAS-p	1	Constant	31.66	29.11	34.21
		Group	2.12	-1.14	5.38
		MACE sum	0.05	-0.06	0.15
		Group x MACE sum	-0.12	-0.26	0.01
	2	Constant	32.51	30.21	34.81
		Group	0.03	-2.99	3.06
		MACE mult	0.01	-0.12	0.12
		Group x MACE mult	-0.01	-0.18	0.16
	3	Constant	25.10	16.66	33.55
		Group	-2.07	-13.87	9.74
		GQ	0.22	-0.03	0.46
		Group x GQ	0.06	-0.28	0.41

Note: *$p \leq .05$

MACE mult – multiplicity of CA; MACE sum –severity of CA; Group – dummy coded (1 = gratitude intervention); PHQ9 – depressive symptoms; PANAS-p – Positive affect; PANAS-n – Negative affect; GQ – trait gratitude

CA Multiplicity

ITT

CA multiplicity did not moderate the effectiveness of the two programs on depressive symptoms, negative affect, or positive affect (see Table 2).

PP

CA multiplicity did not significantly moderate the impact of the interventions on any of the three main outcomes, mirroring results indicated by the ITT analyses (Table 3).

Trait Gratitude

ITT

Trait gratitude significantly moderated the effectiveness of the interventions on depressive symptoms. However, the conditional effects did not reveal significant differences between interventions on depressive symptoms at the three levels of trait gratitude (b = 1.88; 95% *CI* [-0.20; 3.96] for low, b = 0.05; 95% *CI* [-1.45; 1,56] for intermediate, and b = -1.25; 95% *CI* [-3.32; 0.82] for high levels of trait gratitude).

Trait gratitude did not significantly moderate the effectiveness of the intervention on negative and positive affect (see Table 2).

PP

Trait gratitude significantly moderated the impact of the intervention on depressive symptoms, gratitude intervention being more effective for individuals with high levels of trait gratitude (b = -2.59; 95% *CI* [-5.18; -0.01]), but equally effective for those with intermediate (b = -1.11; 95% *CI* [-2.96; 0.74]) and low levels of trait gratitude (b = 1.16; 95% *CI* [-1.45; 3.78]) relative to control. Trait gratitude did not moderate the effectiveness of the interventions on negative and positive affect (see Table 3).

Effect Modifiers for Adherence and Drop-Out

CA Severity

We ran moderation analyses for adherence and drop-out on the entire sample. CA severity significantly moderated the impact of the intervention type on program adherence (b = -0.14, 95% *CI* [-0.22; -0.05]). The gratitude intervention had a significant higher adherence than control only for participants with low (b = 5.66, 95% *CI* [3.73; 7.61]) and intermediate levels of CA severity (b = 4.24, 95% *CI* [2.77; 5.72]), but not for participants with severe CA (b = 0.92, 95% *CI* [-1.25; 3.08]).

Likelihood ratio test of higher order unconditional interaction indicated that CA severity significantly moderated drop-out (χ^2 = 8.44, p = .004; b = 0.05, 95% *CI* [-0.09; -0.02]). Participants were more likely to complete the program in the gratitude condition than in the control condition if they had low (b = 2.15, 95% *CI* [1.26; 3.08]) or intermediate levels (b = 1.61, 95% *CI* [0.93; 2.29]) of CA severity, but not if they had severe CA (b = 0.34, 95% *CI* [-0.53; 1.20]).

CA Multiplicity

CA multiplicity (i.e., chronicity) did not significantly moderate the impact of the two interventions on program adherence (b = 0.08, 95% *CI* [-0.03; 0.19]). CA multiplicity did not significantly moderate the impact of the two interventions on drop-out (χ^2 = 3.03, p = .086; b = 0.05, 95% *CI* [-0.01; 0.11]).

Trait Gratitude

Trait gratitude did not significantly moderate the impact of the two interventions on program adherence (b = 0.01, 95% *CI* [-0.22; 0.23]) or drop-out (χ^2 = 0.39, p = .530; b = 0.03, 95% *CI* [-0.06; 0.21]).

3.6.4. Conclusions

In this randomized controlled trial, we tested the effectiveness of a gratitude intervention in reducing depressive symptoms and negative affect and increasing positive affect, against neutral, but active control condition (Dickens, 2017). While we did not find a time*group interaction effect for any of these outcomes, a time-effect emerged for depressive symptoms and negative affect, with positive symptoms remaining stable.

Likewise, while we did not find a time*group interaction effect for reward processing, a time effect emerged. This finding is consistent with previous work employing similar neutral controls (Patalano et al., 2018) and may suggest that reward processing may be improved using easy to administer strategies, such as journaling. Finally, given that the two groups did not

differ on any of the outcomes, we did not find support for the potential mediating role of reward processing for these outcomes.

Mirroring previous work (Dickens, 2017; Geraghty et al., 2010), we found that participants allocated in the gratitude condition were more adherent to the intervention and were less likely to drop out. This may suggest that more individuals may benefit from gratitude interventions as compared to active control conditions, by sticking into the program. Even though similar changes may emerge in these conditions, gratitude interventions may be more appealing and thus impact on program adherence.

ITT analyses showed that CA severity moderated condition differences concerning depressive symptoms, negative and positive affect. The gratitude intervention was more effective in reducing depressive symptoms and negative affect in individuals reporting lower levels of CA severity. While the moderation analysis indicated that the two conditions may differ in terms of positive affect for individuals presenting various levels of CA severity, this interaction was not probed when testing for simple slopes at low, intermediate and high levels of CA severity. Together, these findings may suggest that, while gratitude interventions may be effective for individuals with low CA severity, they may be less suited for individuals experiencing high levels of CA severity. However, CA consequences may vary by severity and/or chronicity (Smith & Pollak, 2020). Consistent with this view, the perceived intensity of adverse events, rather than their sheer experience, may be particularly relevant for treatment (Baldwin & Esposti, 2021; Smith & Pollak, 2020). Our findings support this view, and indicate that, contrasting CA severity, CA multiplicity did not moderate the depressive symptoms, negative affect and positive affect.

Similarly, we found that trait gratitude predicted depressive symptoms, negative affect and positive affect in the whole sample. Although ITT moderation analysis suggested that the effectiveness of the two conditions on depressive symptoms may differ as a function of trait gratitude, such differences were not statistically significant at low, intermediate or high levels of trait gratitude. PP moderation analysis revealed a statistically significant result, indicating that the gratitude condition reduced depressive symptoms only in high trait gratitude individuals as compared to control condition. Given that our findings lend partial support for the conductance hypothesis (McCullough et al., 2004), it may require further investigation.

In addition, we found that CA severity moderated adherence and drop-out. Individuals with low and intermediate levels of CA severity were more likely to adhere and complete the gratitude intervention, relative to control. These findings extend existing knowledge on CA impacting treatment (Lippard & Nemeroff, 2020; Nanni et al., 2012; Nelson et al., 2017) and indicate that CA individuals are not only more difficult to treat, but they may benefit less from available treatments due to poor treatment adherence and increased drop-out rates. Moreover, given that CA multiplicity did not moderate adherence and drop-out, the present findings add to evidence that emphasizes that the events themselves may be less relevant than their perceived intensity (Smith & Pollak, 2020). Contrary to our expectations, trait gratitude did not moderate adherence or drop-out, suggesting it may be less relevant for predicting treatment completion.

While these contributions are important, the study has several limitations: (1) the sample consisted of mainly healthy individuals; (2) the sample consisted of mainly women; (3) the proposed mechanism of change and treatment outcomes were simultaneously measured. Replicating these findings in clinical populations and more gender balanced samples would be useful. Likewise, in order to establish temporal precedence, research aimed at investigating the potential mediating role of reward processing may benefit from assessing it prior to treatment outcomes.

CHAPTER IV. GENERAL CONCLUSIONS AND DISCUSSIONS

This thesis sought to: (1) investigate associations between CA, psychopathology, and reward processing, (2) investigate several other variables that may be involved in these associations, such as childhood SES (e.g., Peverill et al., 2021) and current stress (e.g., Goldstein et al., 2020), (3) extend the model to other forms of pathology, (4) investigate interventions aiming to target reward processing, as well as (5) factors impacting on their effectiveness in reducing depressive and anxiety symptoms, negative affect, and increasing positive affect.

Seeking to clarify the association between CA and reward processing and to identify several potential variables impacting on it, we conducted a meta-analysis (Study 1). Its main findings indicated that CA is associated with impaired reward processing and that this association may vary by reward processing dimension. Thus, in Study 2 (Study 2a, Study 2b, Study 2c), we sought to investigate associations between CA, reward processing and psychopathology, parsing out distinct reward processing dimensions, accounting for childhood SES and the psychological impact of current stress. In Study 2a we found that impairments on all three reward processing dimensions mediate the association between CA and depressive symptoms. Given that this model has not been investigated on a clinical sample, nor have associations between distinct reward processing dimensions and depressive symptoms, in Study 2b, we aimed to replicate our findings on a sample of clinically depressed patients. Furthermore, in Study 2c, building on data that indicate high comorbidity among mental disorders and physical health (e.g., James et al., 2018), we sought to extend the model to other conditions, as well as to investigate potential variables, such as current stress, that may impact on it. We found partial support for the potential mediating role of reward processing (i.e., reward learning), and no support for the psychological impact of current stress impacting on this mechanism. Together, these results provide a proof-of-concept for the hypothesis of reward processing being a potential transdiagnostic mechanism underlying the association between CA and psychopathology.

Based on these findings and on empirical data suggesting interventions aiming to target reward processing have encouraging results, in Study 3 (Study 3a, Study 3b), we sought to investigate its potential clinical implications. Thus, we conducted a three-armed clinical trial (Study 3a) using an analogue sample and investigated the effectiveness of two interventions aiming to target reward processing (i.e., behavioural activation and cognitive training) against an active placebo. Following intervention, depressive and anxiety symptoms decreased, while positive affect and satisfaction with life increased, with no differences between the three conditions. Moreover, we did not find support for reward processing as a potential mediator for these interventions. Likewise, we did not find support for the potential moderator role of CA in these interventions. Furthermore, we conducted a two-armed clinical trial (Study 3b) and investigated the effectiveness of an intervention (i.e., gratitude) that may target reward processing against an active control. A similar patterns of results emerged. However, in this study (Study3b), we investigated two theoretically-relevant dimensions of CA (i.e., severity and chronicity), and found that CA severity, but not chronicity, moderated the effectiveness of the intervention, adherence and drop-out.

4.1. Theoretical, Methdological and Clinical Implications

This thesis has several important theoretical, methodological and clinical advances and implications. To date, most research investigating reward processing using self-report measures did not parse out distinct reward processing dimensions, although major theoretical approaches (e.g., RDoC, NIMH, 2016) indicate that this system consists of three dimensions (i.e., reward responsiveness, learning and valuation). This project is the first one to capitalize

on this distinction and to synthesize the association between CA and reward processing, lending support for impairments which vary by dimension. Moreover, this project also indicates that distinct dimensions may be relevant for specific mental disorders. In addition, it provides empirical support for the mediator role of reward processing in the association between CA and psychopathology, suggesting that this mechanism could be targeted through interventions. Finally, it refines existing methodological issues in the field, as well as interventions aiming to target the proposed mechanisms. These implications are discussed below.

In the first quantitative review to systematically investigate the association between CA and reward processing (Study 1), we clarified this association, its direction and magnitude. In addition, this approach allowed us to identify potential sources of heterogeneity. Thus, while we found that while the overall effect for this association was small, larger associations are reported in studies investigating reward learning rather than responsiveness and valuation. Notably, we found that measures used to assess both CA and reward processing moderate the association between these variables. Reflecting a well-established tendency to underreport CA in self-report measures (Baldwin et al., 2019; Smith & Pollak, 2020; Widom & Morris, 1997), the meta-analysis indicated smaller associations between CA and reward processing in studies using self-report measures relative to those that used objective measures. Paralleling these findings, the meta-analysis indicated smaller associations between CA and reward processing in studies assessing the latter using self-report measures. Finally, we found that sample characteristics related to developmental age, sex distribution, and clinical status do not impact on the association between CA and reward processing, adding support for the lifelong and almost universal impact of CA on reward processing.

Second, building on our meta-analytical data (Study 1) supporting existing frameworks (i.e., RDoC; NIMH, 2016) which suggest that reward processing is a multidimensional construct, throughout this thesis, we capitalized on this distinction. Prior work has recently started to focus on these dimensions separately, but no previous study simultaneously investigated all three reward processing dimensions and most data stem from neural studies, which may, only explain small portions of the clinical phenomena (Lange et al., 2021). Distinguishing between reward processing dimensions and identifying, adapting and using self-report measures allowed us to fill this empirical gap. In addition, relatively few studies have directly investigated the potential mediating role of reward processing in the association between CA and pathology. In an attempt to address this empirical gap too, we conducted a large correlational study (Study 2a) on a community sample of young adults (18-35). This design which has relatively low costs and is useful in exploratory phases allowed us to investigate associations between CA and various symptoms (i.e., depressive and manic symptoms, alcohol abuse symptoms, emotional eating and borderline personality traits) that have been previously associated with reward processing and to bring support for CA being a risk factor for psychopatholgy, while also accounting for a possible confound: childhood SES. Moreover, it allowed us to test the potential mediating role of reward processing dimensions in these associations. Thus, one of the most important findings of this study is that distinct reward processing dimensions may be of relevance for specific symptoms. These findings extend existing knowledge which, in general, did not investigate the mediating role of reward processing, nor has capitalized on this distinction or accounted for childhood SES.

We found that reward processing impairments associated with depressive symptoms contrast reward processing impairments in manic symptoms. Moreover, we found support for reward processing (all three dimensions) mediating associations between CA and depressive, but not manic symptoms. While we did not find any associations for reward processing and alcohol abuse symptoms, we found that both reward learning and valuation are associated with emotional eating, and reward valuation mediated the association between CA and emotional

eating. In addition, we found that both reward responsiveness and learning are associated with borderline personality traits, but only reward learning mediates the association between CA and these symptoms. We also found that childhood SES is associated with CA and some forms of psychopathology (i.e., depressive symptoms and borderline personality traits), but reward processing does not mediate these associations. Together, these findings lend support for a coherent theoretical etiopathogenetic model for distinct mental disorders.

Third, in Study 2b which was conducted on a clinical sample of inpatients, we aimed to explore similar associations using this framework, while controlling for childhood SES and to probe the potential mediating role of reward and threat processing. Using partial correlations we were able to examine the unique contribution of CA and reward processing in depressive symptoms, while controlling for childhood SES. We found an association between CA and depressive symptoms, but no associations between CA and reward processing, nor reward processing and depressive symptoms. Extending previous work that has focused on threat processing following CA (Hein & Monk, 2017; Kim et al., 2018; Lange et al., 2019), we found an association between the two and we also found that threat processing is associated with depressive symptoms. Yet, we did not find support for the potential mediating role of threat processing. Finally, while controlling for childhood SES, all significant associations remained stable, and no other significant associations emerged.

Fourth, we extended the proposed model to other conditions: anxiety (Mrazek et al., 2014) and physical health problems (e.g., Kessler et al., 2010; Study 2c). In the first study to simultaneously investigate all three reward processing dimensions in both mental and physical health (Study 2c), we recruited a large community sample and found support for CA being a risk factor for health. Replicating our previous findings (Study 1, Study 2a), we found that CA was associated with reward processing and lent support for reward processing (i.e., reward learning) consistently mediating the association between CA and these outcomes. Given that few studies took into consideration the potential moderating role of psychological impact for this mechanism, we used mediated moderation analyses which allowed us to suggest that our proposed theoretical model is robust. Notably, the psychological impact of recent stress (i.e., COVID-19) does not moderate the mediating role of reward processing. In addition, we also found that the psychological impact of recent stress is associated with health outcomes, with CA increasing this risk for physical health outcomes only.

In conclusion, these studies (Study 1, Study 2a, 2b and 2c) provide empirical support for the association between CA and reward processing, CA and psychopathology and reward processing and both mental and physical health. However, one of the most important findings is that these associations vary by reward processing dimension and that they support the transdiagnostic role of reward processing, justifying interventions aiming to target it (Study 3).

Building on these, we used experimental designs and conducted two randomized clinical trials (Study 3a, and Study 3b), which allowed us to investigate causal relationships between variables and address several important empirical gaps. We conducted a three-armed clinical trial (Study 3a) on an analogue sample (i.e., depressive and/or anxiety symptoms), and investigated the effectiveness of two interventions aiming to target reward processing: behavioural activation and cognitive strategies, against an active control. We chose to deliver these strategies in an online format (i.e., unassisted self-help), and designed 8 modules mimicking traditional therapy (aiming to increase ecological validity). All modules followed a similar structure. In order to ensure manipulation check (i.e., adherence), all participants responses were saved upon completion. These methodological choices ensured internal validity.

We performed both per protocol (i.e., PP, i.e., had ≥ 50% completion rate) and intent to treat (i.e., ITT; last observation carried forward) analyses. Following intervention, all three groups evolved similarly: positive affect and satisfaction with life increased, while depressive

and anxiety symptoms decreased. We also sought to extend previous knowledge (e.g., Craske et al., 2016) and to test changes in distinct reward processing dimensions and test their potential mediating role, but did not find support for this hypothesis. Finally, we also sought to test the moderating role of CA, and did not find support for it. Yet, we suggest that, consistent with previous work suggesting that specific CA features, such as chronicity and severity (Smith & Pollak, 2020), may have distinct implications for psychopathology and treatment.

In Study 3b we capitalized on this distinction when investigating the effectiveness of a gratitude intervention aiming to target reward processing. Although this potential mechanism has been previously proposed (Watkins, 2004), to our knowledge, this was the first study to investigate it directly. Building on recent guidelines (Dickens, 2017), we compared the gratitude intervention against an active placebo and performed per protocol (i.e., PP, i.e., had $\geq 50\%$ completion rate) and intent to treat (i.e., ITT; last observation carried forward) analyses). At sample level, following intervention (2 weeks; online), depressive symptoms and negative affect decreased, while positive affect remained stable. Likewise, we found that both groups evolved similarly, with reward processing increasing following intervention. In addition, we found that participants allocated to the gratitude condition were more adherent and less likely to drop-out of program.

In order to investigate the potential moderating role of CA severity and multiplicity, we used a novel measure (MACE; Teicher & Parigger, 2015), which distinguishes between the two. We translated and adapted this instrument, and, consistent with prior work (Baldwin et al., 2021), found that these specific CA features have distinct consequences for treatment. Notably, we found that CA severity moderated the effectiveness of the gratitude intervention on depressive symptoms and negative affect, but it may be less suitable for individuals with intermediate and high CA severity. However, we did not find a similar pattern for CA multiplicity. Nonetheless, we found a similar trend for adherence and drop-out. Finally, we also investigated the potential moderating role of trait gratitude and found that it moderates the effectiveness of the intervention on depressive symptoms, but not other outcomes, nor adherence and drop-out.

Together, these findings, if replicated, provide useful guidelines for clinicians working with individuals reporting past CA, and may justify incorporating strategies aiming to target reward processing into existing interventions, on the one hand, and developing new interventions, on the other. Given that our findings suggest that both associations between CA and reward processing and reward processing and psychopathology may vary by reward processing dimension, we suggest that clinicians ought to make use of these models when working with these individuals. Moreover, they may suggest that onsite and/or assisted interventions may be more suitable and effective, as compared to online interventions. In addition, given that gratitude interventions have better retention rates, we suggest that they may be preferable. Yet, they may not be the best fit for everyone and individual characteristics, such as CA severity and trait gratitude should be considered. Finally, using additional strategies, especially when working with individuals reporting severe CA, may increase treatment effectiveness, adherence and reduce drop-out.

4.2. Limitations and Future Directions

While specific limitations of each study have been already presented in previous sections of the thesis, general limitations and future directions that may address them are outlined below.

The first general limitation pertains to sample characteristics. In an effort to address this limitation, participants were recruited from diverse samples (i.e., including clinical samples). Given that they were mostly women, residing in urban areas and having at least some high-school education, generalizing present results to other populations may be difficult. It may

be useful to replicate these findings on more balanced samples, in terms of demographic characteristics.

Another limitation of this thesis is the cross-sectional nature of Study 2 (Study 2a, Study 2b, Study 2c). Even though the design was fit for study objectives, its correlational and cross-sectional nature hampers interpreting present results. Future studies employing longitudinal designs that would allow establishing precedence between variables may be useful.

Moreover, we solely relied on self-report measures for all variables of interest. Given that these measures may not correlate with more objective/clinician rated ones, future research may benefit from using complementary measures. In addition, we assessed CA using retrospective measures. Yet, these measures poorly correlate with prospective measures and may be influenced by recall bias (Baldwin et al., 2019). Even though corroborating several CA measures may be useful, relying on retrospective measures was aligned with our objectives and with recent work suggesting that, independent of objective experience, perceived CA may have important implications for psychopathology (Baldwin et al., 2021). Indeed, our findings (Study 3b) support this hypothesis.

Notwithstanding these inherent limitations, the thesis extends previous knowledge on the associations between CA and psychopathology and provides support for reward processing as a transdiagnostic mechanism in these conditions. Moreover, the thesis indicates that parsing out this mechanism into distinct dimensions may clarify associations between variables and inform treatment. Finally, this thesis advances prior work and investigates interventions aiming to target reward processing, probing for this mechanism of change.

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