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Insights in:Psychopathology research

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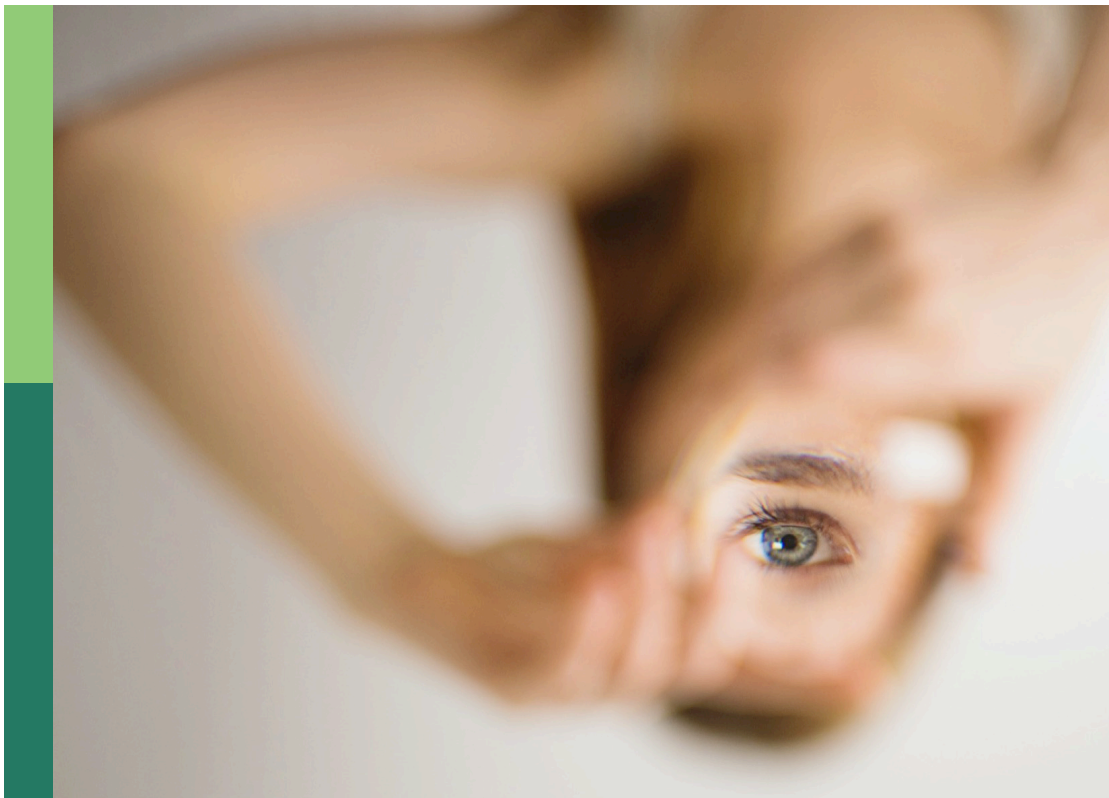

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Insights in: Psychopathology research

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Table of contents

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Editorial: Insights in: Psychopathology research

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Editorial on the Research Topic
Insights in: Psychopathology research

Modern psychopathology is going through a period of necessary transition. Traditionally, it has been associated with the historical legacy of Franco-German and Russian classical authors who studied symptoms and syndromes with the precision of clinical descriptions. We can mention the milestone contributions of J. E. D. Esquirol and Jules Baillarger (hallucinations), Karl Ludwig Kahlbaum (catatonia and paraphrenia), W. Mayer-Gross and S. T. Stoianov (oneiroid syndrome), Victor K. Kandinsky (pseudo-hallucinations), Valentin Magnan (delusions), Sergey S. Korsakoff and Carl Wernicke (eponymous syndrome), among many others.

Both J. H. Jackson and H. Ey took cross-sectional and longitudinal approaches to the formation of symptoms and the evolution of syndromes. These led to the concept of dissolution.

It was not until the end of the nineteenth century that psychopathology began to focus on the explanatory mechanisms of mental disorders, which at that time were arguably attributed to degenerative factors from a post-Darwinian evolutionary perspective (Bénédict Morel). In the same period, Emil Kraepelin attempted to introduce what he understood to be a medical or nosological system of mental disorders, sparking controversies over the possibility of producing a universal psychiatric classification. His robust approach was almost immediately confronted by the phenomenological psychopathology of Karl Jaspers, which in practice denied categories in psychopathology and higher-order medical taxonomy. This view is still very influential (Stanghellini and Fuchs, 2013).

As a result, psychopathology in the twentieth century was torn apart by diverse and incompatible conceptual explanations of mental phenomena in health and disease. In order to escape from this impasse, instrumentalist descriptive psychopathology was introduced, where diagnostic procedures and criteria followed clinical ratings and structured interviews. This led to scientific anarchy in the late twentieth century, where "anything goes" and diagnostic systems were under constant debate and revision.

The more recent interventions in neuroscience were not successful in providing an epistemological platform for new psychopathology, as there exist major methodological gaps between psychopathology and neuroscience. The majority of neurobiological studies remained exhaustively focused on state-independent measures, combined as endo-phenotypes. Only a limited number of authors and research groups have targeted clinical

states using "symptom" capture paradigms, e.g., verbal acoustic hallucinations (Hugdahl et al., 2022), paranoid delusions, and depressive symptoms (Aryutova et al., 2021).

Despite encouraging advances in molecular neuroscience and functional neuroimaging, especially in the areas of resting-state functional (Stoyanov et al., 2022) and effective connectivity (Kandilarova et al., 2021), the caveats that undermine the production of a meaningful psychiatric nosology remain.

The persistent problem of how to define normal mental functions and classify mental disorders beyond high-level clusters, prototypes, or dimensional diagnosis remains.

This Research Topic is dedicated to new findings in psychopathology research, with the clear understanding that there are many overlaps and shared trans-diagnostic areas of inquiry.

This issue begins with an original paper by Krings et al. that explores the proportion of variance in depressive symptoms that can be explained by processes targeted by behavioral activation. It was concluded that activation, behavioral avoidance, brooding, and anticipatory pleasure are relevant processes to target in order to reduce depressive symptoms, while cognitive control and attentional biases are not (Krings et al.).

The second article in this issue by Marco et al. validates the Multidimensional Existential Meaning Scale in a Spanish-speaking sample. It resulted in an adequate version to assess the three dimensions of meaning in Spanish-speaking participants (Marco et al.).

The third study, by Panov (a), looks at the connection between the degree of dissociation and resistance to therapy in 106 patients with schizophrenia. The author concluded that patients with resistant schizophrenia have a much higher level of dissociation than patients in clinical remission and suggested that resistance to the administered antipsychotics is associated with the presence of high dissociation in the group of resistant patients [Panov (a)].

In the fourth work, also an original study, Panov (b) looks at the relation between functional lateralization and the effect of treatment in patients with schizophrenia. An increased number of patients with cross-dominance left eye dominance was found in patients with schizophrenia [Panov (b)].

The fifth article of this issue, by Vander Zwalmen et al., reviews the current state-of-the-art of cognitive control training as an intervention to reduce vulnerability to depression. Several issues are discussed, such as (i) identifying working mechanisms and potential moderators of CCT; (ii) establishing conditions for the effective use of CCT; and (iii) evaluating possible combinations of CCT with other antidepressant interventions (Vander Zwalmen et al.).

The sixth article included, by Moore et al., consists of a systematic, nationwide survey to assess the relationship between anxiety and depression symptoms and coping skills among Asian American medical students. It was concluded that Asian American students who experience anxiety were more likely to use avoidant or negative coping strategies and that those experiencing depressive symptoms were not more likely to utilize these negative coping strategies (Moore et al.).

The seventh study, by Bodart et al., systematically reviews the physiological reactivity at rest and in response to social or emotional stimuli after a traumatic brain injury. It was concluded that although electrodermal activity responses were frequently reported in patients with traumatic brain injury, other measures did not consistently indicate an impairment in physiological reactivity (Bodart et al.).

The eighth article included, by Carta and Cataudella, consists of a perspective on the historical transformation of adolescence—itself a psychological developmental process embedded in sociocultural history.

The ninth article in this issue is an original study that aims at identifying direct and indirect associations among alexithymia, OCD, cardiac interoception, psychological inflexibility, and self-as-context with DV ASD and depression. The results are discussed in relation to the limitations of the DSM with its categorical focus on protocols for syndromes (Edwards).

The final contribution is a brief research report by Panov (c), which purports to analyze the perceived gender role in patients with schizophrenia, looking for differences between patients with treatment resistance and those in clinical remission. A higher percentage of schizophrenic patients who showed a higher identification with the female gender role was found [Panov (c)].

Author contributions

DS and DT wrote together the manuscript. AB, OT, and XN edited and approved it. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Spanish Validation of the Multidimensional Existential Meaning Scale: Which Dimension of Meaning in Life Is More Associated With Psychopathology in People With Mental Disorders?

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Background: To assess three dimensions of Meaning in Life (comprehension, purpose, and mattering) the Multidimensional Existential Meaning Scale (MEMS) was developed, however, the MEMS's factorial structure has not yet been confirmed in a Spanish-speaking sample. A question that remains unanswered is which of the three dimensions of MiL are associated with psychopathology in clinical samples.

Aims: (1) to analyze the psychometric properties of the MEMS in a Spanish non-clinical population, and (2) to identify which of the three dimensions of MiL shows the strongest relationship with depression, anxiety and positive affect in a clinical population.

Method: The non-clinical sample, consisted of $N = 1106$ Spanish adults, and the clinical sample consisted of 88 adults diagnosed with mental disorders. A Confirmatory Factor Analysis and regression analysis were carried out.

Results: The three-factor model for the MEMS showed an acceptable fit, and full invariance across gender groups. In the clinical sample, the mattering dimension had the highest association with depression and anxiety, and purpose with positive affect.

Conclusion: The MEMS is an adequate instrument to assess the three dimensions of meaning in Spanish-speaking participants. These results support the importance of evaluating the MiL construct from a multidimensional perspective in clinical samples.

Keywords: meaning in life, coherence, purpose, mattering, positive affect

INTRODUCTION

Meaning in life (MIL) can be defined as the extent to which one's life is experienced as making sense, being directed and motivated by important goals, and mattering in the world. Several scales have been developed to assess MiL, both unidimensional scales, such as the Purpose in Life scale (PIL) (1), and multidimensional scales, such as the Meaning in Life Questionnaire (MLQ) (2). Multidimensional models seem to assess MiL more accurately than unidimensional models

by distinguishing different facets or dimensions of MiL. Even the PIL, a classic instrument for the assessment of MiL, has shown better psychometric properties and been found to be more clinically useful when different dimensions have been distinguished (3). Therefore, it appears that multidimensional models for the assessment of MiL are preferrable to unidimensional models.

Martela and Steger (4) elaborated a tripartite conceptualization of MiL, suggesting that MiL would be made up of three clearly interconnected dimensions that interact with each other, making us feel that life has meaning: Comprehension, purpose, and mattering. The comprehension dimension refers to the extent to which people feel their life is coherent, predictable, and connected as a whole (5, 6). Thus, comprehension is the cognitive dimension of MiL. Low comprehension of one's life means that the person feels that his/her life is incoherent, fragmented, and confused. An example would be the feeling of low comprehension that occurs after experiencing a traumatic event that has violated one's schemes about the world and one's life. The violation of these schemes would reduce comprehension and increase distress (7). In contrast, people with high comprehension feels that their life is meaningful, that everything happens in a coherent way, and that the positive or negative events that occur daily are integrated into their global schemes. Previous studies found that the meaning-making process moderates and mediates several mental disorders, such as posttraumatic stress disorder (8), eating disorders (9), adjustment disorders (10), and stress (11).

The purpose dimension refers to the extent to which a person's life is aimed at achieving specific goals and values (12), and the extent to which the person takes responsibility for these goals. Thus, purpose is the motivational dimension. This dimension was originally proposed by Viktor Frankl (13), who suggested that human beings should be directed toward something or someone greater than themselves that transcends them, in order to experience MiL. High-purpose people feel that their life is oriented toward functional, adaptive goals that extend beyond themselves. These people usually develop creative goals (doing something, work, academic career, hobbies, among others) and experiential goals (loving something or someone, feeling, caring, interpersonal relationships, among others). Low-purpose people feel that their life is not oriented toward functional or important goals for them, or they feel that their life has no purpose. The dimension of purpose has been negatively associated with borderline personality disorder psychopathology (14), hopelessness (15), and mortality risk (16).

The mattering dimension, also known as significance (4), refers to the extent to which people feel that their existence is important and significant and has intrinsic value to the world (17). People high in mattering think that they are valuable for merely existing, that life has intrinsic value, and that if they did not exist the world would have been different. People feel that their life matters because it is important to the people around them (e.g., interpersonal relationships). When people experience mattering, they feel that their actions and existence make a difference in the world around them and that their lives are valuable (18). Thus, mattering is based on a global evaluation of one's life from a spiritual or existential perspective. Mattering is the affective dimension of MiL, and it has been found to be positively associated with positive affect, self-esteem, and well-being (19), and negatively associated with hostility, aggression, and negative affect (20, 21).

Although mattering is the dimension of MiL that has been investigated least and, to our knowledge, there are no studies with clinical populations, there has recently been an increased interest in this dimension and its role in the MiL construct. Costin and Vignoles (18), in a longitudinal study with a non-clinical population, analyzed which of the three dimensions of meaning (coherence, purpose, and mattering) made a greater contribution to the feeling of MiL, and they found that mattering was the greatest predictor of MiL. These results suggest the need to use instruments that measure the three dimensions of meaning and analyze their differential contributions to psychopathology and mental health.

To assess the comprehension, purpose, and mattering dimensions of MiL George and Park (22) developed the Multidimensional Existential Meaning Scale (MEMS). To develop the MEMS, 43 items were generated to capture the three dimensions of MiL. These items were qualitatively examined by several experts in measuring MiL, and 29 items were retained. Three samples of university students from the United States were utilized to perform several exploratory and confirmatory factor analyses (CFA), and the MEMS was reduced to 15 items to evaluate the three dimensions of MiL: items 1, 7, 8, 10, and 14 assess comprehension; items 3, 5, 6, 9, and 12 assess purpose; and items two (which is reverse-scored), 4, 11, 13, and 15 assess mattering. The MEMS subscales showed good internal consistency, and good validity (the subscales showed strong associations with the Presence subscale of the MLQ). Moreover, the MEMS subscales were associated with well-being variables, such as positive affect. Comprehension had the highest negative association with psychopathology constructs (depression, anxiety, and negative affect), and purpose had the highest positive association with positive affect.

In a sample with 401 Polish participants a CFA was performed on the Polish version of the MEMS confirmed the reliability and validity of the trifactorial structure of a reduced scale containing nine items (23). The Comprehension factor was composed of items 7, 8, and 10; the Purpose factor consisted of items 3, 5, and 9; and the Mattering factor contained items 2, 13, and 15. Finally, the three subscales were highly and positively associated with MiL, assessed with the PIL and the MLQ Presence subscale.

In summary, the MEMS has been shown to be a reliable and valid instrument to assess the three dimensions of MiL (comprehension, purpose, and mattering) in English- and Polish-speaking samples. However, its factorial structure has not yet been analyzed and confirmed in a sample of Spanish-speaking people. Moreover, previous studies have associated the three dimensions of MiL with psychopathology variables however they have always been carried out in non-clinical populations (2). In addition, a question that remains unanswered is which of the three dimensions presents a greater association with psychopathology and positive affect in patients diagnosed with mental disorders. The identification of these relationships would

allow a better understanding of the functioning of these variables as protective factors that can help to improve prevention or treatment programs for some mental disorders.

The present study has two aims: (1) to analyze the psychometric characteristics and confirm the factorial structure of the MEMS in a Spanish non-clinical population (Sample 1); and (2) to identify which of the three dimensions of MiL, assessed with the MEMS (comprehension, purpose, or mattering), shows the strongest relationship with psychopathological distress and positive affect in a clinical population (Sample 2).

MATERIALS AND METHODS

Participants

The non-clinical sample (Sample 1) consisted of $N = 1106$ Spanish participants between 18 and 83 years old ($M = 35.05$; $SD = 13.72$); 80.4% were women. The majority of the participants were married (51.1%) or single (42%), 5.9% were separated or divorced, and 1% widowed. Regarding their level of education, 49.6% of the sample had a university degree, 33.1% had a university master's degree, 16.3% had secondary studies, and 1% had primary studies. All participants were Spanish. The exclusion criterion was having been diagnosed with any mental disorder.

The clinical sample (Sample 2) consisted of 88 participants with a mean age of 29.34 ($SD = 11.95$), and a range of 19–67 years; $n = 80$ (90.9%) were women. The inclusion criteria were being an adult, having a diagnosis of a mental disorder, and receiving psychiatric or psychological treatment at the time of the evaluation. Regarding the residence country, 52 participants (59.1%) were from Spain, and 33 participants (40.9%) were from other Spanish-speaking South American countries. Regarding marital status, 54 participants (60.4%) were single or separated, and 34 participants (38.6%) were married. Most of the participants ($n = 68$, 77.3%) did not have children, and 38.6% were employed.

Regarding clinical characteristics of the sample, 88 participants (100%) were undergoing pharmacological or psychological treatment, 42 participants (47.72%) were diagnosed with anxiety disorders, 24 participants (27.27%) were diagnosed with depressive disorders, nine participants (10.22%) were diagnosed with bipolar disorders, nine participants (10.22%) were diagnosed with obsessive compulsive disorder, and four participants (4.54%) were diagnosed with posttraumatic stress disorder.

Instruments

The Multidimensional Existential Meaning Scale (MEMS) (22) assesses the MiL dimensions: Comprehension, purpose, and mattering, with a total of 15 items (e.g. "My life makes sense"; "I have overarching goals that guide me in my life"; "I understand my life"; "I know what my life is"). Likert type responses are given on a seven-point scale (1 = Very strongly disagree; 7 = Very strongly agree). This self-report is described in the introduction section. In our sample, the three MEMS subscales showed adequate internal consistency: Comprehension ($\overline{\omega} = 91$), Purpose ($\overline{\omega} = 92$), and Mattering ($\overline{\omega} = 86$). For this study, the MEMS was translated from English to Spanish by two PhD researchers who are experts in MIL assessment, and subsequently a back translation from Spanish to English was carried out by two other expert PhD researchers. The whole translation and back translation process were overseen by a bilingual native English editor.

The Brief Symptom Inventory 18 [BSI-18; (24, 25)]. The BSI-18 was designed to assess psychopathological distress. This instrument consists of 18 items rated on a five-point Likert scale (0 = Not at all; 4 = Extremely) indicating the presence of the symptom in the past seven days. The BSI-18 yields a global score, the General Severity Index, and three subscale scores: somatization, depression, and anxiety. In this study, we used the depression, anxiety subscale and the General Severity Index. In the present study, excellent internal consistency was found for the BSI-18 total scale ($\overline{\omega} = 0.96$).

The Positive and Negative Affect Schedule [PANAS; (26, 27)]. The questionnaire includes 20 adjective items, 10 assessing positive affect (PANAS-P) and 10 assessing negative affect (PANAS-N). Respondents are asked to rate the extent to which they had experienced each particular emotion within a specified time period, using a five-point scale (1 = Very slightly or not at all; 5 = Very much). In this study, both affect subscales showed adequate internal consistency: PANAS-P, $\overline{\omega} = 0.92$, and PANAS-N, $\overline{\omega} = 0.88$.

Purpose In Life Test-10 [PIL-10; (28)]. This scale is a reduced Spanish version of the PIL (29), and it is composed of a 10-item Likert scale related to different aspects of meaning in life (e.g., "In life I have many definite goals and longings"). The PIL-10 has two subscales. The total score ranges from 10 to 70: higher scores indicate greater MiL. In this study, the PIL-10 showed adequate internal consistency ($\overline{\omega} = 0.94$).

Procedure

For the present study, two samples were selected: Sample 1 was composed of non-clinical participants, and Sample 2 was composed of clinical participants. For the two samples, we used snowball sampling techniques to recruit participants through main social networks (Facebook, WhatsApp, Twitter, Linkedin, and Instagram) and a massive mailing to the researchers' contacts in May and July 2020. In Internet announcements, we described the study and requirements for participation. All participants provided their consent to participate in the study, and they answered a 20-min survey using the Google Forms online platform. The inclusion criteria were being 18 years old, speaking Spanish, and signing the informed consent. In this online survey, the following question appeared: "Are you currently diagnosed with a mental disorder?" "Indicate which one"; and "Are you in psychiatric or psychological treatment for your mental disorder at this time?" yes/no. If the participants did not have any diagnosis and were not receiving psychiatric or psychological treatment, we considered them for the non-clinical sample. If, on the other hand, the participants had a diagnosis of a mental disorder and were currently undergoing psychiatric or psychological treatment, they were part of the clinical sample. Participants did not receive any compensation for participating in the study.

Data Analyses

With the participants in the non-clinical sample, we carried out the following analyses: First, descriptive statistics, skewness, kurtosis, and internal consistency (McDonald's ω) of the scales used in this study were calculated. Second, descriptive statistics of the MEMS items as well as the item-rest correlations and the average inter-item correlations of the MEMS subscales were calculated. Third, a Confirmatory Factor Analysis (CFA) was carried out to evaluate the structural validity of the MEMS, and a Multi-Group Confirmatory Factor Analysis (MG-CFA) was performed to evaluate the structural invariance of the MEMS subscales across gender and age groups (30). Because Mardia's coefficient, normalized estimate, was higher than five (that is, multivariate normality was not assumed) and the MEMS subscales are ordinal scales, robust methods (31) and the Diagonally Weighted Least Squares method (DWLS) were used (32). Fit indices included the Comparative Fit Index (CFI) (values ≥0.90 indicate acceptable fit; values ≥0.95 indicate good model fit) and the Root Mean Square Error of Approximation (RMSEA) (values ≤0.08 indicate acceptable model fit; values ≤0.05 indicate good model fit) [e.g., (33)]. To evaluate the fit difference between nested models, the differences between both the CFI and RMSEA indices (ΔCFI and ΔRMSEA, respectively) were used (values ≤ 0.01 in both the ΔCFI and an increasing <0.015 in the ΔRMSEA indicate non-significant differences between the models) [e.g., (34, 35). Fourth, the convergent validity of the MEMS subscales was reported with the Average Variance Extracted AVE, which should be > 0.50) (33), and the discriminant validity was obtained by squaring the correlation between the factors of the scale. Fifth, the correlations with the PIL-10 (meaning in life) and PANAS-P (positive affect) were analyzed to report the concurrent validity of the MEMS subscales. The correlations between the MEMS subscales and the BIS and PANAS-N (negative affect) were calculated to report the divergent validity. Sixth, the differences between men and women and between the age groups on the MEMS subscales were analyzed using the Mann-Whitney test and the Kruskal-Wallis test, respectively.

With the participants in the clinical sample, we performed four linear regression analyses with the participants diagnosed with mental disorders, taking the model composed of comprehension, purpose, and mattering as predictor variables and the BSI-18 depression subscale, BSI-18 anxiety subscale, general distress (BSI-18 overall score), and PANAS-P as dependent variables. For all these statistical analyses, the JASP 0.14.1© statistical software (36) was used. Interpretations of effect sizes were based on Cohen (37).

RESULTS

Descriptive Statistics of the Scales Used in This Study

Table 1 shows the means, standard deviations, skewness, and kurtosis of the items on the MEMS, the McDonald's omega, and the item-rest correlations.

TABLE 1 | Descriptive statistics and internal consistency of the scales used in this study in the non-clinical sample.

	MEMS subscales						
	Comprehension	Purpose	Mattering	PIL-10	BSI	PANAS-P	PANAS-N
M	28.39	30.26	26.41	53.94	23.45	36.90	26.84
SD	5.60	5.09	7.12	10.60	17.57	7.13	8.42
Sk	−0.94	−1.35	−0.78	−0.78	0.41	−0.42	−0.04
K	0.83	2.01	−0.09	0.46	−1.15	0.07	−0.73
$\tilde{\omega}$	0.91	0.92	0.86	0.94	0.96	0.92	0.88

N = 1,106. Sk = Skewness; K = Kurtosis. Skewness Standard Error was 0.07. Kurtosis Standard Error was 0.15.

Table 2 shows the descriptive statistics, skewness, and kurtosis of the MEMS items, as well as the corrected item-total correlations, all of which showed values >0.40, indicating very good discrimination (38).

The average inter-item correlations of the MEMS subscales were higher than 0.30 and lower than 0.80: 0.658 for the Comprehension subscale, 0.702 for the Purpose subscale, and 0.545 for the Mattering subscale. That is, the MEMS subscales did not show homogeneity and multicollinearity problems (39).

Structural Validity of the MEMS and Invariance Across Gender and Age Groups

The MEMS showed a good fit: $SB\chi^2_{(87)} = 262.953$, $p < 0.001$, CFI = 0.991, RMSEA = 0.043 [0.037, 0.049] (**Figure 1**). All parameters were significant, $p < 0.05$.

Configural invariance, metric invariance, scalar invariance, and strict invariance across gender groups, as well as configural invariance across age groups, were obtained (**Table 3**).

Construct Validity of the MEMS

Convergent validity. The AVE values were good, >0.50, for the MEMS subscales: Comprehension, AVE = 0.67; Purpose, AVE = 0.70; and Mattering-R, AVE = 0.64; indicating good convergent validity of these scales (33).

Discriminant validity. The squared correlations between the MEMS subscales were lower than the AVE values, indicating discriminant validity (40): Comprehension-Purpose, $r^2_s = 0.65$; Comprehension-Mattering, $r^2_s = 0.59$; and Purpose-Mattering, $r^2_s = 0.43$.

Concurrent Validity of the MEMS Subscales

The MEMS subscales showed strong, positive correlations with both the PIL-10 and PANAS-P, and small to intermediate, negative correlations with both the BSI and PANAS-N (37) (**Table 4**).

Differences on the MEMS Between Gender and Age Groups

Because the Shapiro-Wilk test suggested a deviation from normality, the Mann-Whitney test for independent samples was used for the gender-related differences in the MEMS subscales. Women showed higher means than men on the three MEMS

TABLE 2 | Descriptive statistics of the MEMS items.

MEMS subscale	Item	Statement	*M*	*SD*	*Skw*	*K*	Corrected $r_{item\text{-}total}$
Comprehension	1	My life makes sense / Mi vida tiene sentido	6.05	1.193	−1.40	1.93	0.691
	7	I know what my life is about / Yo sé de qué trata mi vida	5.65	1.40	−1.11	1.00	0.804
	8	I can make sense of the things that happen in my life / Puedo construir un sentido de las cosas que pasan en mi vida	5.83	1.21	−1.09	1.11	0.798
	10	I understand my life / Comprendo mi vida	5.59	1.34	−0.95	0.60	0.840
	14	Looking at my life as a whole, things seem clear to me / Mirando mi vida como un todo, las cosas parecen evidentes	5.27	1.43	−0.65	−0.04	0.689
Purpose	3	I have aims in my life that are worth striving for / Tengo objetivos en mi vida por los que vale la pena luchar	6.30	1.05	−1.74	3.25	0.782
	5	I have certain life goals that guide me to keep going / Tengo ciertas metas en la vida que me obligan a seguir adelante	6.10	1.15	−1.50	2.44	0.792
	6	I have overarching goals that guide me in my life / Tengo objetivos globales que me guían en mi vida	5.99	1.21	−1.41	2.18	0.809
	9	I have goals goals in my life that are very important to me / Tengo metas y objetivos en mi vida muy importantes para mí	6.09	1.14	−1.40	2.02	0.855
	12	My direction in life in motivating to me / Mi sentido en la vida es motivador para mí	5.79	1.28	−1.20	1.37	0.744
Mattering	2	There is nothing special about my existence / No hay nada que haga especial mi existencia	5.93	1.72	−1.59	1.40	0.454
	4	Even a thousand year from now, it would still matter whether I existed of not / Incluso dentro de mil años, todavía importaría si yo existiera o no	4.71	2.06	−0.53	−0.95	0.701
	11	Whether my life ever existed matters even in the grand scheme of the universe / Si mi vida alguna vez existió, fue importante en el esquema general del universo	4.73	1.94	−0.55	−0.79	0.742
	13	I am certain that my life is of importance / Estoy seguro de que mi vida es importante	5.75	1.40	−1.25	1.28	0.714
	15	Even considering how big the universe is, I can say that my life matters / Incluso considerando lo grande que es el universo, puedo decir que mi vida importa	5.39	1.70	−1.09	0.45	0.762

N = 1,106. Sk = Skewness; K = Kurtosis. In parentheses, the standard error. Skewness Standard Error was 0.07; Kurtosis Standard Error was 0.15.

subscales. The difference was significant for the Purpose subscale (**Table 5**).

For the differences in the MEMS subscales between age groups, because the normality test was significant, the non-parametric Kruskal-Wallis test was used for comparisons. Likewise, because Levene's test for equality of variances was significant for the MEMS subscales (Comprehension: $F_{(2,1103)} = 8.360$, $p < 0.01$; Purpose: $F_{(2,1103)} = 3.404$, $p < 0.05$; Mattering: $F_{(2,1103)} = 7.964$, $p < 0.01$), the Games-Howell *post-hoc* test was used (**Table 6**).

On both the Comprehension and Purpose subscales, the higher the age range, the higher the mean. On the Mattering subscale, the age group that showed the highest mean ranged from 25 to 41 years old, followed by the 42-year-old and up group and the 15–24-year-old group. Mean differences were significant for all the comparisons, except for those between the 15–24-year-old group and the 25–41-year-old group on the Purpose subscale, $p_{Tukey} = 0.743$, and between the 25–42-year-old group and the 42-year-old and up group on the Mattering subscale, $p_{Tukey} = 0.288$.

The Predictive Role of Each MiL Dimension in Psychopathology in Participants With Mental Disorders

Regarding psychopathology of participants with mental disorders comprehension was highly and negatively associated with depression, and psychopathological distress. Purpose and mattering were highly and negatively associated with depression. Mattering was highly and negatively associated with depression, and psychopathological distress. Positive affect, was moderately and positively associated the three dimensions of MiL. The rest of the correlations can be seen in **Table 7**.

Depressive symptoms. The model composed of comprehension, purpose, and mattering was a significant predictor of depressive symptoms ($r^2 = 0.52$, $F_{(3,84)} = 30.32$, $p < 0.001$). The proposed model accounted for 52 % of the variance in depressive symptoms. When the individual contribution of each dimension of MiL was analyzed, mattering was the most strongly associated with depressive symptoms, followed by comprehension (**Table 8**).

Anxiety symptoms. The proposed model was a significant predictor of anxiety symptoms ($r^2 = 0.22$, $F_{(3,84)} = 8.052$, $p < 0.001$). The proposed model accounted for 22 % of the variance in anxiety symptoms. When the individual contribution of each dimension of MiL was analyzed, only mattering was a significant predictor of anxiety symptoms (**Table 8**).

Psychopathological distress. The proposed model was a significant predictor of general psychopathology (BSI-18 total scale) ($r^2 = 0.35$, $F_{(3,84)} = 14.88$, $p < 0.001$). The proposed model accounted for 35% of the variance in general psychopathology. When the individual contribution of each dimension of MiL was analyzed, only mattering was a significant predictor of anxiety symptoms (**Table 8**).

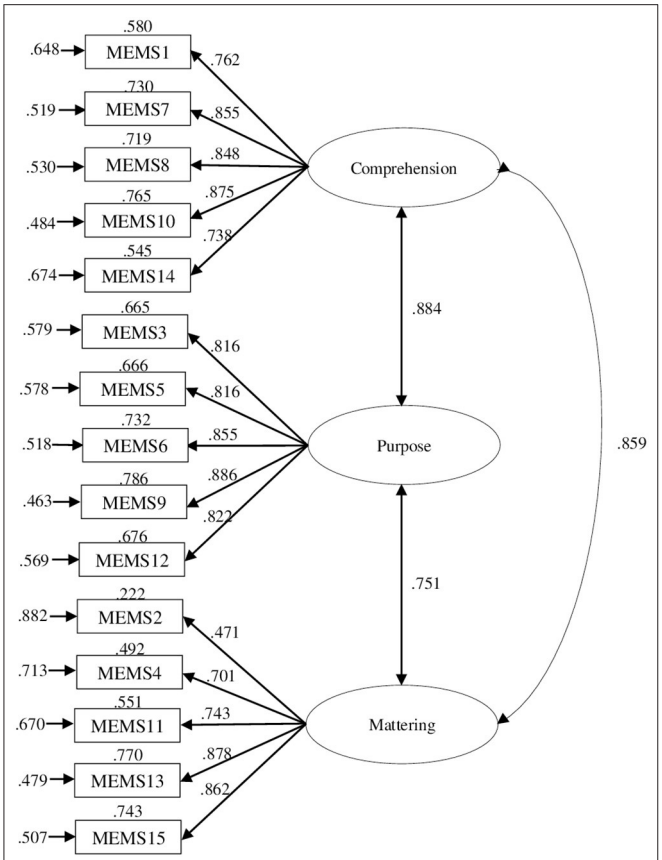

FIGURE 1 | Model for the MEMS obtained in this study. Values at the top of each rectangle are R^2 and values at the left of each rectangle are errors.

Positive affect. Finally, the proposed model was a significant predictor of positive affect ($r^2 = 0.24$, $F_{(3,84)} = 8.807$, $p < 0.001$). The proposed model accounted for 24% of the variance in positive affect. When the individual contribution of each dimension of MiL was analyzed, only purpose was a significant predictor of positive affect (**Table 8**).

DISCUSSION

The results obtained in the present study indicate that the three-factor model for the MEMS (comprehension, purpose, and mattering) showed an acceptable fit, similar to the original structure (22), in a sample of Spanish participants. The scale showed good internal consistency in the three factors, with acceptable indexes. The MEMS showed full invariance across gender groups, whereas only configural invariance across age groups was obtained. Moreover, our results showed good convergent validity and discriminant validity of the three MEMS subscales. Regarding concurrent validity, the MEMS subscales showed high, positive correlations with both the PIL-10 and PANAS-P, and low to medium, negative correlations with both the BSI-18 and PANAS-N.

Thus, our results support the original three-factor structure (22), and they coincide with Gerymski and Krok's study (23), which analyzed the factorial structure of the MEMS questionnaire in Poland. However, in the Polish validation, although the factorial structure with three factors was confirmed, the scale was reduced to nine items. In our study, in addition to confirming the original factorial structure, the same items were maintained in each factor as in the original. Thus, this is the first study to fully confirm the MEMS factorial structure in a sample of non-American participants.

Women showed higher means than men on the three MEMS subscales. The difference was significant for the purpose subscale. On the one hand, these results are consistent with those found in Spanish validation studies of one-dimensional MiL measures, such as the PIL, where women had higher scores than men (41). On the other hand, in studies of one-dimensional MiL measurements carried out in Anglo-Saxon samples, no differences were found in the MiL constructs depending on gender (1, 2). Thus, the differences in MiL scores between men and women could be due to sociocultural factors. Future studies should investigate the role of social, cultural, and religious factors in the elaboration of MiL, and analyze the properties of MEM in non-Western samples, such as African or Asian populations) (42).

On both the comprehension and purpose subscales, the higher age ranges showed higher scores. On the mattering subscale, the age group that showed the highest mean was the 25–41-year-old group, followed by the 42-and-up group and then the 15–24-year-old group. These results are similar to other studies that found that MiL assessed with the MLQ (presence of meaning) was positively associated with age (2), confirming that MiL and its dimensions is positively associated with age.

After confirming the factorial structure of the MEMS in the Spanish population, the second objective of the present study was to analyze which dimension of the MiL was most associated with different types of psychopathology, distress, and positive affect in a sample of participants diagnosed with mental disorders who were undergoing psychological or pharmacological treatment. Our results indicate that the different MiL dimensions are differentially associated with different symptoms of psychopathology and positive affect. Depressive symptoms were more robustly associated with both the mattering and comprehension dimensions. Symptoms of anxiety were associated with the mattering dimension. Psychopathological distress (composed of symptoms of anxiety, depression, and somatization together) was predicted primarily by the mattering dimension. Thus, in our clinical sample, the mattering dimension had a higher association with psychopathology than comprehension or purpose. These results support previous studies that found that mattering was negatively associated with suicide ideation (43) and other studies that showed the positive influence of mattering on mental health (44, 45). However, these results differ from other studies in non-clinical populations where the comprehension dimension showed a stronger association with psychopathology than the purpose and mattering dimensions [e.g., (22)]. Mattering, consists of two dimensions: interpersonal mattering and societal

TABLE 3 | Invariance model for the MEMS across gender and age groups.

	Model	SBχ^2 (*df*)	*p*	CFI	RMSEA [90% CI]	ΔSBχ^2 (*df*)	ΔCFI	ΔRMSEA
Gender	Baseline men	113.960 (87)	0.028	0.992	0.035 [0.012, 0.052]			
	Baseline women	175.093 (87)	0.000	0.995	0.034 [0.027, 0.042]			
	Configural	289.053 (174)	0.000	0.994	0.035 [0.027, 0.042]			
	Metric	304.980 (186)	0.000	0.994	0.034 [0.027, 0.041]	15.927 (12)	0.000	0.001
	Scalar	315.038 (198)	0.000	0.994	0.033 [0.026, 0.039]	10.058 (12)	0.000	0.001
	Strict	324.494 (213)	0.000	0.994	0.031 [0.024, 0.037]	9.456 (15)	0.000	0.002
Age	Baseline 18–24	63.340 (87)	0.974	1.000	0.000 [0.000, 0.000]			
	Baseline 25–41	124.919 (87)	0.005	0.996	0.029 [0.017, 0.040]			
	Baseline 42–83	70.903 (87)	0.895	1.000	0.000 [0.000, 0.015]			
	Configural	259.162 (261)	0.521	1.000	0.000 [0.000, 0.020]			
	Metric	395.885 (285)	0.000	0.994	0.033 [0.024, 0.040]	136.723 (24)	0.006	0.033
	Scalar	495.337 (309)	0.000	0.990	0.040 [0.034, 0.047]	99.452 (24)	0.004	0.007
	Strict	557.750 (339)	0.000	0.988	0.042 [0.036, 0.048]	62.413 (30)	0.002	0.002

TABLE 4 | Correlations between the MEMS subscales and the PIL-10, BIS, and PANAS scales.

	MEMS subcale		
	Comprehension	Purpose	Mattering
PIL-10	0.745**	0.726**	0.647**
BSI	−0.272**	−0.343**	−0.073*
PANAS-P	0.618**	0.599**	0.500**
PANAS-N	−0.229**	−0.282**	−0.070*

Spearman's Rho was used.
*$p < 0.05$ (bilateral); **$p < 0.01$ (bilateral).*

TABLE 5 | Descriptive statistics for men and women in the MEMS subscales and Mann-Whitney test.

			Descriptive statistics			Mann-Whitney test		
MEMS subscale	**Group**	***N***	***M***	***SD***	***SE***	***W***	***p***	r_b
Comprehension	Men	251	28.016	5.592	0.353	100846.000	0.152	−0.059
	Women	854	28.500	5.603	0.192			
Purpose	Men	251	29.618	5.027	0.317	93865.500	0.002	−0.124
	Women	854	30.451	5.096	0.174			
Mattering	Men	251	26.000	7.244	0.457	102443.500	0.285	−0.044
	Women	854	26.542	7.088	0.243			

For the Mann-Whitney test, effect size is given by the rank biserial correlation, r_b.

mattering (46). Interpersonal mattering refers to a person's perception that he or she matters to others and societal mattering is "the feeling of making a difference in the broader scheme of sociopolitical events—of feeling that one's thoughts and actions have an impact, create ripples, are felt" (46). In people with mental disorders, both dimensions of mattering could be impaired. Previous studies about mental health symptoms and socio-economic conditions found that people with mental disorders showed poor social support, high unemployment rate (61.4% in our sample), and have functional disability (47).

Finally, positive affect was predicted by the purpose dimension. The association between purpose and positive affect obtained in our clinical sample coincides with the results of previous studies with non-clinical populations (22).

Our results support previous studies that demonstrated that multidimensional questionnaires to evaluate MiL showed better psychometric properties and better results when related to well-being or psychopathology variables than one-dimensional models (2).

These results have important clinical implications. Although previous studies found a strong association between MiL and psychopathology (9, 10, 14, 15), these studies considered MiL as a one-dimensional construct, which made it difficult to know what the most important MiL components were and, thus, develop specific interventions focused on the most important MiL dimensions for each patient. On the one hand, our results suggest that when distress symptoms, especially anxiety and depressive symptoms, are present, it would be helpful to carry out psychological interventions that focus on the mattering dimension. On the other hand, to increase positive affect, our results suggest that it might be necessary to intervene in the purpose dimension. Review studies suggest that meaning-centered therapies strongly improve quality of life and reduce psychological distress, particularly in transitional moments in life, participants with chronic illnesses, and patients with low meaning in life (48).

Our study has several limitations. First, the sampling method employed snowball techniques to recruit participants through main social networks (Facebook, WhatsApp, Twitter, Linkedin, and Instagram). Therefore, the sample may not be representative

TABLE 6 | Descriptive statistics, Kruskal-Wallis test, and *post-hoc* test for the differences between groups in the MEMS subscales.

			Descriptive statistics		Kruskal-Wallis test			Games-Howell *post-hoc* comparisons age groups					
MEMS subscale	**Age group**	***N***	***M***	***SD***	***H***	***df***	***p***	**Comparison**	**Mean Difference**	***SE***	***t***	***df***	p_{Tukey}
Comprehension	15–24	298	26.46	5.74	59.527	2	0.000	15–24/25–41 years	−2.275	0.417	−5.461	615.525	0.000
	25–41	513	28.73	5.68				15–24/42+ years	−3.283	0.433	−7.590	572.991	0.000
	42+	295	29.74	4.75				25–41/42+ years	−1.008	0.373	−2.700	703.386	0.019
Purpose	15–24	298	29.73	5.04	17.207	2	0.000	15–24/25–41 years	−0.276	0.376	−0.735	652.018	0.743
	25–41	513	30.01	5.36				15–24/42+ years	−1.516	0.393	−3.861	585.134	0.000
	42+	295	31.25	4.51				25–41/42+ years	−1.240	0.353	−3.508	699.909	0.001
Mattering	15–24	298	23.12	7.47	89.959	2	0.000	15–24/25-41 years	−4.773	0.524	−9.112	566.433	0.000
	25–41	513	27.89	6.69				15–24/42+ years	−4.055	0.572	−7.095	579.420	0.000
	42+	295	27.17	6.41				25–41/42+ years	0.718	0.476	1.508	633.980	0.288

TABLE 7 | Correlations between the variables studied in clinical participants.

	***M* (*SD*)**	**2**	**3**	**4**	**5**	**6**	**7**
1 Comprehension (MEMS)	24.93 (7.06)	0.78*	0.78*	−0.67*	−0.42*	−0.55*	0.45*
2 Purpose (MEMS)	28.62 (6.32)		0.76*	−0.64*	−0.36*	−0.48*	0.46*
3 Mattering (MEMS)	21.65 (8.12)			−0.67*	−0.46*	−0.56*	0.36*
4 Depression (BSI)	10.62 (6.42)				0.71*	0.86*	−0.19*
5 Anxiety (BSI)	9.86 (6.32)					0.93*	−0.12
6 General Psychopathology (BSI)	29.02 (16.79)						−0.01
7 Positive Affect (PANAS)	31.92 (5.30)						

MEMS, Multidimensional Existencial Meaning Scale; BSI, Brief Simptoms Scale; PANAS, Positive Negative Affect Schedule.
*$p < 0.01$.

TABLE 8 | Regression analyses predicting depression, anxiety, general psychopathology, and positive affect in participants with mental disorders.

Dependent variable	**Predictor variable**	**B standardized**	***SE***	***t***
Depressive symptoms	Comprehension	−0.248	0.124	−2.001*
	Purpose	−0.187	0.134	−1.396
	Mattering	−0.256	0.104	−2.467*
Anxiety	Comprehension	−0.164	0.155	−1.056
	Purpose	0.065	0.168	0.385
	Mattering	−0.287	0.130	−2.204*
General psychopathology	comprehension	−0.676	0.377	−1.792
	Purpose	−0.003	0.408	−0.007
	Mattering	−0.700	0.316	−2.214*
Positive affect	Comprehension	0.213	0.129	1.652
	Purpose	0.269	0.139	1.931*
	Mattering	0.068	0.108	−0.626

*$p < 0.01$; **$p < 0.001$.

of the general Spanish population. Furthermore, although the Spanish version of the MEMS has shown adequate psychometric characteristics, an analysis of test-retest reliability could not be performed. Future studies should be longitudinal and confirm the test-retest reliability of the MEMS. To recruit the clinical sample, no diagnosis was made by psychologists specialized in clinical psychology or psychiatrists, and so the diagnoses were not confirmed. The results must be understood in terms of association, rather than prediction or causality, because the study was cross-sectional and not experimental.

Despite the aforementioned limitations, our study suggests that the MEMS is an adequate instrument to assess the three dimensions of MiL (comprehension, purpose, and mattering) in Spanish-speaking participants. Moreover, our results suggest that it is necessary to assess MiL from a multidimensional perspective. The present study tries to make a modest contribution to this line of research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Valencian University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM drafted the manuscript with important contributions from JG-A and VG. JM in collaboration with JG-A,

VG, RB, SR and MT-I, designed the study and participated in each of its phases. JG-A, VG, RB, SR and MT-I translated and adapted the MEMS. All authors participated in the review and revision of the manuscript and have approved the final manuscript to be published.

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BRIEF RESEARCH REPORT
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Dissociative Model in Patients With Resistant Schizophrenia

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Background: Schizophrenia is a severe mental illness in which, despite the growing number of antipsychotics from 30 to 50% of patients remain resistant to treatment. Many resistance factors have been identified. Dissociation as a clinical phenomenon is associated with a loss of integrity between memories and perceptions of reality. Dissociative symptoms have also been found in patients with schizophrenia of varying severity. The established dispersion of the degree of dissociation in patients with schizophrenia gave us reason to look for the connection between the degree of dissociation and resistance to therapy.

Methods: The type of study is correlation analysis. 106 patients with schizophrenia were evaluated. Of these, 45 with resistant schizophrenia and 60 with clinical remission. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scales were used to assess clinical symptoms. The assessment of dissociative symptoms was made with the scale for dissociative experiences (DES). Statistical methods were used to analyze the differences in results between the two groups of patients.

Results: Patients with resistant schizophrenia have a higher level of dissociation than patients in remission. This difference is significant and demonstrative with more than twice the level of dissociation in patients with resistant schizophrenia.
The level of dissociation measured in patients with resistant schizophrenia is as high as the points on the DES in dissociative personality disorder.

Conclusion: Patients with resistant schizophrenia have a much higher level of dissociation than patients in clinical remission. The established difference between the two groups support to assume that resistance to the administered antipsychotics is associated with the presence of high dissociation in the group of resistant patients. These results give us explanation to think about therapeutic options outside the field of antipsychotic drugs as well as to consider different strategies earlier in the diagnostic process.

Keywords: resistance, schizophrenia, dissociation, resistant schizophrenia, treatment, diagnosis, antipsychotic drugs

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BACKGROUND

Schizophrenia is a serious mental illness which is characterized by changes in information processing as a consequence of misinterpretation of stimuli from the external environment. As a result, the clinical picture is characterized by positive symptoms (delusions and hallucinations), negative (apathy, anhedonia, dull affect, and loss of social cohesion), and cognitive ones with

changes in attention and working memory. In addition to these clinically important symptoms for the diagnosis of schizophrenia, depressive, anxious, and cognitive symptoms are common if not always present (1). These psychiatric manifestations are associated with metabolic, lipid, and immune changes, often requiring additional therapeutic approaches (2, 3). Interesting observations on the level of serum lipids have been made in patients with schizophrenia and in persons using psychostimulants. Decreases in serum lipid levels were observed in both groups (3). Studies assessing self-perception and assessment of interpersonal space have been performed (4). There is evidence that as anxiety increases, interpersonal space increases (5). Such analyzes have also been performed in patients with schizophrenia who show that they have an increase in interpersonal space (6). Impaired cognitive assessment of reality and self-perception is associated with changes in behavior and the appearance of typical symptoms of schizophrenia associated with metabolic disorders as well as changes in neural connections between brain regions (7). This complex picture of changes in perception, behavior, metabolic characteristics, and functional connectivity makes schizophrenia a therapeutic challenge.

This is the reason despite the constant expansion of various therapeutic interventions, a significant percentage of patients remain resistant and pose a serious personal family and social problem. Some authors try to consider patients with resistant schizophrenia as a separate category. This raises the question of looking for different therapeutic approaches in them (2, 8, 9).

Janet presented the concept of dissociation for the first time at the end from 1,800, which is defined as a failure to integrate experiences that are usually related to each other in stream of consciousness (10). Dissociation is the partial or complete loss of normal integration between memories of the past, awareness of one's identity and immediate sensations, and control of bodily movements (11). Dissociation is a special form of consciousness in which events that would normally be related are separated from each other (12). Some authors (13) believe that dissociation is not only pathological, but may also play a role in some adaptive functions. It is also observed in healthy individuals in certain conditions (14).

Historically, dissociation as a clinical phenomenon has been associated with the presence of traumatic events leading to dissociative symptoms (15). A link has been found between dissociative symptoms and traumatic childhood events. Putnam (13) found that the most important traumas originate from childhood due to physical or sexual abuse with subsequent development of symptoms often after many years. According to the same author, dissociative symptoms also often occur in adults with severe traumatic event or a series of traumatic events. He found this in about half of the cases of dissociation. On the other hand, in direct clinical practice with adult patients, it is difficult to make a retrospective assessment of childhood experiences in order to give them the appropriate clinical weight. The authors found that 59.6% of 468 patients with a proven history of childhood sexual abuse were unable to recall episodes of past violence (16). Contradictory data are also available. The problem with the analysis of trauma in early childhood in the evaluation of adult patients is related to the fact that the manifestation of false memory experiences for the presence of trauma is often provoked (17).

It was found a traumagenic neurodevelopmental (TN) model of schizophrenia. Authors find the similarities between the effects of traumatic events on the developing brain and the biological abnormalities found in persons diagnosed with schizophrenia (12). The current diathesis-stress model of schizophrenia proposes that a genetic deficit creates a predisposing vulnerability in the form of oversenstivity to stress (15).

Corresponding changes in interpersonal space and self-esteem have been found in patients with dissociative disorders as well as in patients with schizophrenia (5, 18). Low levels of serum lipids have been reported (19) as well as impaired functional connectivity between brain regions (20).

The connection between dissociation and psychosis has been examined by Eugen Bleuler in patients with schizophrenia (21). In his Textbook of Psychiatry, he writes (21): "It is not only in hysteria that one finds an arrangement of different personalities who inherit from each other. Through such a mechanism, schizophrenia gives rise to different personalities existing side by side [(21), p. 138]. Bleuler has suggested that schizophrenia is a division of mental relationships similar to hysteria, but in a very extreme form. Psychotic decompensation of some individuals with psychotic symptoms, such as hallucinations, may occur. There are also a large number of observations showing a high level of dissociation in patients with schizophrenia (15, 22–27). The above data suggest a close link between schizophrenia and dissociative disorders. Several studies have found surprisingly high coincidences in the symptoms of these diagnoses (27–30). Even the symptoms described by Kurt Schneider as pathognomonic for schizophrenia have been proposed to be more characteristic of dissociative disorders (31, 32). Other studies suggest that there are similarities only in hallucinatory production as a characteristic of voices and their expression, but not in the presence of formal thought disorders, bizarre delusions, and negative symptoms (33). Studies indicate that up to 50% of patients with psychosis have severe dissociative symptoms (34, 35). This established overlap of symptoms in schizophrenia and dissociative disorder raises questions about therapy and expectations that a similar pattern of response will be observed. The data show results contrary to expectations. On the one hand, the treatment of schizophrenia is mainly with antipsychotic drugs, and on the other hand, the treatment of dissociative phenomena with antipsychotic drugs is generally ineffective (36). Examining the relationship between schizophrenia and dissociation, some authors raise the question of the existence of a subtype of schizophrenia, allowing for a new conceptualization of the relationship between them (37).

Resistance to drug therapy is registered in about 30–50% of patients with schizophrenia (38–44). The analysis of the relationship between dissociation in patients with schizophrenia and the course of the disease in them shows that those with a high degree of dissociation have a more severe course and more pronounced symptoms (45).

In the analysis of the literature available to us, we did not find a comparative study of the differences in dissociative

symptoms in patients with resistant schizophrenia and those in clinical remission.

Working hypothesis: We suppose that the level of dissociation in patients with resistance to therapy will be higher than those in clinical remission.

MATERIALS AND METHODS

105 patients with schizophrenia were observed. Of these, 45 have resistant schizophrenia and the remaining 60 are in clinical remission.

Including criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia (46). They are:

1. Assessment of symptoms with the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scale (47, 48).
2. Prospective monitoring for a period of at least 12 weeks.
3. Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg chlorpromazine equivalents.
4. Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.
5. The assessment of social dysfunction using the SOFAS scale is below 60.

The exclusion criteria are:

1. Mental retardation
2. Presence of organic brain damage
3. Concomitant progressive neurological or severe somatic diseases.
4. Expressed personality change
5. Score of MMSI below 25 points.

The Dissociative Experiences Scale (DES) was used to assess dissociative symptoms (22).

The statistical software package SPSS, was used for statistical data processing.

Descriptive analyzes, correlation analysis, dispersion analysis, ANOVA, and a non-parametric statistical method were used [Mann Whitney U-test, (49)].

RESULTS

The mean age of patients in the group of resistant schizophrenia was 36.98 years. The minimum age is 21 years and the maximum is 60 years.

The mean age of patients in the group of schizophrenia in clinical remission was 37.25 years. The minimum is 23 years and the maximum is 63 years.

We do not find a difference in the mean age of the patients in the both groups at the time of the study.

The mean value of the dissociative symptoms scale found in all patients with schizophrenia was 29.1356, standard deviation was 22.3898, and the lowest and highest values were 0 and 97, respectively.

TABLE 1 | Descriptive analysis, the mean values, the median value, the standard deviation, and the standard error in the sample.

Report

Dissociation scale

Effect of therapy	Mean	*N*	Std. deviation	Std. error of mean	Median
Resistant	45.733	45	19.3313	2.8817	46.000
Remission	17.073	60	15.7153	2.0288	11.750
Total	29.356	105	22.3898	2.1850	22.500

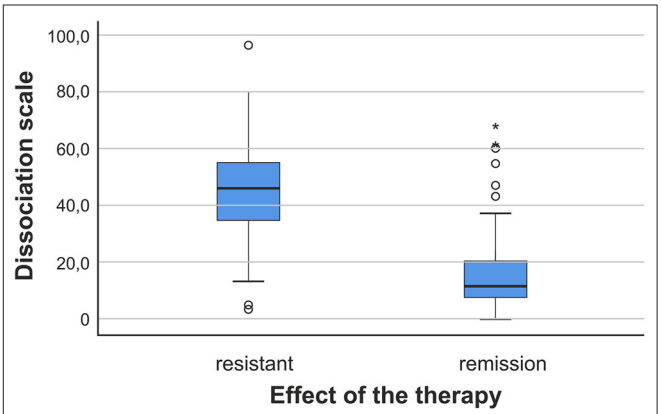

FIGURE 1 | The variance of the results measured with DES in both groups of patients. The variance—in blue.

The mean value of the measured points with the Carlson and Putnam scale in patients with resistant schizophrenia is 42.578, and the standard deviation is 20.8977. Their average level of dissociation is commensurate with the level needed to diagnose dissociative personality disorder according to the interpretation of the scale (requires values above 48 on the scale).

For patients in clinical remission, the mean was 15.907 and the standard deviation was 14.530. Their mean level of dissociation is commensurate with the level required to diagnose schizophrenia according to the interpretation of the scale (requires values of 15.4).

Up to three times the incidence of dissociation values is observed in patients with resistance compared to those in remission. The analysis of the median value in the two groups showed an even greater difference—up to four times higher in the group with patients resistant to therapy (**Table 1**; **Figure 1**).

In the analysis of the intragroup distribution of level of dissociation in patients with resistant schizophrenia, it was found that the main grouping of results is in the range of 30–60 on the scale used. This result shows that the majority of patients have a very high level of dissociation.

From the analysis of the distribution of data in patients in clinical remission, we found that the main distribution of patients is grouped in the range from 0 to about 20. We observe a much lower level of dissociation in patients in remission.

The statistical analysis of the results of Mann-Whitney U test is shown in **Table 2** (Ranks) and **Table 3** (Statistics) (***$p < 0.001$).

A variance analysis of the relationship between the level of dissociation and resistance to treatment is presented in **Table 4**.

The difference in the degree of dissociation registered by us in the two groups of patients raised the question: Is there a correlation between the value of dissociation and the values of the PANSS and BPRS scales.

The performed correlation analysis showed the presence of correlation $p < 0.05$, **Table 5**.

Conducting a correlation analysis showed that there was a statistically significant correlation between the registered psychotic and dissociative symptoms (**Table 6**).

DISCUSSION

Our results show a high degree of dissociation in patients with resistant schizophrenia, which is up to three times higher than in patients in clinical remission. We also find a correlation between the high values of the symptoms measured with the PANSS and BPRS scales and the dissociative symptoms registered with the DES.

Our study of dissociative symptoms coincides with the analysis of other teams, which show the presence of dissociative symptoms in patients with schizophrenia in the range from 11.9 to 44.24 (50–52). Some authors, in addition to assessing the dissociation, also make an analysis in dynamics: in admission and in stabilizing the condition. They do not get much change in the points on the DES from 19.2 to 14.1 (53). We find a mean score on dissociation level in all patients of 29.1356. Our data occupy an intermediate position compared to those described in the literature. Our results confirm the views of pioneers in schizophrenology such as Eugen Bleuler that schizophrenia is a state of extreme degree of dissociation (21).

In the previous studies, patients with resistance and those in clinical remission were not considered separately. The results of the points on the scale for dissociative experiences (DES) in patients in remission observed by us coincide with the criteria of the scale for patients with schizophrenia-−15.4. The results of other studies are mixed. We believe that this is because they have not considered patients separately—resistant and those in remission. Given that schizophrenia is a heterogeneous disease, it is also quite understandable the difference in the values of dissociative symptoms described in the individual studies. Over the years, there have been many analyzes of the overlap of symptoms of dissociative personality disorder and schizophrenia. Numerous studies have shown that up to 50% of patients with schizophrenia meet the diagnostic criteria for dissociative personality disorder (34, 35). These observations, as well as our data, do not show that in fact a probable reason for the lack of efficiency is the high degree of dissociation, which correlates positively with the high scores

TABLE 2 | Mann-Whitney U test—description.

Ranks

	Effect of therapy	*N*	Mean rank	Sum of ranks
Dissociation scale	Resistant	45	75.18	3383.00
	Remission	60	36.37	2182.00
	Total	105		

TABLE 3 | Mann-Whitney U test—statistics.

Test Statistics

	Dissociation scale
Mann-Whitney U test	352.000
Wilcoxon W	2182.000
Z	−6.465
Asymp. Sig. (two -tailed)	0.000
Exact Sig. (two-tailed)	0.000
Exact Sig. (one-tailed)	0.000
Point probability	0.000

TABLE 5 | The assessed mean values of the PANSS, BPRS, and DES scales.

	Mean	Std. deviation	*N*
PANSS positive	14.50	5.242	105
PANSS negative	16.95	6.316	105
PANSS disorganized	31.64	10.181	105
PANSS general	62.97	19.241	105
BPRS	45.12	13.266	105
DES	29.356	22.3892	105

TABLE 4 | The variance analysis of the results of the two groups of patients.

ANOVA Table

			Sum of squares	*df*	Mean square	*F*	Sig.
Dissociation scale Effect of therapy	Between groups	(Combined)	21121.601	1	21121.601	70.146	0.000
	Within groups		31014.037	103	301.107		
	Total		52135.638	104			

*$p < 0.001$.

TABLE 6 | Dispersion analysis between the dissociation scale (DES) and the clinical scales PANSS and BPRS.

ANOVA Table

			Sum of squares	*df*	Mean square	*F*	Sig.
PANSS/Dissociation	Between groups	(Combined)	28544.064	58	492.139	2.274	0.002
	Within groups		9956.850	46	216.453		
	Total		38500.914	104			
BPRS/Dissociation	Between groups	(Combined)	12428.015	58	214.276	1.678	0.035
	Within groups		5875.375	46	127.726		
	Total		18303.390	104			

*$p < 0.05$.

made with the PANSS and BPRS scales. This high level of resistance that we observe and register challenge of discussing the term resistance to treatment with "antidopaminergic drugs." Dissociative disorders and symptoms have no effect from antipsychotic treatment (36).

In this sense, the question can be asked whether resistant schizophrenia is a form of dissociative disorder or mixture of the both entities. On the other hand, our results provide a basis for rethinking the diagnostic categories and research criteria used in the context of the relationship between the mind and the brain (54). The question remains whether high dissociation scales are the cause or consequence of the development of the neurodegenerative process in these patients (40, 55). Studies show that in some patients there is a progression of the disease, while in others there is a stationary condition that lasts for years. Magnetic resonance imaging data show that we can distinguish two groups of patients in comparative follow-up. Some have a neurodegenerative process and others do not (56).

The limitation of our study is related to the fact that we make a cross-section of the patient's condition in terms of dissociative symptoms. Longitudinal studies are needed to determine how the symptoms change over time. On the other hand, it is not clear whether the dissociative symptoms did not develop in parallel over time in patients with schizophrenia from the perspective of hospitalizations and in the process of treatment with various antipsychotic drugs. Some authors in a study found in the general population up to 1.7% of people at high risk of developing psychosis (57). No data have been established on the level of dissociative symptoms in them. Our study provides direction to consider assessment of dissociation early in the diagnostic process, especially in patients with the first psychotic episode, in order to discuss prognosis and associated therapy.

CONCLUSION

We find a high degree of dissociation in patients with resistant schizophrenia. There is a high correlation between psychotic symptoms measured with the PANSS and BPRS scales and dissociative symptoms assessed with the DES. We found that the points on the scale for the level of dissociation in patients with resistant schizophrenia are as high as the requirement of the points on the scale for the assessment of dissociative personality disorder. The data we found for a high scale of dissociation in patients with resistance entitles us to seek therapeutic interventions outside the field of antipsychotic drugs. Therapeutic approaches in dissociative disorders may be considered (symptomatic and psychotherapeutic) as well as consideration of earlier use of electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical committee of the University Hospital of Trakia University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Can Cognitive Control and Attentional Biases Explain More of the Variance in Depressive Symptoms Than Behavioral Processes? A Path Analysis Approach

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Background: This study explored the proportion of variance in depressive symptoms explained by processes targeted by BA (activation, behavioral avoidance, anticipatory pleasure, and brooding), and processes targeted by cognitive control training (cognitive control, attentional biases, and brooding).

Methods: Five hundred and twenty adults were recruited. They completed a spatial cueing task as a measure of attentional biases and a cognitive task as a measure of cognitive control and completed self-report measures of activation, behavioral avoidance, anticipatory pleasure, brooding, and depressive symptoms. With path analysis models, we explored the relationships between these predictors and depressive symptoms.

Results: BA processes were significant predictors of depressive symptoms, and activation partially predicted anticipatory pleasure, which in turn predicted depressive symptoms. However, cognitive control and attentional biases predicted neither brooding nor depressive symptoms. A comprehensive model including all processes fit the data but did not explain more of the variance in brooding or depressive symptoms than a model including only BA processes.

Limitations: The spatial cueing task was associated with low reliability and the use of a non-clinical sample limited the generalizability of the conclusions.

Conclusion: Activation, behavioral avoidance, brooding, and anticipatory pleasure are relevant processes to target in order to reduce depressive symptoms, while cognitive control and attentional biases are not.

Keywords: behavioral activation, cognitive control training, depression, brooding, cognitive control

INTRODUCTION

Depression is a very prevalent condition (World Health Organization, 2020) and one of the leading causes of disability worldwide (Kessler and Bromet, 2013). Although there are currently several evidence-based interventions for depression associated with a significant reduction of depressive mood, the rates of relapse and recurrence of depression remain high (Vittengl et al., 2007; Bockting et al., 2015). One possible explanation is that existing treatments do not sufficiently target vulnerability processes involved in the etiology and maintenance of depression. A combination of several existing treatments could be a promising way to improve depression care.

Inspired by behavioral models in psychology, behavioral activation (BA) aims to increase activation and reduce avoidance patterns in order to increase reinforcing experiences and consequently reduce depressive symptoms (Lejuez et al., 2001; Martell et al., 2001; Manos et al., 2010). Empirical data revealed that avoidance positively predicts depressive symptoms while activation negatively predicts them (Wagener et al., 2016). Moreover, brooding, perceived as frequent covert avoidance, positively predicts depressive symptoms (Nolen-Hoeksema et al., 2008; Watkins and Roberts, 2020). BA is a well-established empirical treatment that improves depressive symptomatology (Ekers et al., 2014; Cuijpers et al., 2020), wellbeing (Mazzucchelli et al., 2010), and quality of life (Orgeta et al., 2017) of clinically and subclinically depressed individuals. More specifically, empirical data show that BA improves activation (Dimidjian et al., 2017) and decreases avoidance (Krings et al., 2020) and brooding (McIndoo et al., 2016). In addition, preliminary research using fMRI found that depressed participants treated with BA showed decreased activation in the prefrontal neuronal structures involved in cognitive control (CC; Dichter et al., 2010), as well as improved functioning of appetitive reward–related neuronal structures involved in the anticipation of pleasure (Dichter et al., 2009).

Behavioral models suggest that BA increases positively reinforcing experiences from engagement in rewarding activities (Hopko et al., 2003). Some authors have recently emphasized the importance of further investigating the role of the appetitive reward system in BA models (Blairy et al., 2020; Forbes, 2020; Nagy et al., 2020). The appetitive reward system is associated with two distinct temporal orientations of pleasure. The first one involves savoring future positive events, also called anticipatory pleasure or *wanting*, while the second involves savoring present events, also called consummatory pleasure or *liking* (Berridge and Kringelbach, 2008; Admon and Pizzagalli, 2015). Both components have been reported to be disturbed in depression (Treadway and Zald, 2011; Wu et al., 2017). However, in a subclinically depressed sample, anticipatory pleasure was identified as a significant predictor of subsequent consummatory pleasure, suggesting that, in depression, the wanting component is more clinically relevant than the liking component (Li et al., 2019). Additionally, lack of anticipatory pleasure is predictive of a poorer course of depression (Morris et al., 2009) and suicidality (Winer et al., 2014). Regarding the interplay between anticipatory pleasure and activation, previous research suggests two hypotheses. First, anticipatory pleasure might affect depressed individuals' motivation to engage in potentially rewarding experiences. Empirical data support this hypothesis, as previous studies reported that anticipatory pleasure was a significant predictor of motivation to exert effort for rewards in non-depressed (Geaney et al., 2015) and depressed samples (Sherdell et al., 2012). Second, anticipatory pleasure might be influenced by engagement in rewarding experiences. Indeed, Beevers and Meyer (2002) reported that rewarding experiences predict positive expectations, which then significantly predict symptoms of depression. Furthermore, Bakker et al. (2017) reported that active behaviors influenced reward anticipation in a subclinically depressed sample. Given previous findings suggesting that activation, behavioral avoidance, anticipatory pleasure, and brooding predict depressive symptoms, the present study sought to examine the relationships between these processes and depressive symptoms, as well as between activation and anticipatory pleasure.

Even though BA is associated with medium to large effect sizes in the reduction of depressive symptomatology, its efficacy could still be enhanced (Cuijpers et al., 2020). A promising way to enhance the efficacy of BA is to combine it with another therapeutic intervention (Averill et al., 2019; Van den Bergh et al., 2020). Cognitive Control Training (CCT) is a recent empirically validated cognitive treatment of depression, which activates prefrontal neural networks with repeated cognitive exercises designed to engage those structures (Koster et al., 2017). CCT uses working memory tasks to strengthen prefrontal neural activation (Koster et al., 2017). It aims to increase CC abilities in order to reduce cognitive biases (i.e., attentional biases- AB_s) and non-adaptive cognitive regulation strategies (e.g., brooding) and consequently reduce depression (De Raedt and Koster, 2010; Koster et al., 2011). As the impaired disengagement hypothesis posits, low CC resources lead to generally impaired attentional disengagement (Koster et al., 2011). This impaired disengagement maintains AB_s (i.e., disengagement from sad cues and from happy cues) and brooding, which are two vulnerability factors for depression [for a review, see LeMoult and Gotlib, (2019)]. Indeed, empirical data suggest that CCT may reduce depressive symptoms and brooding in depressed patients treated with a CCT (Siegle et al., 2014; Vanderhasselt et al., 2015). In addition, previous studies have indicated that CC's influence on depressive symptoms might be at least partly mediated by brooding (Hsu et al., 2015; Hoorelbeke and Koster, 2017), as well as the impact of AB_s on depressive symptoms (Sanchez et al., 2019; Yaroslavsky et al., 2019). Given previous findings suggesting that CC and AB_s predict brooding and depressive symptoms, this study examined the relationships between these processes and depressive symptoms, as well as among the different processes.

In light previous results, the combination of BA and CCT could amplify the efficacy of BA because the two treatments act on different depressive vulnerability processes (activation, behavioral avoidance, and anticipatory pleasure for BA; CC and AB_s for CCT), as well as on a common process, namely brooding. Indeed, if cognitive resources influence brooding, it is possible that the combination of BA and CCT could strengthen

individual capacities to disengage from brooding in the long term. To date, one study has investigated the combination of a CCT and a BA treatment in a clinically depressed sample (Moshier and Otto, 2017). Both conditions (BA in adjunction to CCT and BA in adjunction to a sham procedure) were associated with a substantial reduction in depressive symptoms and brooding. However, repeated measures ANOVAs used to examine symptoms as functions of the interaction between time and treatment condition were non-significant and all effect sizes were small (all $\eta p^2 < 0.07$). The absence of the expected significance could be attributable to the small sample size ($n = 34$), which also hindered the identification of potential mediators of treatment effects, including brooding.

Using path analysis models and a large sample of participants, we sought to investigate whether the adjunction of certain cognitive processes to BA processes could predict more depressive symptoms. If this is the case, adding cognitive training to BA could make the treatment more efficient (i.e., reduce depressive symptoms). This study investigates relationships between depressive symptoms and, on the one hand, the target processes of BA treatment (activation, behavioral avoidance, anticipatory pleasure and brooding), and on the other hand, the target processes of CCT (CC, AB_s, and brooding). Overall, four models were tested. First, we tested the relevance of two behavioral models with Activation, Behavioral Avoidance, Brooding and Anticipatory Pleasure as processes predicting depressive symptoms. Model 1 tested the hypothesis that Anticipatory Pleasure would partially predict Activation, which in turn would predict depressive symptoms. Model 2 tested the reverse hypothesis: that activation would partially predict Anticipatory Pleasure, which in turn would predict depressive symptoms. Second, we tested a cognitive model (Model 3) with CC, AB_s and Brooding as predictors of depressive symptoms. In Model 3, we also tested the hypothesis that CC would partially predict Brooding, which in turn would predict depressive symptoms, and that AB_s would partially predict Brooding, which in turn would predict depression symptoms. Third, a comprehensive model was tested (Model 4) with the hypothesis that the integration of behavioral and cognitive processes would explain more of the variance in brooding and depressive symptoms than each model separately. Schemas depicting the four models are presented in **Figures 1** and **2**. Finally, we identify the unique variance in depressive symptoms that is explained by behavioral and cognitive processes, independent of the other variables. This analysis helps to investigate the most promising therapeutic targets and isolate the most relevant therapeutic levers.

MATERIALS AND METHODS

Participants

The participants were 549 unselected French-speaking adults aged from 18 to 64 years. Advertisements, university intranets, and the waiting rooms of healthcare centers were used to recruit participants. Data analyses were based on 520 adults (338 females, 182 males) with a mean age of 30.99 years (SD = 11.89; range: 18–64). Five participants were excluded because of a history of psychotic mental disorders, two were excluded because of a history of substance abuse or dependence including alcohol (less than 3 years of abstinence—except nicotine or caffeine), 11 for a history of neurological disorder, and two for the use of anxiolytics or other drugs on the day of the assessment. In addition, two participants were excluded because of anti-psychotic medication, two because of recent changes in antidepressant medication (less than 4 weeks). Participants had normal or corrected vision and no history of bipolar disorder. Five participants were also excluded from the analysis due to extensive missing data.

A Priori Power Analysis

For path analysis, a sample size of more than 500 participants is considered as very good to test confirmatory models (Comfrey and Lee, 1992). However, some authors suggest that these rules are problematic because they are not model-specific and may lead to grossly over-or underestimated sample size requirements (Wolf et al., 2013). Therefore, we have estimated the optimal sample considering the expected effect size (RMSEA <0.05), type of model (path analysis), degrees of freedom based on the number of parameters estimated by the model (df = 12) to reach a statistical power of 0.80. The analysis revealed that the optimal sample size for the comprehensive model (Model 4) is 578 participants.

Materials

The cross-sectional study was conducted before the COVID-19 lockdown. The materials consisted of a computerized task and self-report questionnaires.

Demographic Questionnaire

A sociodemographic questionnaire addressed questions about age, gender, marital status, employment status, medication, quality of vision, neurological history, and past depressive episodes.

Depressive Symptomatology

The Beck Depression Inventory—Second Edition (BDI-II) is a 21-item scale that assesses the severity of depressive symptoms in the previous 2 weeks (Beck et al., 1996). Higher scores indicate greater severity. We used the validated French version of the scale (Centre de Psychologie appliquée, 1996). In the present sample, Cronbach's α for the whole scale was 0.86.

Activation and Behavioral Avoidance

The Behavioral Activation for Depression Scale—Short Form (BADS-SF) is a 9-item scale assessing behavioral activation (Manos et al., 2011). Two subscales are identified: Activation (four items) and Avoidance (three items). We removed one item from the Avoidance subscale (item 7), which refers to brooding, to avoid a conceptual overlap between behavioral avoidance and brooding. Higher scores indicate higher behavioral activation and behavioral avoidance levels, respectively. We used the validated French version of the

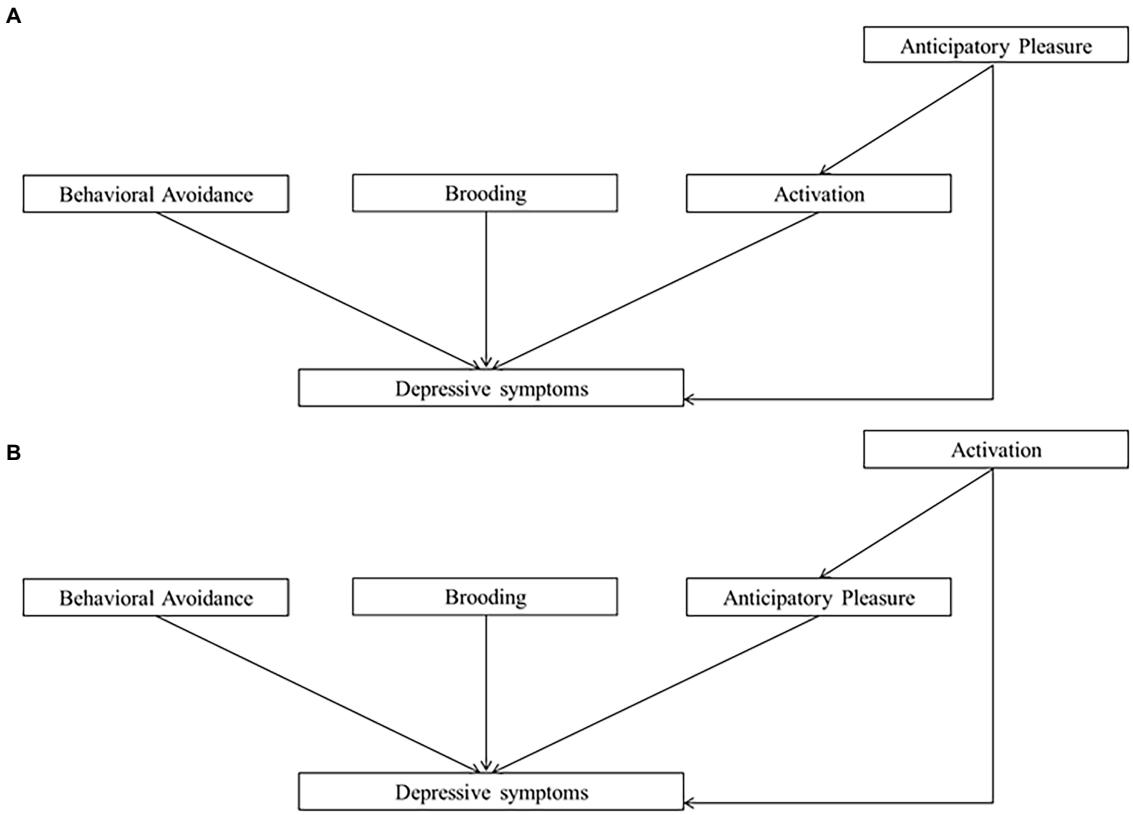

FIGURE 1 | Behavioral models. **(A)** Model 1 (behavioral model 1). **(B)** Model 2 (behavioral model 2).

scale (Wagener et al., 2015). In our sample, Cronbach's α was 0.77 for the activation subscale and 0.68 for the behavioral avoidance subscale.

Anticipatory Pleasure

The Savoring Belief Inventory (SBI) is a 24-item scale assessing individuals' attitudes regarding savoring positive experiences (Bryant, 2003). Three subscales are identified, one related to pleasure in reminiscence of past events, one related to pleasure in relation to the present moment, and one related to pleasure in anticipation of future events, each represented by eight items. We used only the last subscale to measure anticipatory pleasure. The score is calculated by subtracting the sum score of the negatively phrased items from the sum score of positively phrased items. Higher scores indicate a higher level of savoring of pleasant events. We used the validated French version of the scale (Golay et al., 2018). In our sample, Cronbach's α was 0.77 for positive anticipation and 0.67 for negative anticipation.

Brooding

The Ruminative Response Scale (RRS) is a 22-item scale assessing rumination when respondents feel depressed, sad or discouraged (Treynor et al., 2003). Two subscales are identified, one related to brooding (five items) and one related to reflection. The reflection subscale was not reported because this aspect of rumination is more adaptive than brooding and less related to depression. Higher scores on the brooding subscale indicate a higher level of brooding. We used the validated French version of the scale.[1] In this sample, Cronbach's α for the brooding subscale was 0.72.

Disengagement From Sad Cues and Attention to Happy Cues

The exogenous cueing task (ECT) is a reaction-time-based attention task, which was programmed using OpenSesame software and was run on a computer with a 60 Hz, 15-inch color monitor. The original exogenous cueing task asked participants to detect a visual target presented in the left or right peripheral location of the screen (Posner, 1980). In affective science, the paradigm has been modified by using emotional and neutral cues to allow a comparison of their attentional processing.

The task was created with faces (14 happy, 14 sad and 14 neutral) selected from the Karolinska Directed Emotional Face (KDEF) database (Lundqvist et al., 1998; Goeleven et al., 2008). Faces were sized 280 pixels high X 280 pixels wide with visual angles of 5.81°×5.81°. Each trial started with the presentation of a fixation cross for 1,000 ms in the center of the screen. Then, the emotional cue was presented on the left or right side of the screen for 1,000 ms followed by

[1]To have more information about this scale, please contact the first author of the manuscript.

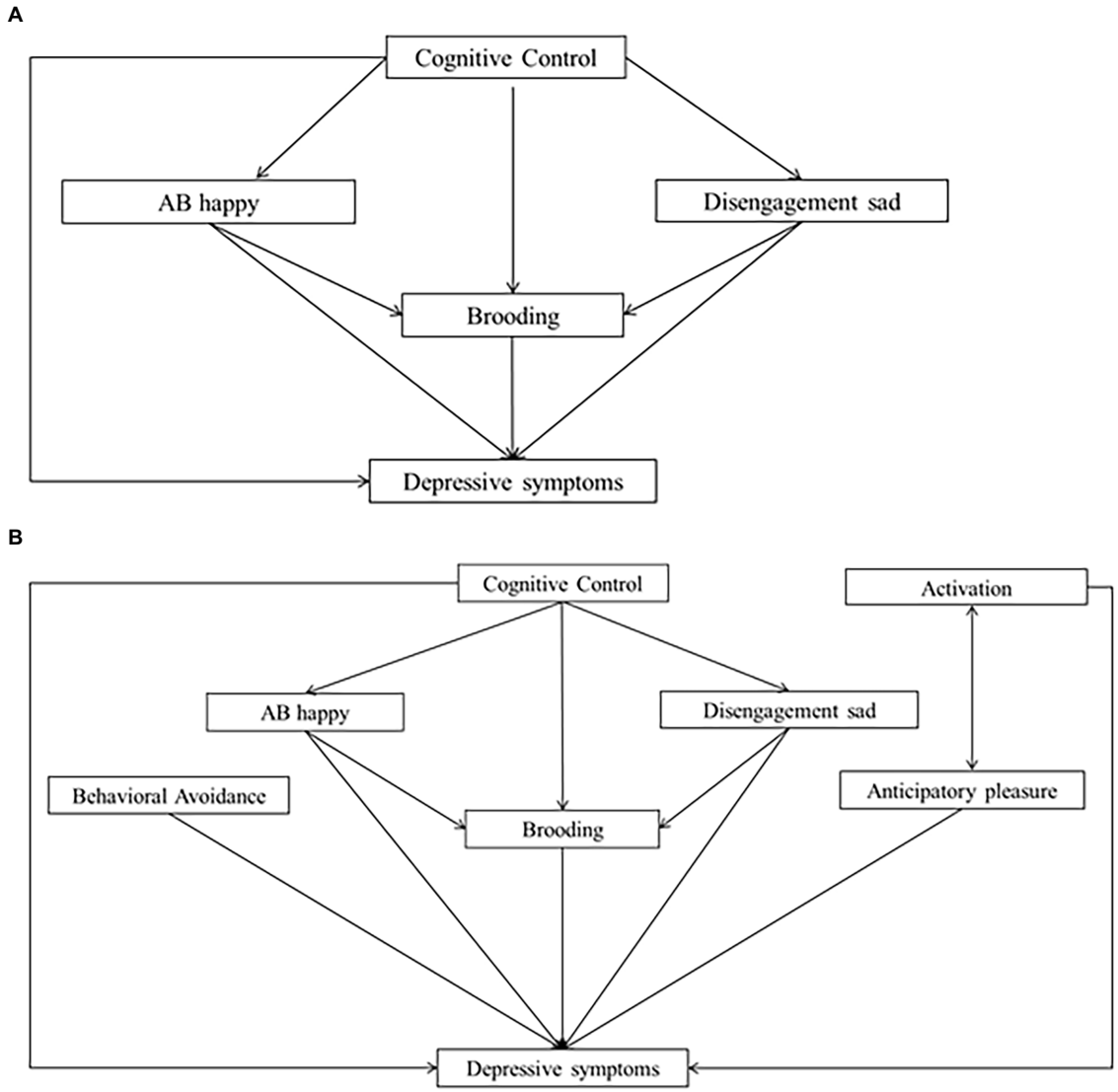

FIGURE 2 | Cognitive and comprehensive models. **(A)** Model 3 (cognitive model). **(B)** Model 4 (comprehensive model).

a "mask" screen for 45 ms. Finally, the target ("*") was presented until a response was made. A black background intertrial was then presented for 300 ms before the next trial started. The sequence of events in a test trial is depicted in **Figure 3**. In the test trials, half of positive faces were valid (28 trials; left cue–left target and right cue–right target) and half were invalid (28 trials). The same proportions were used for sad and neutral faces, with half valid (28 trials) and half invalid (28 trials; left cue–right target and right cue–left target). Fifty-six of the remaining stimuli were no-cue and 10 were digital trials to enhance the probability that participants would maintain their gaze in the middle of the screen. The fixation cross was replaced by a digit for 450 ms, after which no cue or target followed and participants were instructed to report the digit aloud as quickly as possible. The stimuli were presented at random in the left or right hemifield with an equal number of presentations for each stimulus (twice) and each emotional category (sad, happy, and neutral; 56 trials each).

For sad faces, an attentional disengagement score was calculated by subtracting the mean reaction times (RTs) of invalid neutral trials from the mean RTs of invalid emotional trials (Koster et al., 2005). For happy faces, we subtracted the mean RTs for valid trials from the mean RTs for invalid trials in order to compute a cue validity (CV) index. Although preliminary research data suggest that depressed participants engage more slowly with positive stimuli than non-depressed participants (Sanchez et al., 2017), the nature of the attentional components involved in bias related to positive cues remains poorly understood. Then, we computed CV scores to measure attentional bias to positive cues to include both attentional components. With longer stimulus-onset asynchronies, as were

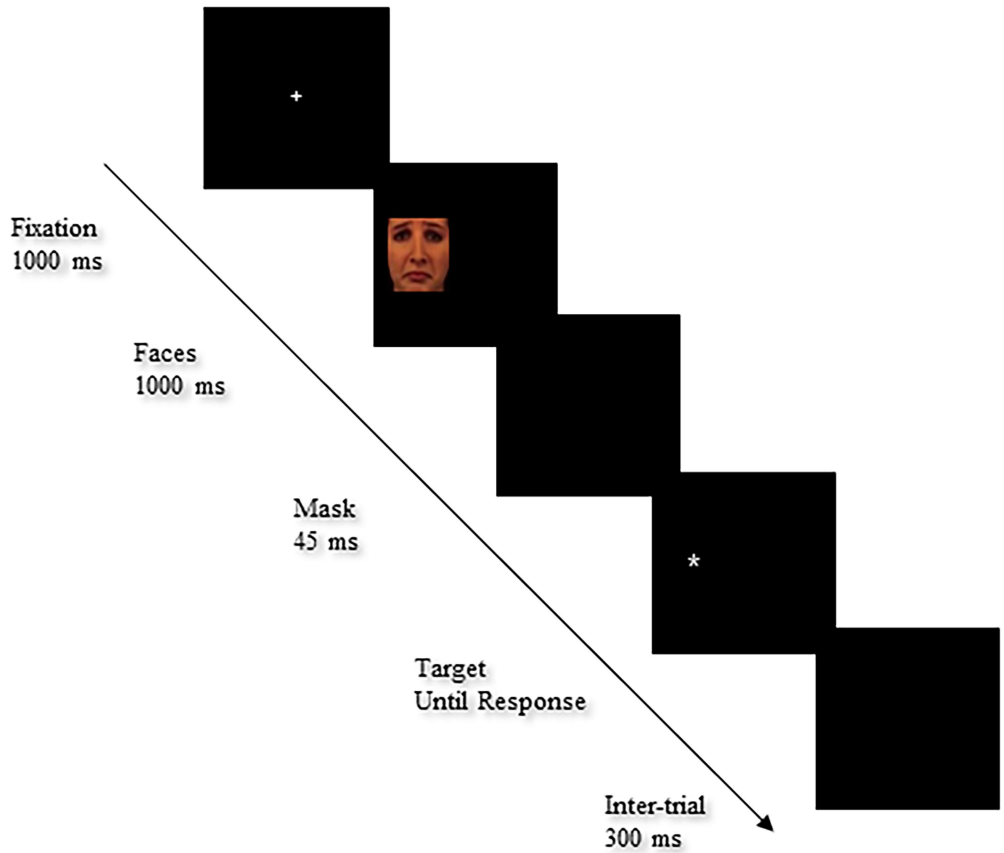

FIGURE 3 | Sequence of events in the detection cueing task. Facial image reproduced from Karolinska Directed Emotional Face (KDEF; Lundqvist et al., 1998; AF13SAS).

used in this study, a positive cue validity effect suggests that attention is maintained on the cue.

The split-half reliability indices were computed separately for each task *via* Spearman-Brown correlations with the first and second half of trials in each experimental condition. Spearman-Brown correlations ranged from 0.43 (Happy valid) to 0.48 (Happy invalid). We ran the same analyses for CV scores for happy cues and disengagement scores from sad cues. The Spearman-Brown correlations computed were 0.006 for disengagement from sad cues and 0.048 for CV for happy cues.

Cognitive Control

A computerized version of the Paced Auditory Serial-Addition Task (PASAT) was used to measure participants' updating abilities and monitoring of representations within working memory, one aspect of CC (Gronwall, 1977; Tombaugh, 2006). In the task, 60 numbers (from 1 to 9) are presented successively. Subjects were asked to add each number to the one that immediately preceded it, which interferes with the updating of the last heard digits in working memory. The task is divided into four trials that differ in terms of the speed with which the numbers are presented (one number every 2.4, 2.0, 1.6, or 1.2 s). The outcome measures were the number of correct responses for each of the four experimental trials. The total accuracy score served as a behavioral indicator of CC. The split-half reliability of this measure (Spearman-Brown corrected) computed with the first two series and the last two series of trials was 0.89.

Procedure

The evaluations were administered individually in a quiet room with dim light. Participants first completed the computerized tasks and then the self-report questionnaires. Participants started with the two computerized tasks, introduced in a counterbalanced order. The questionnaires were administered in the same order for all participants. To complete the spatial cueing tasks, participants were seated 60 cm from the computer screen. They were asked to detect, as quickly as possible, the location of the target ("*")—left mouse button with left index finger; left side; right mouse button with right index finger, right side—without sacrificing accuracy. The instructions were presented on screen. Participants were informed that a cue would precede the presentation of the target and that the cue correctly predicted the location of the target in some but not all trials. Participants practiced the attentional task for 15 trials. The test phase consisted of one block with 234 trials. We presented the trials in a new random order for each participant. The total time for data acquisition was approximately 1 h (i.e., preparation of the participant, familiarization with the tasks, breaks, and debriefing).

The local Ethics Committee approved the study.[2] All participants gave their written informed consent.

Data Preparation

First, we discarded trials with errors from the analyses (0.007% of all data). To take each participant's processing speed into account, we followed Ratcliff's (1993) guidelines for dealing with outliers. To do so, we decided to rely on an individual approach based on deviations below or above each participant's mean for each experimental condition. Participants' RTs more than three standard deviations from their individual mean RT for all indices (Invalid Sad, Valid Sad, Invalid Happy, Valid Happy, Invalid Neutral, and Valid Neutral) were considered as outliers. These outlying RTs were excluded on the basis that they indicated anticipatory responses (0.001% of all data) or delayed responses (0.01% of all data). None of the participants exhibited more than 10% of erroneous response or outliers. We conducted the analyses on the remaining 99.98% of the data.

Statistical Analysis

The Shapiro–Wilk test suggested that all variables were non-normally distributed (all $p_s < 0.002$). First, we computed non-parametric Spearman correlations between all variables to describe our group characteristics using JASP Version 0.13.1 (JASP Team, 2020).

Thereafter, path analysis with a maximum-likelihood estimation method was computed with the Lavaan package in R, version 0.6–8 (Rosseel, 2012). According to Rosseel, the parameters estimated by this method are consistent with non-normal data.[3] The goodness of fit is indicated by a non-significant χ^2. If the chi-square is significant, a χ^2/degrees of freedom ratio of less than 2 indicates a good fit, while a result of less than 3 is acceptable (Cangur and Ercan, 2015). We also computed several other fit statistics, including the Root Mean Square Error of Approximation (RMSEA), the Standardized Root Mean square Residual (SRMR), the Tucker-Lewis Index (TLI), and the Comparative Fit Index (CFI; Bentler, 1990; Hu and Bentler, 1999; Cangur and Ercan, 2015). An RMSEA between 0.05 and 0.08, SRMR <0.10, TLI > 0.95, and CFI > 0.95 are generally interpreted as indicating an acceptable fit (Bentler, 1990; Schermelleh-Engel et al., 2003). To compare Models 1 and 2, we computed two additional indices: Akaike's Information Criterion (AIC) and Sample-size adjusted Bayesian Information Criterion (BIC). Lower AIC and BIC scores indicate a better model fit (Akaike, 1973). Standardized path coefficients are reported in each figure (Wright, 1934). To control for measurement error, we conducted an additional bootstrap on standard errors by randomly resampling the data 10,000 times.

In order to more directly test the influence of behavioral processes (Activation, Behavioral Avoidance, Anticipatory Pleasure), cognitive processes (CC, AB_s) and the common process (Brooding) on depressive symptoms, seven hierarchical linear regression analyses were performed on depressive symptoms to measure the variance in depressive symptoms that is explained by each predictor separately after controlling for the effect of the others. Hierarchical regression model analyses were done with JASP Version 0.13.1 (JASP Team, 2020).

Following recommendations on research transparency and replicability, the OpenSesame version of the task, the stimuli, and the de-identified data can be freely downloaded *via* the following link: https://osf.io/hfj8a/.

RESULTS

Group Characteristics

The full sample had a mean BDI-II (Beck et al., 1996) score of 10.02 (SD = 7.36, range 0–48). Their demographic characteristics appear in **Table 1** and the means and standard deviations of all measures are shown in **Table 2**. **Table 3** presents Spearman non-parametric correlations between all variables. Most correlations were statistically significant except the correlations including disengagement from sad cues and attentional bias to happy cues (ranging from $r = 0.00$ to $r = -0.07$, all $p_s > 0.05$). In addition, non-significant correlations were reported between CC and brooding ($r = -0.06$, $p > 0.05$), and CC and behavioral avoidance ($r = -0.05$, $p > 0.05$). The strongest correlations were found between brooding and depression ($r = 0.50$, $p < 0.001$), behavioral avoidance and depression ($r = 0.46$, $p < 0.001$), activation and depression ($r = -0.41$, $p < 0.001$) and brooding and behavioral avoidance ($r = 0.32$, $p < 0.001$).

Path Analysis Models

We defined our path analysis models based on literature and theoretical frameworks. First, we tested a behavioral model in which activation, behavioral avoidance, brooding and anticipatory pleasure were defined as predictors of depressive symptoms and anticipatory pleasure was defined as an additional predictor of activation (Model 1). To explore an alternative relationship between anticipatory pleasure and activation, we tested Model 2, in which activation, behavioral avoidance, brooding and anticipatory pleasure were defined as predictors of depressive symptoms and activation was defined as an additional predictor of anticipatory pleasure. In Models 1 and 2, covariances were indicated between activation, behavioral avoidance and brooding. In the cognitive model (Model 3), we defined CC, the two kinds of AB_s and Brooding as predictors of depressive symptoms, CC as a predictor of the two AB_s and brooding, and the two AB_s as additional predictors of brooding. Finally, Model 4 tested a comprehensive model comprising a combination of the best behavioral model (Model 1 or Model 2) and Model 3.

The statistics for Model 1 did not suggest an adequate fit for the data ($\chi(2)^2 = 14.19$ $p < 0.001$, $\chi^2/df = 7.10$, RMSEA of 0.108, SRMR = 0.058, TLI = 0.862, CFI = 0.972, AIC = 15188.482, and BIC = 15202.517). However, all predictors of depressive symptoms were statistically significant ($\beta = -0.36$ for activation,

[2]The central ethics committee at University of Liège located at CHU Sart-Tilman, B35, 4,000 Liège approved this study in 2018 (Belgian number: B707201629390, reference number: 2016–215).

[3]All analyses were also conducted with diagonally weighted least squares method, as the choice of parametric or non-parametric statistical method may be controversial. Analyses revealed similar results and conclusions.

TABLE 1 | Group characteristics.

Measure	
N	520
Age	31 (11.89)
Gender (M/F)	182/338
Education level (number of years successfully completed)	14.12 (2.26)
Origin	
Caucasian	87.31%
African	12.31%
Asian	0.38%
Employment status	
Student	37.50%
Laborer	8.27%
Employee	35.96%
Executive	4.81%
Self-employed	6.15%
Homemaker	1.15%
Unemployed	5.38%
Retired	0.19%
Missing data	0.58%
Unable to work	1.54%
Marital status	
Single	69.23%
Married	17.88%
Legally cohabiting	5.77%
Widowed	0.39%
Divorced	6.73%
Other	0%
Live in a couple	60.96%
Have children	33.08%
Report at least one past depressive episode with medical treatment	24.42%
Current depressive episode	5%
Currently on psychotropic medication (antidepressant)	2.12%
SSRI	8/11
SNRI	3/11
Currently on psychotropic medication (anxiolytic)	0.77%

Standard deviations are shown in parentheses. SSRI, selective serotonin reuptake inhibitor. SNRI, selective norepinephrine reuptake inhibitor.

TABLE 2 | Means and standard deviations for all variables.

Measure	Range (min-max)	Mean (SD)
Depressive symptoms (BDI-II)	0–63	10.02 (7.36)
Activation (BADS-SF)	0–24	13.40 (4.76)
Behavioral avoidance (BADS-SF)	0–12	4.23 (4.30)
Anticipatory pleasure (SBI)	−24–24	12.15 (7.52)
Brooding (RRS)	5–20	10.79 (3.30)
Disengagement from sad cues	–	0.08 (27.02)
CV for happy cues	–	−22.79 (42.55)
Cognitive control (PASAT)	0–60	50.83 (9.02)

SD, standard deviation; BDI-II, beck depression inventory-II; BADS-SF, behavioral activation for depression scale—short form; SBI, savoring belief inventory; RRS, ruminative response scale; CV, cue validity; PASAT, paced auditory serial-addition task.

$\beta = 0.68$ for behavioral avoidance, $\beta = 0.74$ for brooding, and $\beta = -0.14$ for anticipatory pleasure, all $p_s < 0.001$). Anticipatory pleasure was a significant predictor of activation ($\beta = 0.13$, $p < 0.001$) and each covariance was significant (all $p_s < 0.001$). The model explained 42% of the variance in depressive symptoms and 4% of the variance in activation.

Model 2 was associated with high goodness-of-fit indices ($\chi(2)^2 = 4.41$ $p = 0.11$, RMSEA of 0.048, SRMR = 0.028, TLI = 0.973, CFI = 0.995, AIC = 15178.712, and BIC = 15192.747). In this model, activation, behavioral avoidance, brooding and anticipatory pleasure were significant predictors of depressive symptoms ($\beta = -0.36$ for activation, $\beta = 0.68$ for behavioral avoidance, $\beta = 0.74$ for brooding, and $\beta = -0.14$ for anticipatory pleasure, all $p_s < 0.001$). In addition, activation was a significant predictor of anticipatory pleasure ($\beta = 0.39$, $p < 0.001$). The model explained 43% of the variance in depressive symptoms, and 6% of the variance in anticipatory pleasure. In both models, all path coefficient signs corroborated the expectations. AIC and BIC indices were lower in Model 2 than in Model 1, suggesting that Model 2 fit the data well. Model 2 is represented in **Figure 4**.

High goodness-of-fit indices were associated with the cognitive model (Model 3; $\chi(1)^2 = 0.081$, $p = 0.776$, RMSEA <0.001, SRMR = 0.003, TLI = 1.00, CFI = 1.00). However, not all hypothesized predictors of depressive symptoms were statistically significant. As expected, brooding and CC were significant predictors of depressive symptoms ($\beta = 1.11$, $p < 0.001$ for brooding, $\beta = -0.80$, $p < 0.05$ for CC). However, non-significant regressions were reported between the two AB_s and depressive symptoms ($\beta_s = 0.00$, $p_s > 0.05$), between CC and the two AB_s ($\beta = 0.19$ for happy cues and $\beta = 0.64$ for sad cues, $p_s > 0.05$) and between CC and brooding ($\beta = -0.03$, $p > 0.05$). The model explained 26% of the variance in depressive symptoms and less than 1% of the variance in Brooding ($R^2 = 0.004$) and AB_s ($R^2 = 0.00$ for happy cues, $R^2 = 0.001$ for sad cues). Model 3 is depicted in **Figure 5**.

A majority of path coefficient signs corroborated expectations except the signs between CC and disengagement from sad cues and between attention to happy cues and brooding. Furthermore, the path signs between disengagement from sad cues and brooding, as well as between disengagement from sad cues and depressive symptoms, were unexpected.

Finally, Model 4 tested a comprehensive model (incorporating Model 2 and Model 3). Model 4 produces high goodness-of-fit indices ($\chi(12)^2 = 18.98$, $p = 0.09$, RMSEA of 0.033, SRMR = 0.040, TLI = 0.963, CFI = 0.984). In Model 4, activation, behavioral avoidance, brooding, and anticipatory pleasure were significant predictors of depressive symptoms ($\beta = -0.35$ for activation; $\beta = 0.68$ for behavioral avoidance; $\beta = 0.73$ for brooding, and $\beta = -0.14$, for anticipatory pleasure, all $p_s < 0.001$). However, the two AB_s and CC did not significantly predict depressive symptoms ($\beta = -0.002$ for happy cues, $\beta = -0.001$ for sad cues, and $\beta = -0.05$ for CC, all $p_s > 0.05$). In addition, CC did not significantly predict the AB_s ($\beta = 0.19$ for happy cues and 0.64 for sad cues, $p > 0.05$) or brooding ($\beta = -0.01$, $p > 0.05$), and the AB_s did not significantly predict brooding ($\beta = -0.000$ for happy cues, and $\beta = -0.001$ for sad cues, all $p_s > 0.05$). Finally, activation was a significant predictor of anticipatory pleasure ($\beta = 0.39$, $p < 0.001$). Model 4 explained 43% of the variance in depressive symptoms, 6% of the variance in anticipatory pleasure, and less than 1% of the variance in brooding and AB_s. **Figure 6** presents Model 4.

TABLE 3 | Spearman's correlations between all variables.

Measures	Activation	Behav. avoidance	Ant. pleasure	Brooding	CV happy	Dis. sad	CC
Activation	–						
Behav. avoidance	−0.23***	–					
Ant. pleasure	0.26***	−0.13**	–				
Brooding	−0.27***	0.32***	−0.11*	–			
CV happy	−0.10*	0.11*	−0.06	0.10*	–		
Dis. sad	0.02	−0.01	−0.003	−0.07	0.00	–	
CC	0.12**	−0.05	0.07	−0.06	−0.04	0.02	–
Depressive sympt.	−0.41***	0.46***	−0.26***	0.50***	0.04	−0.03	−0.14**

****p < 0.001; **p < 0.01; *p < 0.05.*

Behav. avoidance, behavioral avoidance; Ant. pleasure, anticipatory pleasure; CV happy, cue validity for happy cues; Dis. sad, disengagement from sad cues; CC, cognitive control; Depressive sympt., depressive symptoms.

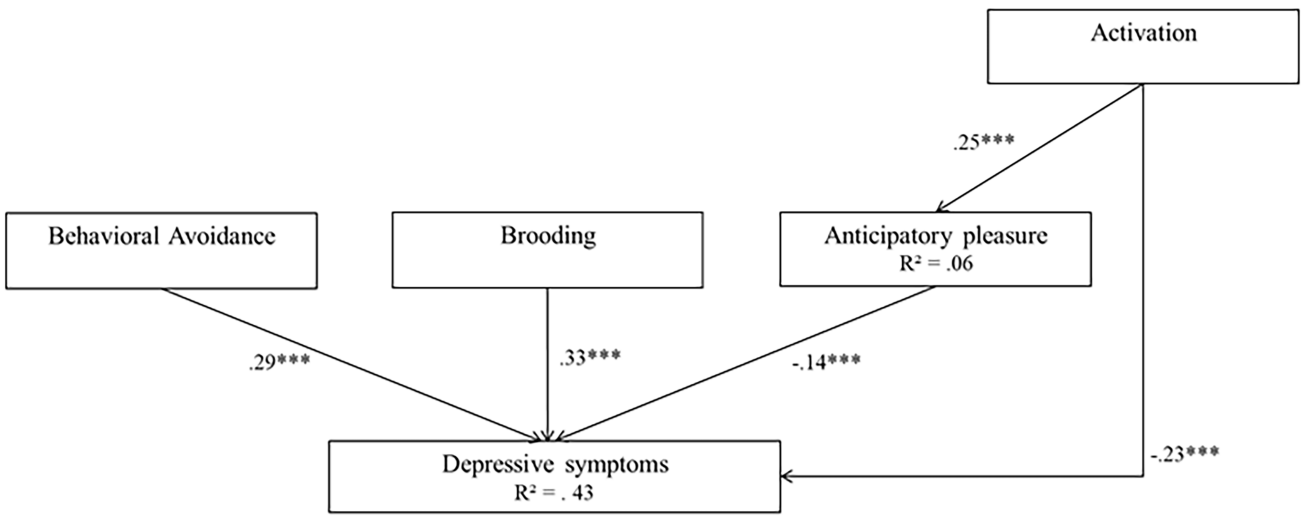

FIGURE 4 | Model 2 (behavioral model 2). Initial structural equation model. Rectangles represent observed measured variables. Values are path-standardized coefficients. R^2 represents the proportion of the variance for a dependent variable that is explained by an independent variable or variables in a regression model. ***indicates a significant path coefficient at $p < 0.01$. *indicates a significant path coefficient at $p < 0.05$. (black: $p < 0.05$; gray: $p > 0.05$).

Complementary Analyses

Bootstrap analysis conducted on standard errors generated similar standard errors and *Z* values than previous results and lead to the same conclusions. Four supplemental tables reporting the estimate, standard error, *Z* value with and without bootstraps, and path-standardized coefficients can be downloaded *via* the following link: https://osf.io/hfj8a/.

Because the comprehensive model shows a large number of statistically insignificant paths, making this model more complex than necessary, we computed additional analysis testing a comprehensive model where ABs were removed considering the high standard error for the ABs variances and insignificant paths between ABs and brooding, and ABs and depressive symptoms. The analyses generated similar results with similar conclusions with still non-significant paths between CC and depressive symptoms and CC and brooding. The simplified Model 4 tested produce acceptable fit indices ($\chi(5)^2 = 14.513$ $p = 0.013$, $\chi^2/df = 2.90$, RMSEA of 0.060, SRMR = 0.046, TLI = 0.937, CFI = 0.979). In this simplified comprehensive model, activation, behavioral avoidance, brooding, and anticipatory pleasure were significant predictors of depressive symptoms ($\beta = -0.35$ for activation; $\beta = 0.68$ for behavioral avoidance; $\beta = 0.73$ for brooding, and $\beta = -0.13$ for anticipatory pleasure, all $p_s < 0.001$). However, CC did not significantly predict depressive symptoms ($\beta = -0.05$ $p > 0.05$). In addition, CC did not significantly predict brooding ($\beta = -0.01$, $p > 0.05$). Finally, activation was a significant predictor of anticipatory pleasure ($\beta = 0.38$, $p < 0.001$). This simplified model explained 43% of the variance in depressive symptoms, 6% of the variance in anticipatory pleasure, and less than 1% of the variance in brooding.

Hierarchical Regression Analyses

We computed hierarchical regression models to measure the unique variance in depressive symptoms that might be explained by each

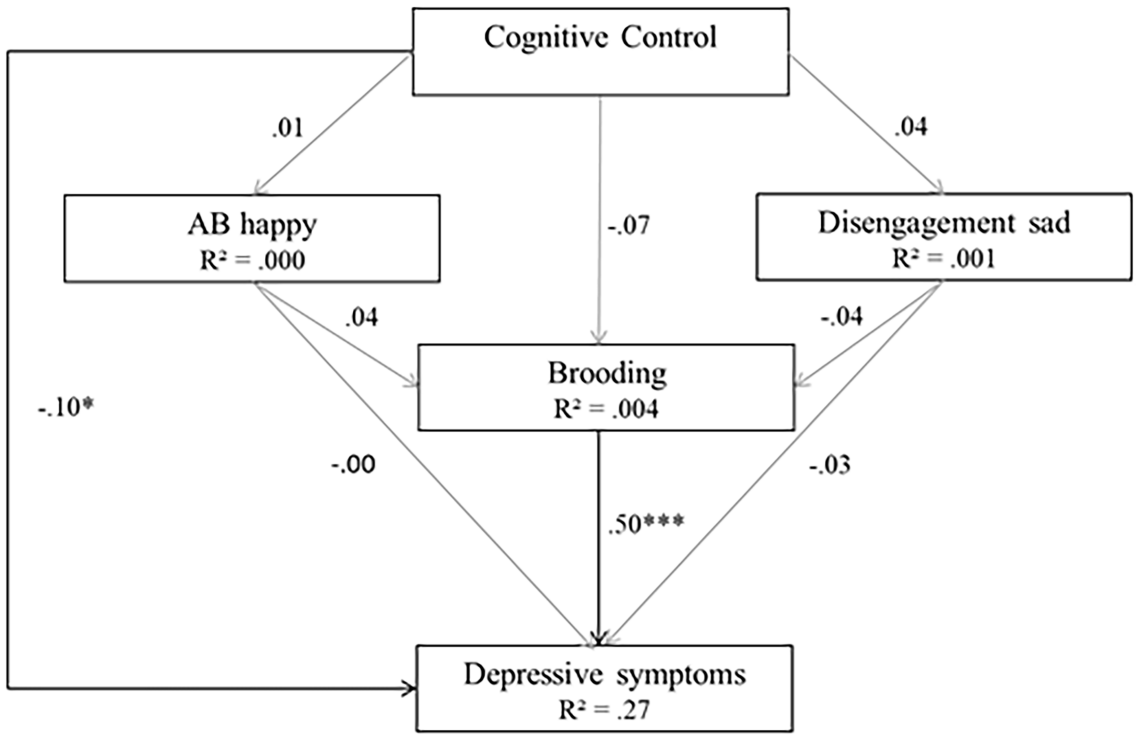

FIGURE 5 | Model 3 (cognitive model). Initial structural equation model. Rectangles represent observed measured variables. Values are path-standardized coefficients. R^2 represents the proportion of the variance for a dependent variable that is explained by an independent variable or variables in a regression model. ***indicates a significant path coefficient at $p < 0.01$. *indicates a significant path-coefficient at $p < 0.05$. (black: $p < 0.05$; gray: $p > 0.05$).

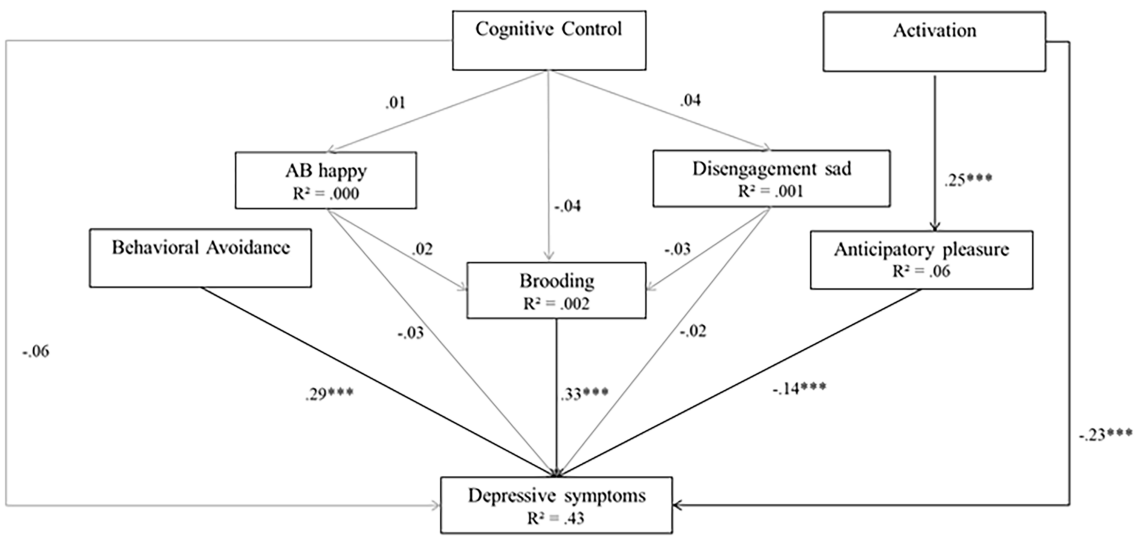

FIGURE 6 | Model 4 (comprehensive model). Initial structural equation model. Rectangles represent observed measured variables. Values are path-standardized coefficients. R^2 represents the proportion of the variance for a dependent variable that is explained by an independent variable or variables in a regression model. ***indicates a significant path coefficient at $p < 0.01$. *indicates a significant path-coefficient at $p < 0.05$. (black: $p < 0.05$; gray: $p > 0.05$).

predictor after controlling for the effects of the other predictors. Step 1 provides simple linear regressions assessing the amount of variance that could be attributed to each predictor. In order to verify whether the contribution of one predictor might be reduced to a non-significant account after controlling for all other predictors, step 2 includes the six remaining processes as predictors. We also

computed hierarchical regression models to measure the variance in brooding that might be explained by CC and AB_s after controlling for the effects of the others. We compared predictors for statistically significant changes in the explained variance R^2 by computing a partial *F*-statistic. The results are summarized in **Table 4**.

The Step 1 models revealed that activation, behavioral avoidance, anticipatory pleasure, brooding and CC explained a significant proportion of the variance in depressive symptoms (18.3% for activation, 21.4% for behavioral avoidance, 25.6% for brooding, 9.3% for anticipatory pleasure, and 1.7% for CC). AB_s were not significant predictors of the variance in depressive symptoms, with less than 1% of the variance in depressive symptoms explained by the two AB_s ($R^2 < 0.01$). The Step 2 models revealed that activation, behavioral avoidance, anticipatory pleasure, and brooding were still significant predictors of depressive symptoms after controlling for the influence of other predictors ($\Delta R^2 = 0.045$ for activation, $\Delta R^2 = 0.074$ for behavioral avoidance, $\Delta R^2 = 0.090$ for brooding, $\Delta R^2 = 0.017$ for anticipatory pleasure). However, the variance in depressive symptoms explained by CC became non-significant after controlling for the influence of other predictors ($\Delta(F1,512) = 3.029$, $p = 0.08$, $\Delta R^2 = 0.003$).

DISCUSSION

This study aimed to investigate whether the addition of certain cognitive processes to BA processes could predict a larger proportion of depressive symptoms and brooding. First, we explored the amount of variance in depressive symptoms that was explained by the target processes in BA treatment according to behavioral models (activation, behavioral avoidance, anticipatory pleasure, and brooding), by the target processes in CCT according to cognitive models (CC, AB_s, and brooding), and by all processes together. Then we measured the relationships among these processes with path analysis in order to gain a comprehensive view of the interplay between them especially between activation and anticipatory pleasure and between CC, AB_s and brooding. Finally, we tested the amount of variance in depressive symptoms that was explained by the target processes in BA and by the target processes in CCT after controlling for the effect of the other predictors.

First, the analyses of the behavioral models revealed that activation, behavioral avoidance, anticipatory pleasure, and brooding are significant predictors of depressive mood. This result suggests that each process is a relevant therapeutic target for BA interventions. All the behavioral processes together explained a substantial amount of the variance in depressive symptoms (43%). In contrast, the analyses of the cognitive model revealed that only CC and brooding are significant predictors of depressive mood. Moreover, CC is no longer a significant predictor of depressive mood when the influence of other predictors is controlled for, as the hierarchical regression analysis, showed. Furthermore, our results did not support any claim that CC predicts ABs or brooding, or that ABs predict brooding. All the cognitive processes together explained 27% of the variance in depressive symptoms, with 25.6% explained by brooding and less than 1 and 2% explained by the ABs and CC, respectively. Analysis of the comprehensive model revealed that the combination of behavioral and cognitive models fit the data well but did not explain more of the variance in depressive symptoms or brooding than the behavioral models. These findings may corroborate the empirical data reported by Moshier and Otto (2017), which showed that CCT did not enhance

TABLE 4 | Hierarchical linear regressions of depressive symptoms.

Step	Predictors	R^2	Adjusted R^2	ΔR^2	ΔF	Value of *p*
1	Activation	0.185	0.183	0.183	117.46	< 0.001
1	Behav. avoid. & Ant. pleas. & Brood. & CV H & Dis. sad & CC	0.402	0.395	0.402	57.36	< 0.001
2	Activation	0.446	0.439	0.045	41.494	< 0.001
1	Behavioral avoidance	0.216	0.214	0.216	142.49	< 0.001
1	Act. & Ant. pleas. & Brood. & CV H & Dis. sad & CC	0.372	0.365	0.372	50.64	< 0.001
2	Behavioral avoidance	0.446	0.439	0.074	68.81	< 0.001
1	Brooding	0.258	0.256	0.258	179.80	< 0.001
1	Act. & Behav. avoid. & Ant. pleas. & CV H & Dis. sad & CC	0.356	0.349	0.356	47.35	< 0.001
2	Brooding	0.446	0.439	0.090	83.21	< 0.001
1	Anticipatory pleasure	0.078	0.076	0.094	43.942	< 0.001
1	Act. & Behav. avoid. & Brood. & CV H & Dis. sad & CC	0.429	0.422	0.429	64.28	< 0.001
2	Anticipatory pleasure	0.446	0.439	0.017	15.94	< 0.001
1	CV happy	0.000	–0.002	0.000	0.192	0.66
1	Act. & Behav. avoid. & Ant. pleas. & Brood. & Dis. sad & CC	0.444	0.437	0.444	68.18	< 0.001
2	CV happy	0.446	0.439	0.003	2.519	0.11
1	Disengagement sad	0.002	–0.000	0.002	0.875	0.35
1	Act. & Behav. avoid. & Ant. pleas. & Brood. & CV H & CC	0.446	0.440	0.446	68.91	< 0.001
2	Disengagement sad	0.446	0.439	0.000	0.093	0.76
1	CC	0.018	0.017	0.018	9.73	0.00
1	Act. & Behav. avoid. & Ant. pleas. & Brood. & CV H & Dis. sad	0.443	0.437	0.443	68.03	< 0.001
2	CC	0.446	0.439	0.003	3.029	0.08

Act., activation; Behav. avoid., behavioral avoidance; Ant. pleas., anticipatory pleasure; CV H, cue validity for happy cues; Dis. sad, disengagement from sad cues; CC, cognitive control.

the effect of a BA intervention on brooding and depression in a clinical sample. Of course, this should be weighed regarding cognitive functioning associated with clinical characteristics, including comorbidities of populations and must continue to be investigated.

Overall, given that none of the selected cognitive processes significantly predicts brooding, our findings do not corroborate the idea that brooding is partially due to deficits in working memory or AB_s, as suggested by recent reports (Watkins and Roberts, 2020). Although unexpected, the lack of relationship between the monitoring of representations within working memory and brooding is consistent with a recent meta-analysis that reported null findings regarding the association between these processes (except for discarding cognitive function) in a sample of participants with and without depression diagnosis (Zetsche et al., 2018). Furthermore, the lack of relations between AB_s and brooding and AB_s and depressive symptoms is consistent with a recent cross-sectional research conducted in a clinically depressed, subclinically depressed and never-depressed sample (Krings et al., 2020) and even prospective research on AB_s and depressive symptoms in a sample of participants who were remitted from Major Depressive Disorder (Elgersma et al., 2019).

These null findings might be due to the inadequate reliability of the paradigm used. Indeed, the exogenous cueing task is associated with less than ideal level of psychometric properties, as suggested by the high standard error for the AB variances and the low split-half reliability of the AB indices. The use of eye tracking during the task to continuously monitor the focus of visual attention would be a more appropriate alternative to measure AB_s. Furthermore, CC was measured by an updating task. However, different CC functions such as inhibition, shifting, or even discarding formerly relevant information from working memory could also be used to assess CC abilities (Zetsche and Joormann, 2011; Zetsche et al., 2018). The lack of relationships between AB_s and CC and depressive symptoms might also be explained by the heterogeneity of depression. There are numerous depressive symptoms and they represent distinct entities (e.g., some are good predictors of psychosocial impairment and others are not, or some are well predicted by stress and others are not; Fried and Nesse, 2014; Fried et al., 2015). Furthermore, AB_s and CC might be related to specific depressive symptoms or part of a network of related symptoms (Kraft et al., 2019). In addition, AB_s and CC might be related to other disturbed psychological processes not included in this model (e.g., interpretive bias, memory bias). Future research may benefit from exploring the interplay between these processes and specific depressive symptoms, as well as other disturbed psychological processes.

The behavioral path analysis models support the relevance of the behavioral model, showing that activation partially predicts anticipatory pleasure, which in turn predicts depressive symptoms. This result is in line with previous studies reporting that activation can influence reward anticipation and reward motivation in a subclinical depressed sample (Bakker et al., 2017) but also in an unselected sample of undergraduate students (Beevers and Meyer, 2002). In behavioral activation treatment, people are encouraged to become increasingly involved in goal-directed activities, which should increase the number of positive situations or events they experience, in order to improve their depression. Our findings suggest that this BA strategy may actually affects a significant proportion of depressive symptoms through its influence on anticipatory pleasure. This strategy acts partly as "reward exposure" and the repeated activation of reward networks normalizes the reward system. In addition to results reported by Bakker et al. (2017) and Beevers and Meyer (2002), other empirical data support this rationale, with findings suggesting that "Engage" therapy using exposure to meaningful activities helps to reduce depression in clinical samples (Alexopoulos et al., 2016, 2017). However, even if it is significant, it is important to note that activation explained only 6% of the variance in anticipatory pleasure. This result suggests that, to increase the efficacy of BA interventions, the treatment may include other therapeutic strategies that directly target anticipatory pleasure, in addition to activation. Recent empirical data suggest that enhancing the specificity and detail of episodic future thinking by increasing vividness and mental imagery represents a promising strategy to increase anticipatory pleasure in a clinically depressed sample (Hallford et al., 2020). Moreover, a recent study in healthy volunteers revealed that multisensory imagery of planned rewarding activities increased both anticipatory pleasure and engagement in these activities (Renner et al., 2019).

Some promising new treatments have recently emerged to enhance reward responsiveness in relation to anhedonia and depression. First, Positive Affect Treatment consists of an augmentation of a behavioral activation training module, a cognitive training module, and a compassion training module (Craske et al., 2016). This intervention is associated with an increase in positive affect, and depression for subjects suffering from anhedonia that lasted 6 months (Craske et al., 2019). Another treatment, Behavioral Activation Treatment of Anhedonia (BATA), includes several additional specific modules to BA (see Forbes, 2020; Nagy et al., 2020). BATA is associated with an improvement in reward processing for subjects suffering from anhedonia (Cernasov et al., 2021).

Finally, hierarchical regression analyses based on the magnitude of each predictor suggest that brooding was the best predictor of the variance in depressive symptoms, followed by behavioral avoidance, activation and then anticipatory pleasure. These findings support the relevance of BA processes as primary therapeutic targets. Because brooding is a good predictor of depressive symptoms, it is important to investigate empirically validated treatments that might target cognitive aspects of brooding and could serve as adjuncts to psychotherapy. One promising intervention targeting cognitive aspects related to brooding is memory specificity training, which targets autobiographical memory specificity (Martens et al., 2019). Concreteness training

designed to teach individuals to become more concrete and specific in their thinking is another promising intervention that can be added to BA (Watkins and Moberly, 2009; Spinhoven et al., 2018). The unique contribution of selected processes is weaker than expected. Past studies reported a higher contribution of brooding with 46% of the variance in depressive symptoms explained by brooding in an unselected adults sample (Krings et al., 2020) and 17% in a subclinical sample of bereaved adults (Eisma et al., 2020). Behavioral avoidance explained 41% of the variance in depressive symptoms and activation explained 22% in an unselected adults sample (Krings et al., 2020). Past studies reported inconsistent results for cognitive control (Zetsche and Joormann, 2011) and to our knowledge no study have reported results on AB_s or anticipatory pleasure contributions. However, most of these past studies did not control for the common variance between these processes that may be significantly correlated. The minimal effects reported in our study may be explained by the control of this common variance. Future studies should estimate the unique contribution of depressive symptoms predictors as little is known yet in the literature.

Limitations

Some limitations should be taken into account when interpreting these results. First, our findings use a cross-sectional design, making it impossible to examine causal relationships between variables or to be confident about the directionality of effects. The use of a non-clinical sample also limited the generalizability of our conclusions. Additionally, the data are associated with floor or ceiling effect of variables, including those of CC. Most participants did fairly well on the PASAT, which is not characteristic of psychiatric populations. As such, it would be difficult to detect relationships between the PASAT and outcome measures. However, the total sample of clinical participants was too small to reliably compare clinical and non-clinical depressed participants. Future studies should then explore the impact of these predictors on depressive symptoms in a clinical sample. Furthermore, path coefficients were examined in only one direction for the purpose of this study, but most factors may have reciprocal relationships and be mutually reinforcing (Roberts et al., 2017). In addition, the lack of results related to cognitive targets in our sample may mirror the heterogeneous symptoms characterizing depressive symptomatology but the total sample of participants was too small to reliably examine the interplay between the aforementioned processes and specific symptoms (e.g., fatigue, feeling guilty). Finally, the selected processes were theory-driven but were not exhaustive. The role of other relevant vulnerability processes in predicting depressive symptoms (e.g., consummatory pleasure, interpretive bias, memory bias, reappraisal) should be investigated in future studies.

CONCLUSION

Our results suggest that behavioral models including activation, behavioral avoidance, brooding and anticipatory pleasure can explain much of the variance in depressive symptoms. Moreover, activation partially predicts anticipatory pleasure, which in turn predicts depressive symptoms. Our results also revealed that the cognitive model was relevant but CC and AB_s did not predict brooding or depressive symptoms. Consequently, they raise questions about the claim that AB_s and CC figure prominently in the maintenance of depressive symptoms and brooding. A comprehensive model including every process did not explain more of the variance in brooding or depressive symptoms than the behavioral models suggesting that cognitive training may not be a promising add-on treatment to behavioral activation in our participants with such clinical characteristics. Our findings cast some doubt on the robustness of earlier findings in the field, and future research should carefully investigate the cognitive models of depression. Findings also indicate further investigation of mechanisms of change in BA and CCT treatments in depressed patients is warranted/indicated at this time.

AUTHOR'S NOTE

AC is a member of the Federative Research Structure in Health, Prevention, Quality of Life of the Université Savoie Mont Blanc.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/hfj8a/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central ethics committee at University of Liège. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK and AC: data collection and article preparation. JS and SB: article preparation. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Comparative Analysis of Lateral Preferences in Patients With Resistant Schizophrenia

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Background: Schizophrenia is a chronic brain disorder of diverse etiology and clinical presentation. Despite the expansion of treatment methods, between 30 and 50% of cases remain resistant to treatment. In patients with schizophrenia, specifics in the dominant lateralization in the brain function have been discovered. This gave a reason to seek the relation between functional lateralization and the effect of treatment.

Methods: Of the 105 people observed with schizophrenia, 45 (42.9%) were treatment resistant, and 60 (57.1%) were considered responders. We compared functional lateralization (hand, foot, and eye) between the two groups. Handedness was ascertained by using the Edinburgh Handedness Inventory. The assessment was made at 12 weeks of treatment.

Results: Of all patients with schizophrenia, 41.89% have mixed lateralization, 53.34% are right winged, and 4.76% of the patients are left winged. Resistance of the symptoms shows that 26 (57.78%) are cross-dominated, 18 (40%) are right winged, and 1 (2.22%) is left winged. In patients with clinical remission, 18 (30%) are of mixed dominance, 38 (63.33%) are right winged, and 4 (6.66%) are left winged. From the results for the separate lateralization of the hand, foot, and eye, we found a significant difference only in terms of the dominance of the eye. In 44 (41.9%) of the patients, we found dominance of the left eye. In patients with resistance, the percentage established by us is higher—at 26 (57.8%). These results indicate that the increased percentage of mixed dominance in patients with schizophrenia is mainly due to left-sided lateralization of the eye, especially in those with resistance to treatment.

Conclusion: We find an increased number of patients with cross-dominance и left eye dominance in patients with schizophrenia. Cross-dominance and left eye dominance are associated with a higher probability of symptom resistance than other forms of lateralization (left-handed or right-handed). The high percentage of cross-dominance is due to the high percentage of left-sided dominance of the eye.

Keywords: schizophrenia, resistance, cross-domination, left-handed, right-handed, mixed lateralization, eye dominance, functional lateralization

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BACKGROUND

Schizophrenia is a chronic mental illness with a heterogeneous etiology and a polymorphic clinical picture. The symptoms of schizophrenia are classified into positive, negative, and cognitive. In addition to these main symptoms, frequently anxious and affective symptoms have been identified (1). Studies that assess functional connectivity in patients with schizophrenia have shown disturbances in information transfer between brain centers, particularly between the frontal lobe and cuneus and other neuronal regions (2–4).

The grouping of the clinical manifestations is a reflection of the changes in the neuronal organization as well as the changes in the different levels of loss of connectivity (5). Studies show that the left and right hemispheres are asymmetric in their morphological structure and in the cognitive functions they mediate (6). This asymmetry seems to underlie the development of basic cognitive processes, such as language acquisition (7), and it is suggested that variations in the development of this asymmetry also contribute to the pathogenesis of schizophrenia (7, 8). T. J. Crow suggests that the genetic variation associated with the evolution of *homo sapiens* and the hemispheric dominance of language development is also associated with an increased likelihood of developing psychotic symptoms (7). Other authors also suggest that the loss of left hemispheric dominance is a central neurological feature of this disease (3, 4, 9–11).

One method of assessing lateralization is to establish the dominant hand of the subject. Hand dominance has also been shown to correlate with cerebral lateralization of language expression (12), visual processing (13), declarative memory (14, 15), and emotional processing (16). An analysis of more than 40 studies has concluded that the left hand is more common in mental illness (17). When comparing the prevalence of left-handedness among 107 patients with psychotic disorders and in patients with affective disorders and anxiety, a significant difference was observed (18). In patients with psychotic disorders, some authors find a high percentage (including schizoaffective and schizophrenia) of up to 40% left-handedness (18). Other studies have found almost two times less left handers in patients with schizophrenia (between 15 and 20%) (17). There are also reverse studies. An assessment of several hundred patients showed no difference in lateralization in patients with schizophrenia, their relatives, and the control group (19).

Schizophrenia is a disease of various etiologies, and this could be the reason for the observed deviation in dominance in different studies due to the fact that different clinical subgroups have been studied. Several analyses point to such possible differences. Left-handed and those with cross-dominance with psychotic disorders report more severe impairment in social functioning and have poorer results in psychological studies (20, 21). These results may suggest that dominance may be considered a marker for a particular subtype of psychosis.

Although dominance is a constant feature (there is continuity over time) (22), a definite approach to dominance is not established in current research practice in psychiatry. A three-modal classification is most commonly used, in which subjects are classified into categories with left, right, and mixed dominance, although there are several authors who continue to view dominance as a simple dichotomy (23, 24). The mixed group includes individuals without a clear dominance or consistent preference of the hands, i.e., no pronounced lateralization. Mixed dominance is thought to reflect left hemispheric dysfunction, which may be the result of early (prenatal or perinatal) brain damage (25, 26) or other causes of neurodevelopment (27–29). Mixed dominance, which is more common in patients with schizophrenia than in normal subjects, is even considered characteristic of schizophrenia (28). An analysis of 93 patients with schizophrenia and 105 controls revealed cross-dominance in 20% of patients with psychosis compared with 3.8% in the control group (29). Another study with almost the same number of patients with schizophrenia (30) compared with controls found that the number of patients with pure left dominance was not different from that in the rest of the control group. The authors registered an increased frequency of those with mixed dominance in patients with psychosis (three times more often than the control group). They find that mixed dominance is more pronounced in chronic cases. The results of another research study suggest that some researchers consider schizophrenia as a disorder of lateralization of cerebral function. They analyze the eye/hand relationship for dominance. A meta-analysis found that 35% of right-handers and 57% of left-handers had a dominant left eye (31). Another study assessed the dominant eye in 68 patients with schizophrenia and 118 controls. The patients were aged 17–60 years, with a predominance of males −60 people, and females, 28 people, respectively. The authors found an increased incidence of cross-dominance in patients with schizophrenia. Interestingly, male patients with schizophrenia have an increased incidence of left eye dominance, and such a relationship is not found in females, given the fact that they are the smaller group in the study (32).

An increased incidence of cross-dominance has also been reported in patients with the first psychotic episode, but also associated with more pronounced mild neurological symptoms. The mixed dominance reported by them was associated with poorer school performance as well as poorer social adaptation in the premorbid period (20).

The definition of a mixed dominance category depends on the choice of a questionnaire that divides the continuum of the coefficients for considering dominance as mixed or as more pronounced on the left or right. With a few exceptions (33, 34), most existing hand questionnaires do not have valid criteria for separating dominance. In contrast, measures based on another widely used instrument in the Edinburgh Classification (EHI) (35) have repeatedly been the subject of arbitrary division of classes according to the degree of dominance.

The analysis gives us reason to draw the following conclusions: There are many studies with conflicting results on the topic. We did not find a study to analyze the differences in lateralization in patients with resistance to treatment and in patients in remission.

Working hypothesis: Based on the different results of the studies conducted in patients with schizophrenia, it can be assumed that they were conducted in different subgroups of patients. We hypothesize that we will find differences in

functional lateralization in patients with resistance to treatment and in those in remission.

MATERIALS AND METHODS

Patients (105) with schizophrenia and consecutive psychotic episode were observed in a psychiatric clinic in a hospital setting. Of these, 45 have resistant schizophrenia, and the remaining 60 are in clinical remission.

The gender breakdown showed that 66 were women and 39 were men.

Inclusion criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia (36). They are as follows:

1. Assessment of symptoms with the PANSS and BPRS scale (37, 38).
2. Prospective monitoring for a period of at least 12 weeks.
3. Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg of chlorpromazine equivalents.
4. Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.
5. The assessment of social dysfunction using the SOFAS scale is below 60.

The exclusion criteria are as follows:

1. Intellectual disability.
2. Organic brain damage.
3. Progressive neurological or severe somatic diseases.
4. Advanced personality change.
5. Score of MMSI below 25 points.

Measurement of Lateralization

Lateralization of brain functions was assessed for dominance of the hand, foot, and eye.

Given the specifics of the present study, the comparative analysis of patients with chronic schizophrenia (especially those with persistent and resistant psychotic production) revealed some difficulties in making a detailed assessment of some results.

Handedness

Participants respond to this scale (35) by indicating whether they use their right, left, or either hand for 10 common actions.

Footedness

Chapman foot preference inventory (39) requires participants to respond by indicating whether they use their right, left, or either foot for common actions.

Eye Dominance

In determining the dominant eye, a method, such as looking through a hole [e.g., (32)], was used. To ensure that we have selected the correct dominant eye, we trained the participants.

Procedure

Participants completed the Edinburgh Inventory Scale, Chapman foot preference. Eye preference is determined by three (or more) times attempting to look through a hole.

Given the fact that in some of the patients with pronounced psychotic symptoms it was difficult to assess the intermediate forms of dominance, we decided to group the patients into two groups in terms of hand use, leg, and eye.

Statistical Methods

The statistical software package SPSS, was used for statistical data processing. Because we use categorical variables, and limit group numbers, chi-square test in non-parametric tests was chosen in comparing the groups.

RESULTS

The mean age of patients in the group of resistant schizophrenia was 36.98 years. The minimum age is 21 years, and the maximum is 60 years.

The mean age of patients in the group of schizophrenia in clinical remission was 37.25 years. The minimum is 23 years, and the maximum is 63 years.

We do not find a difference in the mean age of the patients in the both groups at the time of the study.

Hand Lateralization Data Showed the Following Results

Of all the 105 patients we observed, we found that the right-handed were 98 (93.3%) and the left-handed were 7 (6.7%).

From the group of patients with resistance to treatment (45), it was found that 3 (6.7%) are left-handed, and the remaining 42 (93.7%) are right-handed.

In the group of patients with clinical remission, the same process was observed, which we consider to be a coincidence in terms of the percentage distribution: 4 (6.7%) left-handed and 56 (93.3%) right-handed.

From the distribution of patients in terms of lateralization of the dominant hand, we do not find differences between the two groups of patients (f) (**Table 1**).

Foot Lateralization Data Showed the Following Results

The assessment of the lateralization of the foot in all patients (105) showed that 93 (88.6%) are right footed and 12 (11.4%) are left footed. In general, we observed a higher percentage of left-handed dominance than left-handed dominance.

In the group of patients with resistance, it was found that 41 (91.1%) have a dominance of the right foot, and 4 (8.9%) have a dominant left foot.

In the group of patients in clinical remission, we found dominance of the right foot in 52 (86.7%) and dominance of the left foot in 8 (13.3%).

No statistically significant difference was found during the statistical processing. What impressed us, and was contrary to our expectations, is that we find a higher rate of left foot

TABLE 1 | Relationship between functional lateralization of the hand and the effectiveness of therapy.

			Effect of therapy		Total
			Resistant	Remission	
Lateralization hand	Left	Count	3	4	7
		%	6.7%	6.7%	6.7%
	Right	Count	42	56	98
		%	93.3%	93.3%	93.3%
Total		Count	45	60	105
		%	100.0%	100.0%	100.0%

TABLE 2 | Relationship between functional dominance of the foot and the effectiveness of therapy.

			Effect of therapy		Total
			Resistant	Remission	
Lateralization foot	Left	Count	4	8	12
		%	8.9%	13.3%	11.4%
	Right	Count	41	52	93
		%	91.1%	86.7%	88.6%
Total		Count	45	60	105
		%	100.0%	100.0%	100.0%

TABLE 3 | Relationship between functional lateralization of the eye and the effectiveness of therapy.

			Effect of therapy		Total
			Resistant	Remission	
Lateralization eye	Left	Count	26	18	44
		%	57.8%	30.0%	41.9%
	Right	Count	19	42	61
		%	42.2%	70.0%	58.1%
Total		Count	45	60	105
		%	100.0%	100.0%	100.0%

TABLE 4 | Relationship between pure dominance (hand,foot,eye) and cross-dominance with treatment efficacy.

			Lateralization			Total
			Right	Left	Mixed	
Effect of therapy	Resistant	Count	18	1	26	45
		%	32.1%	20.0%	59.1%	42.9%
	Remission	Count	38	4	18	60
		%	67.9%	80.0%	40.9%	57.1%
Total		Count	56	5	44	105
		%	100.0%	100.0%	100.0%	100.0%

dominance in patients in clinical remission compared with those with resistance, despite the lack of statistical difference (**Table 2**).

Eye Lateralization Data Showed the Following Results

The assessment of the dominance of the eye in all observed patients (105) showed the following distribution: dominant right eye was found in 61 (58.1%) and dominant left in 44 (41.9%).

In patients with resistance, we registered a dominant right eye in 19 (42.2%) and a dominant left eye in 26 (57.8%).

In patients in clinical remission, we found dominance of the right eye in in 42 (70%) and dominance of the left eye in 18 (30%).

The obtained results show that we find approximately twice as often dominance of the left eye in the resistance group compared with patients in remission.

Statistical analysis showed the presence of statistical dependence with Chi square 8.150, $p < 0.05$ (**) (**Table 3**).

The Data in Terms of Functional Lateralization (Arm, Leg, Eye), Considered as Pure Left, Right, and Cross Dominance Showed the Following Results

Of the 105 patients studied, 44 (41.89%) have mixed lateralization, 56 (53.34%) are right-handed, and 5 (4.76%) of the patients are left-handed.

The distribution of the dominance of the lateralization in patients with resistance to treatment shows that 26 (57.78%) are cross-dominant, 18 (40%) are right-handed (hand, foot, eye), and 1 (2.22%) is left-handed (hand, foot, eye).

We found that more than half of the patients with resistant schizophrenia have mixed (cross-dominance) and an insignificant percentage are pure left-handed.

The distribution of the dominance of the lateralization in patients in clinical remission shows that 18 (30%) of the patients have mixed dominance, 38 (63.33%) are right-handed, and 4 (6.66%) are left-handed (**Table 4**).

The results show that cross-dominance is more common in patients with resistant schizophrenia than in those in remission. We find twice as many patients with cross-dominance in the group of patients with resistance to treatment as those in remission.

We find a statistically significant difference between the two groups of patients shown in **Figure 1** and **Table 5** ($p < 0.05$, *).

Gender-Related Differences in Functional Lateralization Showed the Following Results

In 66 female patients, 28 (42.4%) are cross-dominant, 35 (53%) are right-handed, and 3 (4.5%) are left-handed.

In 39 male patients, 16 (41.0%) have mixed dominance, 21 (53.8%) are right-handed, and 2 (5.1%) are left-handed.

Our results do not show significant gender differences in the lateralization of brain processes.

Gender-associated differences in terms of only the lateralization of the dominance of the eye showed that in

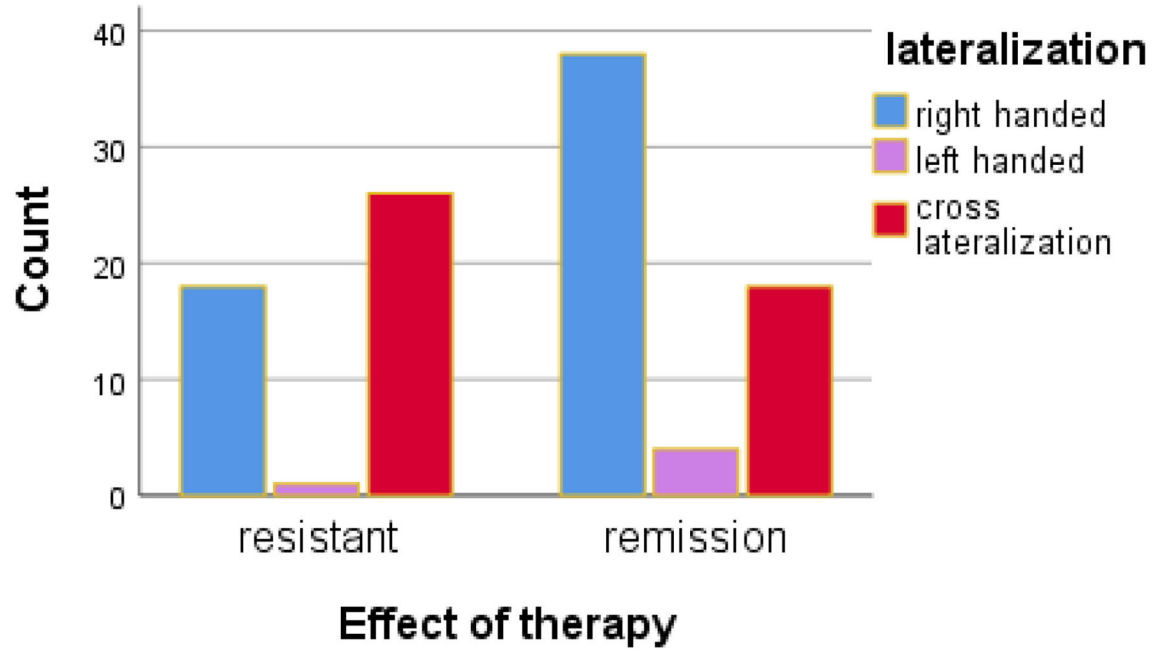

FIGURE 1 | The relationship between functional lateralization /pure and cros-dominance/ and treatment effectiveness.

in 26 (39.4%) females, there is a dominance of the left eye and in 40 (59.6%), there is dominance of the right eye. In males, it was found that 18 (46.2%) has dominance of the left eye, and 21 (53.8%) has dominance of the right eye.

We find a little higher percentage of patients with left eye dominance in males than in females.

The conclusions from the analysis of our results regarding the lateralization of brain processes in patients with schizophrenia show that there is an increased percentage of patients with cross-dominance in the general group of patients with schizophrenia. We registered an increased percentage of patients with a dominant left eye in the patients with schizophrenia we observed. We found a statistically significant difference in the dominance of the left eye with a pronounced predominance in patients with resistance to treatment. The increased percentage of patients with cross-dominance is due to patients with left-sided dominance of the eye.

We did not find an increased percentage of patients with a dominant left arm. We register a higher percentage of patients with dominance of the left leg compared with dominance of the left arm.

TABLE 5 | Statistical significance of the differences between patients in the two groups.

	Value	df	Asymptotic significance (two sided)
Pearson Chi-square	8.427	2	0.015
Likelihood ratio	8.543	2	0.014
Linear-by-linear association	8.045	1	0.005
No of valid cases	105		

DISCUSSION

The use of a trimodal classification model to assess the lateralization of brain processes showed that our study did not reveal gender-related differences, unlike some studies that show one (40). We do not find gender-related differences in the lateralization of cerebral hemisphere dominance. Literature data show that there is a general prevalence of left-handed among males. A study conducted in Greece found that it was observed in 8.26% of men and 6.41% of females (40). In our sample, the difference between left-handed male and female left-handed patients is insignificant. This can be interpreted in the context of the observation of other authors that these gender differences are not universal (41).

Our results do not support the data of other authors on the predominance of left-handedness in patients with schizophrenia (17, 18). We find a high percentage of patients with mixed lateralization (i.e., cross use of hand, foot, or eye). Most likely, some studies did not look at cross-lateralization, but only left-handed or right-handed dominance, and did not use a trimodal classification, but a bimodal one. If we have to use the bimodal classification and look at the lateralization in terms of hand dominance, we found that seven of the patients have a dominant left hand. This makes 6.7% of all patients included in our study. The range of reported results of left-handedness in patients with

schizophrenia varies from 7 to 31%. Our result is in the lower range of reported cases, and we do not confirm the data of other authors for high rates of dominance of the left hand in patients with schizophrenia—up to 40% (18). Other analyses show that differences in lateralization are not universal, and there are many divergent results (41). The results of other analyses indicate that left-handed people have a predominance in patients with schizophrenia. Using a bimodal classification, our study did not support these studies (17, 18). We find a low percentage of patients with a dominant left arm that is comparable with those in the general population. These results support the data of other researchers on the lack of differences in left-handed dominance in patients with schizophrenia and the general population (30). Our results show that when using a trimodal classification in patients with resistant symptoms, those with cross-dominance (mixed lateralization) predominate. We support the researchers' view that mixed dominance is typical of patients with schizophrenia, as we find that more than 40% of all patients have cross-dominance (28). The results of other studies also indicate that mixed or cross-dominance is three times more common in patients with schizophrenia than in the general population (30, 42). The data obtained by us (twice as many), in patients with mixed lateralization with resistance in comparison with those in remission, support the assessment of other authors for the more severe course of the disease in those with cross-dominance (20, 21, 30).

On the other hand, neurophysiological studies to assess the lateralization of background activity in the EEG also do not show the presence of dominant hemisphere in patients with schizophrenia with and without therapy, which also indirectly supports the idea of mixed dominance in patients with schizophrenia (43). Our study shows that the high frequency of cross-dominance we found is due to the left lateralization of eye dominance. Analyses by other authors also found left-sided dominance of the eye in patients with schizophrenia, which is more pronounced in male patients (32). Our study showed a slightly higher percentage of men with left eye dominance than women.

One of the limitations of our study is that due to the presence of psychotic production—delusions and hallucinations (we analyze patients with resistance), it was not possible to assess in detail the continuity of dominance with analysis of mixed forms and their weight in the assessment of refractoriness. On the other hand, an additional problem is the formation of social dysfunction with concomitant change in behavior in many patients, which also leads to a reduction in daily functioning and activity in the use of hands and eyes. A third important factor is the presence of additional comorbidity due to the fact that these patients do not conduct systematic treatment of their health problems, including the care of the visual analyzer, which would call into question attempts for accurate and detailed assessment.

Our study provides guidance for future studies related to resistance and disconnection syndrome in association with the fact that the very presence of cross-dominance raises the question of easier disruption of information flows in the crossover of the neural network associated with them.

CONCLUSION

We found an association between the presence of cross-dominance and the treatment resistance in patients with schizophrenia. We reported that cross-dominance was found in more than half of the patients with resistant schizophrenia. This increased frequency of mixed dominance in them is due to left-sided dominance of the eye. These observations of ours can also be of practical use. The assessment of the dominant eye as well as a more in-depth analysis of the overall lateralization of dominance would provide guidance for early assessment of future development of resistance during treatment. Opportunities for early assessment provide a basis for seeking complex methods of treatment earlier in the course of the development of the schizophrenic process in order to prevent psychosocial complications associated with resistance.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commission of the University Hospital for Active Treatment, Stara Zagora. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Cognitive remediation for depression vulnerability: Current challenges and new directions

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It is increasingly acknowledged that cognitive impairment can play an important role in depression vulnerability. Therefore, cognitive remediation strategies, and cognitive control training (CCT) procedures have gained attention in recent years as possible interventions for depression. Recent studies suggest a small to medium effect on indicators of depression vulnerability. Despite initial evidence for the efficacy and effectiveness of CCT, several central questions remain. In this paper we consider the key challenges for the clinical implementation of CCT, including exploration of (1) potential working mechanisms and related to this, moderators of training effects, (2) necessary conditions under which CCT could be optimally administered, such as dose requirements and training schedules, and (3) how CCT could interact with or augment existing treatments of depression. Revisiting the CCT literature, we also reflect upon the possibilities to evolve toward a stratified medicine approach, in which individual differences could be taken into account and used to optimize prevention of depression.

KEYWORDS

cognitive control training, depression, working memory training, cognitive remediation, prevention of depression

Depression is a highly prevalent psychiatric disorder, affecting millions of people worldwide (World Health Organization [WHO], 2021). One of the core aspects of depression is impaired cognitive control (i.e., the ability to flexibly adapt thoughts and behavior in order to achieve one's goals; Cohen, 2017), which is known to persist even after recovery (Semkovska et al., 2019). Cognitive control impairments are typically not directly targeted by antidepressant treatments (Shilyansky et al., 2016). Importantly, there is increasing evidence suggesting that cognitive control impairments play a key role in risk for (re)occurrence of depression (Buckman et al., 2018). For instance, Vanderhasselt and de Raedt (2009) found that deficits in cognitive control increase with each depressive episode and persist after symptom remission. In addition, Demeyer et al. (2012) found that impaired cognitive control at baseline was predictive of depressive symptomatology at 1 year follow-up in a remitted depressed sample

(RMD). Furthermore, cognitive impairments are an important source of disability in daily life following remission from depression (Knight et al., 2018). Therefore, recent years have seen increased interest in the use of novel approaches to remediate these neurocognitive impairments. One such intervention, previously employed for other psychiatric disorders, is cognitive control training (CCT), in which working memory and executive functioning are trained. CCT has been operationalized in different ways, often using adaptive versions of working memory paradigms, such as the Eriksen Flanker task (Eriksen and Eriksen, 1974), the n-back (Kirchner, 1958) or the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977). Recent studies examining the influence of motivation on CCT found that by adding elements of gamification, training motivation and treatment adherence could be increased, without lowering its effectiveness (e.g., n-back: Mohammed et al., 2017; PASAT: Vervaeke et al., 2020).

In this paper we discuss the current state-of-the-art of CCT as an intervention to reduce depression vulnerability. Initial findings have suggested that this could be a useful intervention to reduce depression vulnerability (Siegle et al., 2007, 2014; Calkins et al., 2015) but challenges in several domains remain to further develop CCT into a successful clinical intervention. Based on the current state of the literature, the key challenges that we discuss are (i) identifying working mechanisms and potential moderators of CCT; (ii) establishing conditions for effectively applying CCT; (iii) evaluating possible combinations of CCT with other antidepressant interventions.

Working mechanisms

The working mechanisms of CCT are currently not completely understood. One possible theory highlights the importance of impaired attentional disengagement in depression (Koster et al., 2011). When experiencing stress, negative self-referent thoughts and feelings can arise. Although most people are able to manage negative thoughts, sometimes people get stuck in this process, and fail to disconnect from their negative thinking, resulting in a loop of negative self-referential thinking. Repetitive negative thinking (RNT) and rumination have been frequently associated with, and are a core part of, depression (Nolen-Hoeksema et al., 2008). CCT is believed to beneficially impact attentional disengagement from self-referential negative thoughts and feelings, allowing one to break free from RNT and its possible effects on depressed mood (Koster et al., 2011). Another model illustrating the relationship between depressive rumination and cognitive control, the H-EX-A-GO-N model from Watkins and Roberts (2020), describes the influence of habitual interactions with other factors in the development of rumination. Here, executive functioning impairments weaken one's ability to disengage from habitual ruminative responses, thereby increasing the likelihood of employing ruminative behavior as a habitual response to negative mood. The formation of ruminative habits, paired with executive functioning impairments, could help explain why people experience trouble interrupting ruminative processes, even when they are aware of its unhelpfulness. Indeed, habits can be resistant and difficult to change, even when they are conflicting with one's goals or intentions. Both the attentional disengagement (Koster et al., 2011) and the hexagon model (Watkins and Roberts, 2020) highlight the importance of cognitive control for RNT. By improving cognitive control, cognitive and behavioral decoupling from depressive rumination could be a possible working mechanism through which CCT could influence depression vulnerability.

Another perspective, the capacity-efficiency framework, focuses on the role of transfer effects of CCT (for a review, please see von Bastian et al., 2022). In this framework, cognitive training can expand cognitive capacity, or it can increase the efficiency of the already present cognitive abilities. These two possible working mechanisms are not mutually exclusive: it is possible that both cognitive capacity increases *and* efficiency increases simultaneously. In the context of CCT interventions targeting depression vulnerability, it is unclear to what extent existing training procedures target capacity, efficiency, or both. This is likely to be impacted by the nature of the training task and the adaptive mechanism underlying the training procedure. Increased cognitive processing efficiency may be reflected in increased performance on tasks which more strongly load on working memory capacity (e.g., working memory span tasks).

Essential in this framework is that potential cognitive gains do not stem from learning specific strategies or general task familiarity. Instead, by training cognitive control the effects transfer to other domains of cognitive or emotional functioning. These transfer effects are thus assumed not to be task-dependent and reflect real cognitive gains. Evidence for near transfer (i.e., transfer to tasks relying on the same underlying cognitive construct, such as working memory) and far transfer (i.e., transfer to different cognitive abilities) has been found in CCT studies, but prior research has yielded inconsistent results, with near transfer more frequently being observed than far transfer (Sala et al., 2019). It has been suggested for future CCT studies to include non-adaptive tasks, so that both near and far transfer can be examined (Koster et al., 2017). In this context, investigating how training progress and cognitive transfer relate to patterns of emotional transfer may shed light on the mechanisms underlying effects of CCT. For instance, Hoorelbeke and Koster (2017) observed task-specific cognitive transfer following CCT to be predictive of change in residual depressive symptomatology in remitted depressed individuals. This effect was partially mediated by immediate effects of CCT on RNT, suggesting that one potential mechanism through which CCT may impact risk for depression may indeed be increased disengagement from negative self-referential thoughts.

In addition to studies investigating effects of CCT on cognitive task performance and measures of emotional transfer, numerous studies have explored neuropsychological effects of CCT. Research has indicated that CCT activates the dorsolateral prefrontal cortex (DLPFC; Siegle et al., 2007). The DLPFC is known to be implicated in executive functioning and plays a central role in maintaining, discarding, and manipulating information in working memory (Barbey et al., 2013). The prefrontal and limbic regions are often activated together and play an important role in the relationship between cognition and emotion. It is hypothesized that the DLPFC is involved in regulating emotions and by improving cognitive control, one might strengthen emotion regulation capabilities. Some studies found that, even after recovery from depression, RMD individuals still show lower levels of DLPFC activation (Hooley et al., 2009). In times of distress, when amygdala activation is high, prefrontal cortical control is required to regulate limbic activity. Indeed, impaired cognitive control and decreased prefrontal activity in (remitted) depressed individuals might in part explain the high recurrence rates. In this context, initial studies suggest CCT to beneficially impact patterns of dysfunctional activation in frontal and limbic regions in patients undergoing treatment for major depressive disorder (MDD; Siegle et al., 2007). Similarly, in a convenience sample, Cohen et al. (2016) found CCT to increase connectivity between the amygdala and prefrontal regions. Such findings allow to link observed patterns of cognitive and emotional transfer, where further investigation into the underlying pathways of training effects is likely to yield possible targets for increasing the efficacy of CCT.

Treatment efficacy and its moderators

In terms of effectiveness, recent meta-analyses examining CCT for depressive symptomatology have found small to medium effect sizes, indicating that CCT could be a useful intervention in the context of depression (Motter et al., 2016; Launder et al., 2021). Interestingly, these effect sizes are very similar to those of other antidepressant treatments, such as pharmacological interventions (Khan and Brown, 2015) and psychological therapies (Cuijpers et al., 2013), highlighting both the clinical need for new treatment options, as well as warranting the use of CCT in clinical practice. In order to increase its efficacy, more insight into moderators of training effects is required. Previous studies have reported effects of CCT on depression vulnerability in different populations, such as patients diagnosed with MDD (Siegle et al., 2014), RMD individuals (Hoorelbeke and Koster, 2017), at-risk (Hoorelbeke et al., 2015; Beloe and Derakshan, 2019) and healthy individuals (Vervaeke et al., 2020). It has been posited that, in order to train cognitive control, interindividual differences might be more indicative of treatment response than categorical population type differences, and that individuals with different baseline levels of cognitive functioning might respond differently to cognitive training (Jaeggi et al., 2013; Borella et al., 2017; Traut et al., 2021). Indeed, some studies suggest that people scoring poorly on cognitive tasks could benefit the most (Karbach et al., 2014, 2017). At the same time, it might be the case that a certain level of cognitive control or executive functioning is required to profit from CCT procedures, meaning that the people showing the most cognitive impairment (regardless of their MDD or RMD status) might first need to reinforce their current cognitive capacity before CCT could improve them substantially (Traut et al., 2021). If this is the case, then cognitive training gains may not necessarily be a linear process: people with low cognitive control might first require an increase in cognitive control before training could further improve cognitive control.

Individual differences in baseline (cognitive) functioning may also reflect differential training needs in terms of training dosage. The utilization of baseline differences to differentiate a potential CCT treatment is currently not in widespread use but could potentially be a way in which CCT could be personalized and tailored to the individual. In this context, several studies have explored the association between specific factors, among which baseline level of cognitive functioning (e.g., Moshier and Otto, 2017), training task progress (e.g., Vanderhasselt et al., 2015), training related cognitive gains (e.g., Peckham and Johnson, 2018), level of RNT (e.g., Daches et al., 2015), and CCT efficacy. This has yielded inconsistent findings and leads us to believe that, similar to other anti-depressant interventions, there might not be a "one-size-fits-all" solution in terms of training operationalization for depression.

In this context, it has been suggested that a more integrative approach may be required in order to better capture profiles of functioning (Hoorelbeke et al., 2022). For instance, in a study examining subgroups based on baseline patient characteristics, interesting profiles emerged for the treatment and prevention of depression (Saunders et al., 2021). Patients with long durations of depression and anxiety, moderate to severe symptoms and past antidepressant use appeared to benefit more from psychotherapy, than antidepressant medication or treatment as usual (TAU). Moreover, profiles with greater risk of poor outcomes appeared to benefit more from more intensive treatment and frequent monitoring. Similar results were found in a study in which latent profile analysis was conducted to identify user profiles based on broad indicators of functioning, among which baseline level of cognitive functioning, use of (mal)adaptive emotion regulation strategies, level of internalizing symptomatology, training progress, user experience, and personality factors (Hoorelbeke et al., 2022). In particular, this study identified three user profiles, reflecting low-, moderate- and high-risk for internalizing psychopathology. These profiles moderated task-specific cognitive transfer effects, as well as change in anxiety-

and stress symptoms following CCT. CCT seemed to be more effective for the moderate- and high-risk groups. Moreover, it was suggested that the high-risk group could potentially benefit from an increased training dosage, as shown by relatively short-lived emotional transfer effects compared to the moderate training group, and less extensive cognitive training gains. Employing a stratified medicine approach by administrating CCT specifically for patients whom would benefit from such training is another possible way through which CCT could evolve into a personalized treatment for depression.

Treatment combinations

Although CCT has shown promise in reducing depression vulnerability, among which level of depressive symptomatology (e.g., Siegle et al., 2007; Hoorelbeke and Koster, 2017), CCT is unlikely to be a sufficiently effective stand-alone treatment for clinical populations. Hence, it is important to consider its combination with other interventions for depression (see also Van den Bergh et al., 2018). Meta-analyses show that combining psychotherapy with anti-depressant medication can result in improved treatment effects compared to monotherapy. However, research examining the antidepressant effects of combining CCT with other interventions is still scarce. One study examined the combination of CCT with the antidepressant vortioxetine (Lenze et al., 2020) and found that combined treatment led to a greater increase in global cognitive performance compared to only CCT (i.e., without antidepressant medication) in a sample of older adults who reported cognitive dysfunctions. The authors concluded that the combined treatment could be beneficial to counteract age-related cognitive decline.

Other studies have evaluated additive effects of CCT when combined with psychotherapeutic interventions. For instance, one study investigated the added value of CCT to a treatment consisting of behavior activation (Moshier and Otto, 2017), whereas another study explored additive effects of CCT using a group-based cognitive behavior therapeutic fear of failure program (Van den Bergh et al., 2020). Both studies failed to find evidence for treatment augmentation when combining CCT with a psychotherapeutic intervention. In contrast, Course-Choi et al. (2017) reported beneficial effects of a combined CCT and mindfulness approach to target RNT.

Another interesting avenue is the combination of CCT with neuromodulation strategies such as transcranial Direct-Current Stimulation (tDCS). It is assumed that tDCS in combination with CCT aims to increase CCT effectiveness, rather than induce effects by itself (Weller et al., 2020). In a study using healthy young adults, anodal tDCS to the left PFC improved performance in an n-back working memory training, compared to a sham group (Ke et al., 2019). The study also reported near-transfer effects to a similar, untrained 3-back version of the task. Similarly, Weller et al. (2020) found that, compared to sham stimulation, anodal tDCS with a 1 mA stimulation intensity applied to the left PFC improved CCT performance gains. Another recent study by Sommer and Plewnia (2021) examined the required tDCS dosage but reported that the addition of tDCS only resulted in a small increase in CCT effectiveness, concluding that any tDCS effects were potentially overshadowed by a larger CCT effect. Segrave et al. (2014) found no immediate effects of tDCS after CCT, but did report decreased depressive symptomatology at 3 week follow-up. It is possible that the effects of CCT might be more pronounced long-term as opposed to immediately after training. In line with this, Hoorelbeke and Koster (2017) reported effects of CCT to be more strongly pronounced at 3 months follow-up than at post-training, suggesting that emotional transfer effects following CCT may gradually develop over time. Indeed, several studies have shown long-term effects of CCT, among which one study reporting reduced need for clinical care at 1 year follow-up in MDD patients (Siegle et al., 2014). Furthermore, Hoorelbeke et al. (2021) observed task-specific cognitive transfer following CCT at 1 year follow-up in RMD patients, in addition to reduced risk for recurrence of depression and lower expressed need for psychotherapeutic interventions during the follow-up period.

Cost-effectiveness

In spite of the challenges mentioned above, CCT is an intervention that lends itself well to online dissemination and could be scalable to meet the needs of the large population vulnerable to depression. Despite previous research reporting cost-effectiveness of internet- and mobile-based interventions (IMIs) for both treatment and prevention of depression (Paganini et al., 2018), studies examining the cost-effectiveness of CCT specifically are largely missing. A study in a sample of post-stroke patients compared the combination of cognitive behavioral therapy (CBT) and occupational and movement therapy to a computerized cognitive training program as a control intervention and found no convincing cost-effective differences (van Eeden et al., 2015). Similarly, economic evaluations on IMIs have found that they were likely to be cost-effective when compared to TAU (Conejo-Cerón et al., 2021). With increasing research and clinical interest in CCT in the context of depression, more research in its cost-effectiveness is required, both as a stand-alone intervention, as well as a combination with other anti-depressant interventions.

Furthermore, cost-effectiveness could potentially be improved by employing a stratified care approach (i.e., identifying patients who benefit most from a specific intervention and providing them access to this treatment) instead of a stepped care approach (i.e., most patients first access only low-intensity treatments and patients who remain symptomatic later access more intensive interventions).

Delgadillo et al. (2021) found that stratified care was efficacious and cost-effective when compared to stepped care for psychological treatment of depressive symptomatology. However, similar studies for CCT specifically have not yet been conducted, even though CCT shows high potential to be integrated within such a treatment approach. As such, further research into the cost-effectiveness of CCT provides an important opportunity to build toward implementation of CCT in clinical practice.

Future directions

Currently, the use of CCT has not been widely employed as an intervention in the context of depression, and more research is required to justify and facilitate the introduction of CCT in clinical practice. In addition to the need for future research into the working mechanisms underlying effects of CCT, moderators of training effects, treatment augmentation, and cost-effectiveness, one important aspect that has currently not received much attention, is the optimal training dosage and method of administration. That is, as to date, the dose (i.e., the number of sessions) required for cognitive and emotional transfer effects to occur, as well as how this relates to the long-term sustainability of those effects remains to be tested. A recent meta-analysis by Launder et al. (2021) found a moderating effect of dose on overall cognition, with larger CCT doses being associated with greater effect size estimates, but the same effect was not statistically significant for depressive symptomatology. The authors refer to higher heterogeneity and imprecision within dose subgroups as possible explanations. Indeed, the absence of a dose-response relationship for CCT results in the use of variable doses in current research, potentially contributing to the heterogeneity in reported effects. The investigation of an optimal dose-response holds several key factors: the length of one training session, the number of sessions employed, and how frequently they are delivered. These three factors have seen a wide variability in scientific literature examining the effects of CCT on depressive symptomatology and often also depend on the training by which the CCT is operationalized. For example, recent adaptive PASAT studies have mostly used ten sessions of 15 min each with a maximum of one session a day (Van den Bergh et al., 2020; Vervaeke et al., 2020; Hoorelbeke et al., 2022). Recent studies using the n-back have generally used slightly longer training sessions of 20–30 min and a higher dose, around 20 sessions (e.g., Beloe and Derakshan, 2019; Zhang et al., 2019). The location where the training sessions take place is variable as well, with some studies inviting participants to a research or clinical facility, whereas others handle CCT as a training a participant can conduct at home, unsupervised. More research into these areas and how they relate to training progress and effectiveness is required for a broader picture of the effects of training dose and training administration on depressive symptomatology. Ideally, a dose-response relationship would be established using preregistered randomized controlled trials (RCT), where individuals randomized over groups receive a different amount of CCT sessions, examining emotional and cognitive transfer effects. Here, it also is conceivable that optimal dosage differs pending individual characteristics and the type of training task used.

Given the finding that for some at-risk groups emotional transfer effects may be short-lived (e.g., Hoorelbeke et al., 2022), another interesting area, closely linked to the effect of training dose, is the examination of the use of booster sessions in CCT. Similar to boosters in other clinical interventions, additional booster sessions may be beneficial in maintaining or increasing long-term effects of CCT. The effectiveness of booster sessions has been examined for psychotherapy and general cognitive training, with reported beneficial effects such as preventing loss of cognitive functioning (Aramaki and Yassuda, 2011; Felix et al., 2021) or maintained effectiveness of psychological treatment (Gearing et al., 2013; Wesner et al., 2015). However, it is currently unclear whether booster sessions increase the effectiveness of CCT in the context of depression. Equally unknown is *when* these booster sessions could prove beneficial, either at a fixed interval (e.g., after a fixed amount of time after completion of the last training session) or at an individualized, variable interval (e.g., when people are experiencing an increase in depressive symptomatology or related risk factors). One possible way to examine the effect of booster sessions would be *via* Experience Sampling Methodology (ESM), which allows to regularly assess functioning of individuals over time. Upon displaying increased depressive symptomatology or other early warning signs for recurrence of depression (e.g., Wichers and Groot, 2016), additional booster sessions could be administered. This type of design would allow to examine if the addition of booster sessions at crucial moments could result in more durable treatment effects.

(Remitted) depressed patients do not uniformly portrait cognitive impairments: whilst some people might have more trouble remembering information, others might complain about attentional deficits. Currently, CCT provides the same type of training for everyone, regardless of their individual cognitive impairments and needs. Future research should focus on examining specific types of cognitive impairments and could investigate if providing a personalized treatment might lead to more beneficial outcomes in both cognitive recovery, as well as decreased risk of recurrence.

Conclusion

CCT has been gaining traction as a psychological intervention in the context of depression. Due to the

advantages and wide-spread availability of modern technologies, individualized CCT could provide rapid and low-cost help. However, several key factors of how CCT can be effectively implemented are still unclear. Future research should focus on open questions, such as investigating a dose-response relationship, examining the efficacy and the optimal timing of booster sessions, as well as exploring the effectiveness of a combination of CCT with other frequently used interventions in the context of depression. Interindividual differences in (cognitive) needs could be considered when planning the use of CCT for ameliorating cognitive impairments and depressive symptomatology. Finally, the efficacy of a stratified medicine approach for CCT should be investigated, focusing on the previously mentioned key points, as well as taking baseline cognitive abilities into account, in order to provide a personalized treatment for depression, tailored to individual needs.

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YVZ, KH, and EK developed the framework of the review. All authors provided critical contributions and revisions.

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Conflict of interest

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Gender-associated role in patients with schizophrenia. Is there a connection with the resistance?

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Schizophrenia is a chronic mental illness observed with equal prevalence in different cultures and ethnic groups. The clinical picture relates to behavior and social adaptation. A significant percentage of patients, despite the implementation of various therapeutic interventions, remain resistant to the ongoing treatment. Occupying a certain gender role depends both on biological belonging and on the way of self-perception characteristic of the given person. Self-perception reflects gender identification, which in social aspect is determined by the choice of social activities performed. Changes in behavior and social adaptation in patients with schizophrenia led us to conduct a study to analyze the perceived gender role in patients with schizophrenia, looking for differences between patients with treatment resistance and those in clinical remission.

Materials and methods: A total of 105 patients with schizophrenia were analyzed. Of them, 45 were with resistant symptoms and 60 in clinical remission. The clinical analysis of the patients was carried out using the PANSS and BPRS scales. The evaluation of the choice of social activity related to a particular gender was done with the Bem Sex-Role Inventory (BSRI).

Results: Out of all 105 patients with schizophrenia, in 80/76.19%/we found a higher identification with the female role, 17/16.19%/made an association with the male role and in 8/7.61%/patients we found the same results, i.e., with both the male and female roles. Among the patients with treatment resistant schizophrenia (TRS)–45, 34/75.56%/identified more with the female gender role, 6/13.33/perceived the male gender role as active, and in 5/11.11%/the identification was equal both with the male and with the female roles. Among the patients in clinical remission (CR)–60, 46/76.67%/accepted the female role as active, 11/18.33/identified with the male one, and three/5%/accepted both roles equally. When assessing the relationship between biological sex and perceived gender role, it was found that among men/a total of 39/half identified with the female gender role and half with the male gender role. Among women/a total of 66/, 90% perceived the female gender role, 7%–the male and 3% equally the male and the female gender role. No relationship was found between the choice of a certain gender role and the onset of psychosis and its duration in the observed patients.

Conclusion: We found a higher percentage of schizophrenic patients who showed higher identification with the female gender role. Approximately half of the males identified with the female gender role. Resistance had no influence on the choice of sex-associated social activity. Factors related to the course of the schizophrenia process such as age of onset of psychosis and duration of psychosis was not associated with an influence on identification with sex-associated social activity. Our research suggests that identification with a particular sex associative social activity is most likely established earlier in the prodromal period.

KEYWORDS

resistant schizophrenia, clinical remission, gender identity, sex, gender, social activity, sex role

Introduction

Schizophrenia is a severe chronic mental illness characterized by specific symptoms divided into three large groups: positive, negative and cognitive symptoms (1). Research in recent years has shown that schizophrenia is not just a mental disorder in the narrow sense of the word. It has multiple disturbances in metabolism, opioid system and immunity, which often require further evaluation and therapeutic approach (2–4). In patients with schizophrenia and associative connections as well as loss of connectivity between individual brains regions were found (5–7). The established changes in the connecting systems between the different brain regions give grounds for some authors to consider schizophrenia as a disconnection syndrome (8). On the other hand, it should be noted that gender differences in brain size have been found, as well as not very convincing differences in the associative connections between individual neuronal centers and functional lateralization in men and women (9). Other authors have looked at morphological differences in different brain regions in males and females, concluding that sex-associated biological differences were observed (10).

The course of the schizophrenic process in men and in women is characterized by certain differences related to both the time of appearance and the prevalence of certain symptoms to the higher rate of resistance found in men (11, 12) Numerous studies have been conducted regarding the gender characteristics of patients with schizophrenia, and the gender differences considered were based on the established dichotomy of "male" and "female" gender (13). Authors define gender role as "all those things that one says or does to reveal oneself as having the status of boy or man, girl, or woman." (14).

In general, communities based on the biological differences between men and women create a set of social expectations that define the behavior that is "appropriate" for men and women (15). Many cultures have different requirements and norms based on gender differences and there is no established universal standard for a male or female role (16, 17) is a cognitive theory that attempts to explain how individuals define their gender in society and how the associated characteristics are maintained and transmitted to other members of the culture (17). The greatest Contribution To The Field of certain social behavior was the attempt to quantify it through the Bem Sex-Role scale. Originally developed as a tool to identify sex-typed individuals, many researchers use it to assess other components of gender, including type of social activity as a measure of masculinity/femininity (18).

Deaux (19) suggests that gender comparison is based on culturally accepted norms regarding the nature of femininity and masculinity. Lewine (20) found it appropriate to use this terminology also in the study of schizophrenic patients. Furthermore, it does not consider how psychological gender, which is primarily a matter of self-perception, may influence illness in men and women with schizophrenia and how this may impact treatment and the recovery process (21). Cultural expectations for men and women with schizophrenia differ according to research. Research has shown that males with schizophrenia have more difficulty performing expected normative role activities than females (21). An analysis of the literature on gender identity and schizophrenia shows that men and women with schizophrenia have disordered gender role identification and this is more characteristic of males, and this fact should be taken into account in the therapeutic approach to patients (22).

An analysis of the literature on gender identity and schizophrenia shows that men and women with schizophrenia have disordered gender role identification and this is more characteristic of males, and this fact should be taken into account in the therapeutic approach to patients (22).

Seeman (23) noted that, based on the major differences between men and women with schizophrenia: from the different age of onset to the different symptomatology, dose, and affective fluctuations, the two sexes cannot be burdened with the same demands in the presence of a schizophrenic process. Authors

have found that patients more easily perceive and identify with the female role than with the male role (24). Many psychotic symptoms are found in patients with identity disorder, and in patients with schizophrenia there is a large percentage of patients with identity disorder (25).

Other authors consider identity disorder and schizophrenia as mutually exclusive, raising the question of exaggerating the relationship between schizophrenia and identity disorder (26). Research has shown fluidity in the timing of gender identity expression, which may fluctuate over time and be associated with thought process disorder (27).

Analysis of the effect of treatment in patients with schizophrenia shows that up to 40% are resistant to treatment (28). Schizophrenia is a complex disorder that can be likened to a "symphonic" orchestration, but as other authors have also found, gender is also a consequence of a complex "symphonic" orchestration (29). Naturally, the question arises whether there are differences in gender identification in patients with resistance to treatment and those who have achieved clinical remission.

Materials and methods

Subjects

A total of 105 patients with schizophrenia with consecutive psychotic episodes have been observed. Of these, 45 have resistant schizophrenia and the remaining 60 are in clinical remission.

The patients were observed in a psychiatric clinic at the University Hospital in Stara Zagora.

Including criteria to all patients:

1. Diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V, 2013];
2. Between 18 and 60 years of age;
3. At least primary education;

Including criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia (28). These are:

1. Assessment of symptoms with the PANSS and BPRS scale (30, 31).
2. Prospective monitoring for a period of at least 12°weeks.
3. Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg chlorpromazine equivalents.
4. Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.
5. The assessment of social dysfunction using the SOFAS (Social and Occupational Functioning Assessment Scale) scale is below 60.

The exclusion criteria are:

1. Intellectual disability.
2. Psychoactive substance abuse.
2. Presence of organic brain damage.
3. Concomitant progressive neurological or severe somatic diseases.
4. Expressed personality change.
5. Score of MMSE (Mini-Mental State Exam) below 25 points.
6. Pregnancy and breastfeeding.

Methods

Sandra Bem's scale (BSRI) was used to assess the perceived gender role (17).

We used the SPSS (version 26) statistical package. Correlation analysis was used to investigate the relationship between the sex-associated role and the resistance to therapy, age of onset of schizophrenia and duration of the disorder in patients with schizophrenia. A non-parametric statistical method was also used (32).

Age, body mass index (BMI), level of education is controlled as covariables.

All research procedures were carried out in accordance with the Declaration of Helsinki.

All patients signed an informed consent before admission to the clinical settings and performing diagnostic tests and therapy.

Results

The mean age of patients in the group of resistant schizophrenia was 36.98 years. The minimum age is 21 years and the maximum is 60 years.

The mean age of patients in the group of schizophrenia in clinical remission was 37.25 years. The minimum is 23 years and the maximum is 63 years.

We did not find a difference in the mean age of the patients in both groups at the time of the study.

No statistical differences were found between the two groups of patients in terms of height, weight, and BMI.

An analysis of patients with resistant psychosis and those in remission using the Bem Sex-Role Inventory (BSRI) found the following results:

Of all patients with schizophrenia, 80/76.19%/showed a higher scale when measuring identification with the female

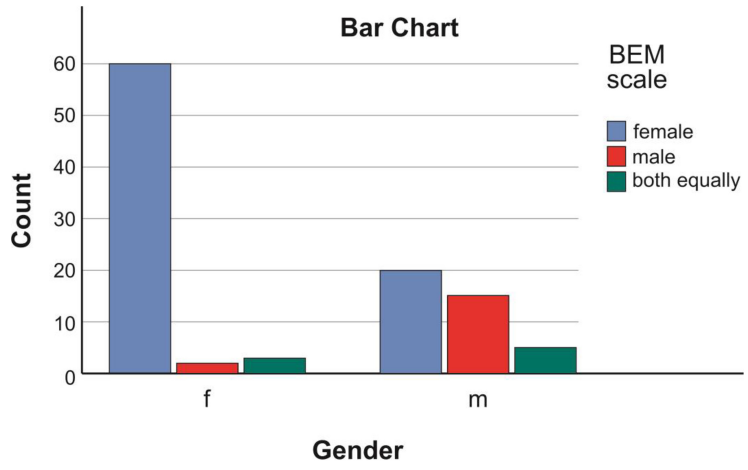

FIGURE 1
Connection between biological sex and accepted gender role I patients with schizophrenia.

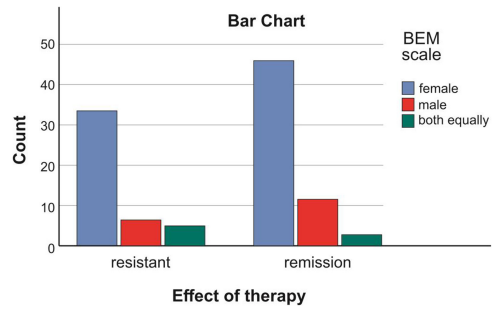

FIGURE 2
Connection between effect of therapy and accepted gender role in patients with schizophrenia.

TABLE 1 Connection between effect of therapy and accepted gender role in patients with schizophrenia.

		BEM scale			Total
		female	male	both equally	
Effect of therapy	resistant	34	6	5	45
	remission	46	11	3	60
Total		80	17	8	105

role, 17/16.19%/made an association with the male role, and 8/7.61%/patients had the same results in identifying with gender roles, i.e., with both the male and female roles.

When conducting a comparative study to compare the real sex of the examined patients with the results of using the Sandra Bem scale, the following data were observed:

Among the 65 female persons, it was found that 60/92.31%/identified with the female gender role, 2/3.07%/with the male gender role, and 3/4.62%/perceived both gender roles equally.

Among the 40 males, it was found that 20/50%/identified more with the female gender role, 15/37.5%/identified with the male gender role, and 5/12.5%/perceived both roles equally Figure 1.

These data show that the recorded predominance of female gender role identification is at the expense of males, with half of them identifying with the female gender role.

The analysis of the relationship between perceived gender role and treatment effectiveness showed the following results:

Among the patients with treatment resistant schizophrenia (TRS)–45, 34/75.56%/identified more with the female gender role, 6/13.33/perceived the male gender role as active, and in 5/11.11%/the identification was equal both with the male and the female roles.

Among the patients in clinical remission (CR)–60, 46/76.67%/accepted the female role as active, 11/18.33/identified with the male one, and three/5%/accepted both roles equally Figure 2 and Table 1.

With this observation of ours in schizophrenic patients, we found that easy identification and acceptance of the female gender role was observed.

In view of the described and assumed factors related to the change in the gender role, we made the following analyses of the relationship with the perceived specific gender role. We analyzed the relationship between the accepted gender role and the age; the age of onset of the schizophrenia process as well as the duration of the schizophrenia process.

TABLE 2 Relationship between features of psychosis and perceived gender role.

	Female	Male	Both equally	Sign.
Age	37.44	32	44	$p > 0.05$
Age of onset	26.23	23.94	21.88	$p > 0.05$
Duration of Sch	11.5	9.18	22.5	$p > 0.05$

When analyzing the relationship between the perceived gender role as male, female, and equally both female and male with the age of the patients, we found the following:

The average age of patients who adopted the female gender role was 37.44 years.
The average age of patients who identified with the male gender role was 32 years.
The average age of those who had the same results in both male and male attitudes was 44 years.
The conducted statistical analyses showed no statistically significant relationship: $p < 0.05$.

Assessment of the relationship between the onset of schizophrenia and perceived gender role showed the following results:

Among those with a perceived female role, the onset of schizophrenia was at 26.23 years. For those identified with the male gender role–23.94 years and for those with identification equally with both roles–21.88 years. Statistical analysis showed no significant relationship $p < 0.05$.

The analysis of the relationship between the accepted gender role and the duration of the schizophrenia process showed the following distribution:

In patients who accepted the female gender role, the duration was 11.25 years. For those with a male perception, it was 9.18 years, and for those who identified with both gender roles–22.5 years. Despite the differences in the length of years, the sample of patients with the same points regarding the evaluation of male and female gender roles was small–eight patients **Table 2**.

The conducted statistical analysis showed no statistically significant difference with $p < 0.05$.

Discussion

The results of the study conducted to assess the identity with a certain role in patients with showed that two thirds of the observed patients identified with the female role. Among the male subjects, half of the patients identified more with the female role. Just under a fifth identified as masculine and just under a tenth scored equally on masculine and feminine gender roles. Our observation showed that it was done by easy identification and acceptance of the female role. These data confirm the observations of other authors that there is a change in gender identification in patients with schizophrenia (21, 22, 24, 25).

There were almost identical results regarding the discrepancy between biological sex and the points indicating dominant gender roles in both resistant and remitted schizophrenic patients. These results showed that this registered change was more deeply affecting the identity of the individual and is not only related to the loss of the patients' social role and autonomy.

The view of some authors (29) that mental illness itself can be considered as silencing other factors of identity is difficult to accept due to the fact that in patients in remission a relatively preserved or largely recovered level of functional activity is observed, despite changing their gender identification. On the other hand, we should not forget the fact that gender places higher demands on men in relation to the need for professional and social connections. These factors, on the other hand, are also a noted problem in schizophrenics in general (33). Seen in this way, some explanation can be given to this "escape" from the male role. We did not find confirmation of the hypothesis that most likely the early onset of the disease and its duration make it difficult to construct sex-associated patterns (33). Our data showed no association between the onset of psychosis, its duration, and gender role identification. We believe that most likely the choice of the female role and identification with it is related to being placed in a subordinate, "protected" position in patients with schizophrenia, on the one hand, and on the other hand, these data can be interpreted through the prism of "burden of normality" (34).

In these cases, a bridge can definitely be drawn between the choice of gender role and the phenomenon of "learned helplessness", which includes cognitive, motivational and emotional disorders appearing as a consequence of the impact of uncontrollable negative life events (35) and places patients in a more "subordinate position". These results of ours indirectly support the idea of a relationship between identity disorder and schizophrenia, not supporting those who believe that such a relationship is absent (26).

The result of the lack of relationship between symptom resistance and perceived gender role is interesting. As a possible explanation, we found that with the onset of psychosis a defensive position within the female gender role was adopted, which, despite recovery from psychosis, was more convenient for patients to abandon. On the other hand, patients with schizophrenia often have prodromal symptoms, sometimes

years before the development of the disease, which enable the adoption of social strategies within the female gender role, as a more protected social position. We believe that the development of this "escape" from the male gender role began even before the onset of psychotic experiences.

One of the main unanswered questions is whether the accepted gender role will remain stable over time or whether there will be dynamics and change in social patterns of behavior. If we proceed from the concept of the fluidity of gender identity, such a process should also be assumed (27, 36). For this, it is necessary to conduct additional longitudinal studies in patients with schizophrenia in order to track the presence of possible dynamics over time.

At this stage, we cannot give an answer to the question whether in the course of social recovery in patients in clinical remission, a gradient shift of the gender role will not be observed in parallel with the re-adaptation processes.

Conclusion

We found a change in gender role choice that is characteristic of male individuals. We did not find a relationship between the choice of gender role and resistance to therapy, nor with the features of the schizophrenic process. These data of ours indicate that the change in the dominant gender role most likely occurred even before the onset of schizophrenia, most likely in the prodromal period.

Our observations are a good direction for work in the process of rehabilitation and recovery for patients with schizophrenia. In the course of this process, we consider it important to pay attention to the assessment of the dominant gender role in order to provide more correct strategies for social rehabilitation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of University Hospital "Stoyan Kirkovich". The patients/participants provided their written informed consent to participate in this study. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee of University Hospital "Stoyan Kirkovich" Stara Zagora, protocol code TR3-02-242/30 December 2021.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intersection of anxiety and negative coping among Asian American medical students

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Purpose: Asian Americans comprise 21% of matriculating medical students in the United States but little is known about their mental health. With the growing focus on addressing the mental health of medical students, this systematic, nationwide survey assesses the relationship between anxiety and depression symptoms and coping skills among Asian American medical students.

Materials and methods: A survey tool comprised of Patient Health Questionnaire-9, General Anxiety Disorder-7, and questions related to coping were emailed to members of the Asian Pacific American Medical Students Association enrolled in a United States medical school during the 2016–2017 academic year. We evaluated associations between anxiety and coping as well as depression and coping.

Results: A total of 511 Asian American medical students completed the survey. Anxiety symptoms were positively correlated with an increase in negative coping skills. Depressive symptoms were not correlated with an increase in negative coping skills.

Conclusion: Professionals and medical schools that aim to improve the mental health of medical students should be aware of the needs of specific populations. Asian American students who experience anxiety were more likely to utilize avoidant or negative coping strategies. In addition, Asian American students who experience depressive symptoms were not more likely to utilize these negative coping strategies. Further research must be done to evaluate the factors that influence the use of negative coping strategies to better address anxiety within the Asian American medical student population.

KEYWORDS

anxiety, negative coping, Asian American, medical students, intersection of anxiety

Introduction

Individuals who identify as Asian American comprise 21% of matriculating medical students in the United States, but there is limited research focusing on the mental health of these students throughout their medical school experience (Dyrbye et al., 2007; Association of American Medical Colleges, 2021). While there are several studies that have looked at stress, depression, and burnout among minority medical students in general (Pyskoty et al., 1990; Camp et al., 1994; Henning et al., 1998; Tjia et al., 2005; Dyrbye et al., 2006a, 2007; Yang et al., 2021), there are fewer studies also examining anxiety among this population and, in particular, a paucity of data on medical students who identify as Asian American (Quek et al., 2019). Existing literature examining the prevalence of anxiety and depression among medical students found that medical students had higher rates of anxiety and depression relative to the general population (Dyrbye et al., 2006b). Anxiety and depressive disorders can negatively impact medical students' health, professionalism, academic performance, and quality of patient care (Burr and Beck Dallaghan, 2019; Quek et al., 2019). Given that Asian American medical students comprise almost a quarter of the students attending medical school, understanding what cultural considerations need to be made to address this population of students is important to consider prior to their completion of training when they are entering the workforce as physicians. Cultural considerations, which take into consideration how stigma related to seeking mental health services and acknowledging symptoms that could lead to emotional stress and burnout, could positively impact interventions and conversations with Asian American medical students regarding their mental health needs while in medical school. Therefore, it is imperative for medical school administrators to understand the consequences of both anxiety and depression on Asian American medical students.

The general population of medical students use a variety of coping skills to manage anxiety and depression (Stern et al., 1993). Coping skills refer to the behavioral and cognitive efforts individuals employ in response to stressors in an effort to minimize the negative implications associated with a stressor (Merrill and Thomas, 2013). A distinction is often made between positive and negative coping skills (de La Rosa-Rojas et al., 2015). Positive or adaptive coping are defined as an active approach that aims to mitigate or change the stressor itself through a means that is beneficial to the overall wellbeing of that individual (Folkman et al., 1986). For instance, contacting a therapist or counselor, exercising, and seeking support from spiritual advisors are typically identified as positive coping skills (Litman, 2006). In contrast, negative or avoidant coping is a passive approach centered on escaping from stressful situations and subsequently often harmful to the individuals wellbeing (Merrill and Thomas, 2013). Engaging in self-harm, over or under-eating, and consuming alcohol are commonly identified as negative coping skills (Litman, 2006). Positive coping skills have been linked to better health outcomes than negative coping, such as lower levels of stress symptoms, decreased depression, and decreased suicidal behavior (Penley et al., 2002; Li and Zhang, 2012; Merrill and Thomas, 2013; Shatkin et al., 2016; Thompson et al., 2016; Nie et al., 2020). Conversely, negative coping skills have been associated with greater alcohol consumption, lower quality of life, burnout, fatigue, and increased risk of mental health problems (Merrill and Thomas, 2013; Ding et al., 2015; Paek et al., 2016; Hou et al., 2020; Smida et al., 2021).

Previous studies in medical students have shown an association between coping skills and depression and anxiety symptoms (Mosley et al., 1994; Steiner-Hofbauer and Holzinger, 2020). Shao et al. (2020) reported that anxiety was negatively correlated to positive coping and positively correlated to negative coping in Chinese medical students. A German study found that students with high scores on anxiety and depression clinical scales also showed high levels of dysfunctional coping (Prinz et al., 2012). Thompson et al. (2016) also reported that greater use of positive or approach-oriented coping strategies, which aim to find cognitive strategies to find a solution to a problem, was inversely correlated with depression. To our knowledge, data on anxiety, depression, and coping strategies of Asian American medical students in the United States are lacking. The intersection of these areas is important for medical schools to understand in order to build culturally sensitive interventions that can lead to a healthy and sustainable workforce after medical school. As previous studies have shown, individuals who identify as minority students often experience unique challenges in how they utilize coping skills to manage mental health symptoms. In addition, Asian American students are often considered the "model minority," which possesses additional stressors on individuals to perform and achieve high standards. This model minority myth, which creates an assumption that one minority group is perceived as higher achieving over other individuals due to their ethnicity, creates misperceptions regarding one's true mental health needs by creating false assumptions regarding the Asian American population (Cheng et al., 2017; Yip et al., 2021). Thus, the aim of this study was to explore the relationship between anxiety and depression symptoms and coping skills among Asian American medical students attending medical schools in the United States.

Materials and methods

Participants and procedures

The sample included 511 Asian American (AA) medical students enrolled at a medical school in the United States during the 2016–2017 academic year. Students were recruited through the Asian Pacific American Medical Student Association,

a national organization that supports AA students and represents 90 medical schools and colleges in the United States. Specifically, students were emailed information regarding the study and invited to complete a brief, online battery of self-report questionnaires. The survey was comprised of questions regarding coping behaviors, the Generalized Anxiety Disorder-7 self-report questionnaire, the Patient Health Questionanire-9 self-report measure, questions related to stigma, mental health history and demographic questions. All questions were included to further understand mental health symptoms, behaviors and attitudes for the respective sample population. All responses were completely anonymous and collected using the professional and encrypted version of Survey Monkey Pro. The study was approved by the institutions' Institutional Review Board.

Students' who completed the survey identified as primarily male (62%) and between the ages of 21–25 (68%). In terms of relationship status, most students reported being single (49%) followed by married or in a committed relationship (51%). Most students were enrolled in their first year of medical school (40%) followed by second (31%), third (19%), and fourth year (10%).

Measures

Coping

Participants were provided with a list of behaviors and asked to select all methods that are used to cope when feeling anxious or depressed. Negative coping behaviors, included the following strategies which were engaging in self-harm, overeating, undereating, smoking cigarettes, using recreational drugs, and consuming alcohol. The negative coping strategies were coded as 1. The score for each individual was summed to create a total score (ranging from 0 to 6) with higher scores indicating poorer coping.

Generalized anxiety

The Generalized Anxiety Disorder-7 (GAD-7) is a 7-item self-report questionnaire designed to assess generalized anxiety symptoms (Spitzer et al., 2006). Participants were asked to read a list of symptoms and indicate how often they have been bothered by each within the past 2 weeks. Items are rated using a four-point Likert-type scale ranging from 0 (*Not at all*) to 3 (*Nearly every day*). Total scores can range from 0 to 21 with higher scores indicating increased symptom severity. The GAD-7 has strong psychometric properties and demonstrated good internal consistently in the current study (Cronbach $\alpha = 0.88$).

Depression

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item self-report questionnaire designed to assess depression symptoms. Participants were asked to read a list of symptoms and indicate how often they have been bothered by each within the past 2 weeks (Kroenke et al., 2001). Items are rated using a four-point Likert-type scale ranging from 0 (*Not at all*) to 3 (*Nearly every day*). Total scores can range from 0 to 27 with higher scores indicating increased symptom severity. The PHQ-9 has strong psychometric properties and demonstrated good internal consistently in the current study (Cronbach $\alpha = 0.87$).

Drop out

Participants were also asked if they had considered dropping out of medical school over the past month using a dichotomous response choices of *Yes* or *No*.

Data analytic plan

All analyses were conducted using IBM SPSS Statistics version 26.0. First data screening was performed. This included calculating descriptive statistics to inspect for data entry errors, missing data, outliers, and normality. Normality, linearity, and homoscedasticity were assessed according to the guidelines sets forth by Tabachnick and Fidell by inspecting the normal probability plot of the regression standardized residual and the scatterplot as well as tolerance and variance inflation factor values (Tabachnick and Fidell, 2006). Second, descriptive statistics including means, standard deviations, and distributions were examined. Variables were considered abnormally distributed if the skewness and/or kurtosis statistic divided by the respective standard error resulted in a value ± 2. In such cases a Log10 transformation was utilized. Third, zero-order correlations among all variables were examined. Fourth, two hierarchical linear regression analyses were conducted to examine the relationship between anxiety, depression, and poor coping. Gender was entered in the first step of each model followed by either anxiety or depression symptom severity.

Results

Preliminary analyses

At the item level, less than 6% of all values were missing. As such, missing data was handled *via* pairwise deletion. Preliminary analyses indicated no threats or violations of normality, multicollinearity, or homoscedasticity. PHQ-9 scores

TABLE 1 Descriptive statistics.

	Mean	Std. deviation	*N*
Gender	0.62	0.485	511
PHQ9_total	6.1255	5.26395	470
GAD7_total	5.3805	4.77567	481
CopingNeg	0.9843	0.92659	511

were significantly skewed (skewness = 11.08) and kurtotic (kurtosis = 6.72). Additionally, GAD-7 scores were significantly skewed (skewness = 9.15). As a result, Log10 transformations were utilized to more closely approximate a normal distribution. The transformed variables were used in all analyses. However, for ease of interpretation, the non-transformed variable was used in Tables 1, 2, when presenting descriptive statistics and zero-order correlations among study variables. In terms of drop-out, 12% of students reported that they had considered dropping out of medical school in the past month, which the authors found to be significant as categorical data.

Primary analyses

The first hierarchical linear regression was designed to examine the relationship between depression and coping. The first step of the model, which included participant gender, accounted for 0% of the variance in negative coping, $F(1,468) = 0.14$, $p = 0.705$. In the second step of the model, PHQ-9 scores were added accounting for no additional variance in coping, F change = 0.53, $p = 0.466$. PHQ-9 scores were not significantly associated with increased negative coping ($B = -0.03$, $t = -0.73$, $p = 0.466$, $sr^2 = 0.00$). Therefore, no relationship was found between reported symptoms of depression and the use of negative coping skills among the sample.

The second hierarchical linear regression was designed to examine the relationship between anxiety and coping. The first step of the model, which included participant gender, accounted for 0% of the variance in negative coping, $F(1,479) = 0.15$, $p = 0.702$. In the second step of the model, GAD-7 scores were added accounting for an additional 4% of variance in coping, F change = 19.76, $p < 0.001$. GAD-7 scores were significantly associated with increased negative coping ($B = 0.20$, $t = 4.45$, $p < 0.001$, $sr^2 = 0.04$). Therefore, a significant relationship was found between individuals reported symptoms of anxiety which were associated with an increase in negative coping skills used. While there were no differences between gender, there was a significant association when examining the sample as a whole.

Discussion

Results of the current study revealed that students' depressive symptoms were not associated with an increase in negative coping skills. Although somewhat unexpected, previous findings for depression among Asian Americans have been mixed with some studies showing that sociocultural factors can play important protective roles against negative mood states (Sue et al., 2012; Leong et al., 2013). However, anxiety symptoms were positively associated with an increase in negative coping skills. That is, students who were experiencing anxiety symptoms were more likely to utilize avoidant or negative coping strategies to mitigate the impact of their emotional state. This includes strategies such as engaging in self-harm, over or undereating, smoking cigarettes, using recreational drugs, and consuming alcohol. The utilization of negative coping has been linked to a decrease in academic performance which is concerning given the majority of individuals studied are enrolled in their first and second year of medical school when the curriculum is heavily focused on retention of course materials. In addition, 12% of students who completed the survey had considered dropping out of medical school which is an important prevalence rate for medical school administration to investigate. In order to promote the wellbeing of Asian American medical students during their medical training, it is important to understand how mental health concerns, specifically anxiety, can negatively impact their experience and possibly their professional trajectory. Further, it is important to ensure that Asian American medical students have access to culturally competent providers and culturally

TABLE 2 Means, standard deviations, and zero-order correlations between all variables.

		Gender	PHQ9_total	GAD7_total	CopingNeg
Gender	Pearson correlation	1	0.082	−0.021	−0.017
	Sig. (2-tailed)		0.076	0.640	0.693
	N	511	470	481	511
PHQ9_total	Pearson correlation	0.082	1	0.072	−0.025
	Sig. (2-tailed)	0.076		0.132	0.591
	N	470	470	442	470
GAD7_total	Pearson correlation	−0.021	0.072	1	0.194**
	Sig. (2-tailed)	0.640	0.132		<0.001
	N	481	442	481	481
CopingNeg	Pearson correlation	−0.017	−0.025	0.194**	1
	Sig. (2-tailed)	0.693	0.591	<0.001*	
	N	511	470	481	511

**Correlation is significant at the 0.01 level (2-tailed).
Gender coded 0 = Female and 1 = Male; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; *$p < 0.001$.

sensitive interventions in the academic setting. Interventions to help identify students desire to change, awareness of the problem, and ability to decrease current negative coping skills could be beneficial to the Asian American student population.

In regard to potential limitations of this study, the survey was voluntary and completed on-line by students and may not be representative of the entire population of Asian American medical students currently enrolled. Given the significance of the findings, there may be a greater need in the community then what this particular study captured. The majority of respondents comprised first and second year students which could skew the results. Gaining a balanced sample size across all years of medical school could strengthen the results of this study. The study also assessed student's intention to consider dropping out of medical school which relates to a potential future behavior. An interesting area of further research would be to assess studies current thoughts about studying less, not attending classes and changes in current behaviors which could affect future performance in medical school. Another potential limitation of the current research was the primary focus on the utilization of negative coping skills rather than assessing if students are using positive coping strategies to mitigate mental health symptoms, which would be helpful to understand in order to build wellness models that align with student's preferred method for coping with negative emotions. Lastly, students also completed this survey between 2016 and 2017. With the unfortunate increase in discrimination toward Asian American individuals during the last 2 years of the COVID-19 pandemic, the mental health needs of the population surveyed may appear different now with additional societal pressures and social injustice present. Therefore, a survey to examine the current mental health state of this particular group of medical students could be beneficial. In closing, medical schools could strengthen their approach to retain students who are struggling with their mental health, provide supportive interventions when concerns are identified, and demonstrate an understanding and attention to the unique needs of students who identify as Asian American.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by LSU Health Sciences Center IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Going beyond the DSM in predicting, diagnosing, and treating autism spectrum disorder with covarying alexithymia and OCD: A structural equation model and process-based predictive coding account

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Background: There is much overlap among the symptomology of autistic spectrum disorders (ASDs), obsessive compulsive disorders (OCDs), and alexithymia, which all typically involve impaired social interactions, repetitive impulsive behaviors, problems with communication, and mental health.

Aim: This study aimed to identify direct and indirect associations among alexithymia, OCD, cardiac interoception, psychological inflexibility, and self-as-context, with the DV ASD and depression, while controlling for vagal related aging.

Methodology: The data involved electrocardiogram (ECG) heart rate variability (HRV) and questionnaire data. In total, 1,089 participant's data of ECG recordings of healthy resting state HRV were recorded and grouped into age categories. In addition to this, another 224 participants completed an online survey that included the following questionnaires: Yale-Brown Obsessive Compulsive Scale (Y-BOCS); Toronto Alexithymia Scale 20 (TAS-20); Acceptance and Action Questionnaire (AAQII); Depression, Anxiety, and Stress Scale 21 (DAS21); Multi-dimensional Assessment of Interoceptive Awareness Scale (MAIA); and the Self-as-Context Scale (SAC).

Results: Heart rate variability was shown to decrease with age when controlling for BMI and gender. In the two SEMs produced, it was found that OCD and alexithymia were causally associated with autism and depression indirectly through psychological inflexibility, SAC, and ISen interoception.

Conclusion: The results are discussed in relation to the limitations of the DSM with its categorical focus of protocols for syndromes and provide support for more flexible ideographic approaches in diagnosing and treating mental health

and autism within the Extended Evolutionary Meta-Model (EEMM). Graph theory approaches are discussed in their capacity to depict the processes of change potentially even at the level of the relational frame.

KEYWORDS

autism (ASD), alexithymia, obsessive-compulsive disorder (OCD), structural equation model (SEM), graph theory, psychological flexibility

Introduction

The Diagnostic and Statistical Manuel 5th Edition (DSM-5) (American Psychiatric Association, 2013a) describes autistic spectrum disorders (ASDs) as involving impaired social interactions, repetitive behaviors, and problems with communication. Additional features can include poor eye contact (Esposito and Venuti, 2008), sensory modulatory dysfunction (Baranek et al., 2005), motor dysfunction (Ozonoff et al., 2008), and cognitive developmental problems (Esposito et al., 2009; Edwards et al., 2012).

There have been several potential advantages of the DSM classification suggested for disorders, such as ASD, as it attempts to standardize diagnosis and treatment across different treatment providers, provides a quick guide, and should eliminate guesswork (Möller, 2014). This should, in principle, provide a useful guide for both clinicians and researchers; however, the DSM classification approach also presents many disadvantages. One such disadvantage is that there may be issues with such a rigid classification taxonomy as the DSM adopts a latent disease model that is suggested by the American Psychiatric Association (2013a,b) and assumes a medical illness model. This approach assumes that symptoms should reflect some specific sets of underlying and latent disease entities; however, latent categories are often not distinct. This can be found in the evidence which has found a high degree of comorbidity between these latent categories, indicating that these categorical clusters of symptoms advocated by the DSM are not linked to discrete functions as they were intended to do (Kupfer et al., 2008). Despite many attempts to overcome the problem of comorbidity, the DSM still does not provide clinicians and researchers with any treatment-specific indications for those cases presenting with psychiatric comorbidity (Dell'Osso and Pini, 2012). These type of problems have led to growing disinterest in the most recent version, the DSM-5 (Hayes et al., 2019).

Such growing disagreement with this rigid classification protocol approach for some times has led to calls for a move toward a process-based approach in the diagnostics and treatment of mental health disorders (Forgeard et al., 2011). This has been most recently formalized in a process-based therapy (PBT) approach, which advocates that diagnostic and therapeutic efforts should focus more on the causal processes that underlie the efforts to produce change and not through rigid categories advocated by the DSM (Hayes and Hofmann, 2017, 2018; Hofmann and Hayes, 2019; Hofmann et al., 2021). PBT research emphasizes the Extended Evolutionary Meta Model (EEMM), which highlights the processes of change as multi-level and multi-dimensional rather than singularly focused through protocols of syndrome as suggested by the DSM. EEMM specifies six dimensions at the individual level where processes of change can occur; affective (positive and negative affects), cognitive (problem-solving skills, reappraisal, etc.), attentional (mindfulness, noticing in the present moment, awareness of feelings), self (self-esteem, self-efficacy, self-compassion, and self-as-context), motivation (individual goals and values), and overt behavior (striving and commitment to goals). There are two additional levels in this model, that being the physiological level (such as autonomic functioning, predictive coding, interoception of the insular cortex), and social level (such as group motivations and values).

This problem of comorbidity when attempting to strictly classify disorders can be seen clearly in many clinical cases. For example, there are several autistic symptoms that have similarities and overlap with the symptoms in other clinically diagnosable conditions, such as schizophrenia, such that both conditions involve problems with emotional functioning and information processing (Lewis and Levitt, 2002; Volkmar et al., 2004). Indeed, evidence suggests that ASD and schizophrenia may share some commonalities in phenomenology (Couture et al., 2010), in biological pathway pathophysiology (Pinkham et al., 2008; Guilmatre et al., 2009; Sugranyes et al., 2011), and in treatment (McCracken et al., 2002). However, these two conditions have been clearly delineated for their unique aspects for many years (Kanner, 1965).

Such delineation has been more difficult when comparing conditions such as ASD and alexithymia (Kinnaird et al., 2019). Alexithymia, which is regarded as a personality trait and relates to the difficulties in emotional processing, such as recognizing emotions, has also been reported in ASD (Silani et al., 2008; Guastella et al., 2010). More specifically, it has been suggested that problems with emotional processing observed in ASD stem from co-occurring alexithymia (Bird and Cook, 2013; Cook and Shah, 2013; Brewer et al., 2015). Alexithymia was first recognized in the 1970s and has been described as a condition involving difficulties in recognizing and distinguishing different emotions,

a lack of imagination, and thoughts centered on the external world rather than internal world (Sifneos, 1973). Though not always identified in individuals who have a diagnosis of ASD, alexithymia has been found to be more extreme in ASD individuals compared to the general population (Hill et al., 2004; Berthoz and Hill, 2005; Fitzgerald and Bellgrove, 2006). Indeed, there is a growing body of research, which suggests that the problems associated with emotional processing in ASD individuals are driven by alexithymia. Evidence supporting this comes from studies that have shown, for instance, that when controlling for alexithymia and autism, it is the levels of alexithymia and not autism which predict problems with facial, vocal, and music emotional recognition (Heaton et al., 2012; Allen et al., 2013; Cook and Shah, 2013). A meta-analysis (Kinnaird et al., 2019) identified 15 studies where alexithymia was found to be higher in an ASD population when compared to a neurotypical population (49.93 compared to 4.89%). They concluded that alexithymia represents a specific subgroup in ASD, and that further research was needed to understand the nature and implications of co-occurring comorbid alexithymia in ASD. This comorbidity is clearly a problem for the DSM, which favors distinct categories.

Another connection that is difficult to delineate is the connection between ASD (including with alexithymia) and obsessive compulsive disorder (OCD) symptoms. For example, ASD traits (such as ritualistic behavior, attachment to objects, and in some cases low levels of sociability) have been identified in individuals with OCD (Ivarsson and Melin, 2008). There are also substantial similarities and overlap in the pathophysiology between OCD and ASD (Meier et al., 2015), though less is known about the clinical etiological cohesion between these disorders. Furthermore, it has been found that individuals with OCD had significantly higher levels of alexithymia than those who did not (Grabe et al., 2006), which echoes the comorbidity problem that ASD has.

Less work has linked ASD with alexithymia and OCD concretely. Some of the work in ASD have speculated; for instance, that deficits in localized areas of basal ganglia and cerebellum abnormalities (Nayate et al., 2005; Rinehart et al., 2006; Qiu et al., 2010) are responsible for gait function, movement problems, and also social and communication issues, which may also be applicable to explain alexithymia and OCD symptoms in some cases, but not all. However, one particularly interesting and promising psychophysiological pathway that may prove to be a crucial link to explain the comorbidity among alexithymia, ASD, and OCD is the interoceptive pathway.

Interoception is the representation of the internal system at any given moment. It is formed in the brain (primarily the insular cortex) by interpreting signals received from the bodily organs *via* general visceral afferent neurons (found in cranial nerves VII, IX, and X) of the autonomic nervous system (ANS) (Cameron, 2001; Craig, 2002). The interoceptive pathway consists of unmyelinated C and myelinated Aδ afferent fibers which transmit a signal from the laminae I vertebra of the spine to the posterior gray column of the spinal column and then to the hypothalamus, anterior insular, and cingulate cortices (Pollatos et al., 2007; Craig, 2008). These brain areas receive information signals from viscera, thermoregulatory, nociceptive, and endocrine systems (Pollatos et al., 2007). Once the brain has received these signals, it then integrates this information in terms of their varying motivational immediacy, such as determining whether to respond to sensations, such as prickly burning pain, warmth-coldness, hunger, need to urinate, and sensual touch (Strigo and Craig, 2016). The signals are then further processed for motivational and emotional relevant behaviors, through organizing it within primary emotional and motivational brain regions of the limbic system, the anterior insular, and cingulate cortices of the homeostatic sensorimotor cortex (Murphy et al., 2003; Craig, 2014). It has been suggested that at this stage, a meta-representation of "self" emerges allows for very specific regulatory responses to the signals to emerge.

Interoception is typically measured through an index of interoceptive accuracy (IAc) or interoceptive sensitivity (IS) (these measures are the same), which are recorded through the heartbeat perception task (Schandry, 1981; Pollatos et al., 2009; Mallorquí-Bagué et al., 2014), which asks participants to count their perceived heartbeats, and then, the following formula is applied:

$$1 - \frac{|\ n\ beats_{actual} - n\ beats_{perceived}\ |}{(n\ beats_{actual} + n\ beats_{perceived})/2} \quad (1)$$

Another approach is to use the multi-dimensional interoceptive awareness questionnaire (MAIA-2) (Mehling et al., 2018), which assesses a more conscious self-report measure (than the heartbeat perception task) of interoception. There is a distinction between the ability to detect interoceptive information (such as heartbeat detection) in the form of IAc and an individual's conscious beliefs about their interoceptive abilities, called interoceptive sensibility (ISen). The MAIA-2 assessment is a self-report questionnaire measure of ISen (Mehling et al., 2018; Smith et al., 2021), whereas another measure of ISen is a simple confidence measure of how accurate the participants felt they were at the heart beat counting task (Mehling, 2016).

Altered interoception is associated with an increase in psychopathological disorders, such as an increase in chronic pain, anxiety, depression, and eating disorders (Paulus and Stein, 2010; Klabunde et al., 2013; Di Lernia et al., 2016; Duschek et al., 2017), but is not predicative of a specific emotional regulation strategy (Pinna and Edwards, 2020). Typically, lower IAc/IS scores lead to greater pathology, and it is suggested that inefficient or an impaired relay of interoceptive information, transmitting a greater number of interoceptive errors than usual from peripheral structures to higher cortical centers, leads to dysfunctional "body mapping"(Craig, 2008; Harshaw, 2015).

This eventually leads to dysfunctional self-regulatory processes and ultimately to aberrant emotional, behavioral, and autonomic sequelae (Craig, 2008).

Increased IAw has been shown to have both positive and negative outcomes. For example, increased focus on physical sensations IAw has been associated with anxiety, hypochondriasis, somatization, and hypervigilance (Paulus and Stein, 2006). It has been suggested that what determines whether increased IAw/ISen leads to maladaptive or healthy outcomes depends on the interoceptive style (Mehling et al., 2018). Mehling et al. suggest that the maladaptive form of IAw/ISen that is associated with the maladaptive outcomes (e.g., of hypervigilance) is anxiety-driven interoception. They suggest that with the emerging field of mindful bodily awareness, maybe a more adaptive form of IAw/ISen can be promoted, rather than that driven by anxiety, which are more likely to lead to more positive mental health outcomes. Some evidence confirm this suggestion, as mindful IAw in the form of a body scan technique (Ussher et al., 2014) has been shown to reduce pain-related distress and the degree to which pain interferes with social relations. Mindful IAw has also shown to reduce stress states in post-traumatic stress disorder (PTSD) and associated depressive symptoms (Colgan et al., 2016).

In autism specifically, interoception appears to be atypical, but the degree and directionality is unclear due to the heterogeneous nature of the condition (DuBois et al., 2016). There have been some controversies as to whether abnormalities in the interoceptive system actually cause autism, with some researchers saying that it does (Quattrocki and Friston, 2014) and others suggesting that it does not (Nicholson et al., 2018). It is perhaps important to note that interoception is not just central to the processing of bodily signals for the requirement of homeostasis and allostasis but also the perception of these bodily signals (Cameron, 2001; Craig, 2002; Critchley et al., 2004). As such, interoception is also central in a range of cognitive and emotional processing which includes memory, decision-making, emotional processing, social interactions, body ownership, a sense of self, and even consciousness (Critchley et al., 2001; Dunn et al., 2010; Shah et al., 2017; Critchley and Garfinkel, 2018; Tsakiris and De Preester, 2018). With such a central system, it is likely that interoception plays a key role in autism and other related conditions.

One of these related conditions is alexithymia, and it has indeed been suggested that alexithymia is the result of impaired interceptive pathway (Herbert et al., 2011; Brewer et al., 2016). For instance, some suggestions are that the interoceptive pathway is thought to relate to developmental dysfunction of the connectivity among the limbic structures, the anterior insular (AntIn), and the anterior cingulate context (ACC) (Lane et al., 1997; Craig, 2002; Singer et al., 2009). This could also mean that alexithymia is the result of dysfunction with the homeostasis mapping of regulatory responses and the generation of a meta representation of "self" that is thought to be an important as part of the interoceptive pathway (Damasio and Carvalho, 2013).

Interoception in the form of IAc has been found to be attenuated in individuals with OCD (Schultchen et al., 2019; Demartini et al., 2021) and did not change over time with standardized cognitive behavioral therapy (CBT). There have been mixed results in relation to whether individuals with OCD have increased or lowered IAc, whereby one study has reported that IAc was higher in OCD than healthy controls (Yoris et al., 2017) and another has indicated that it was lower (Schultchen et al., 2019). In addition to this, an functional magnetic resonance imaging (fMRI) study has shown that sensory phenomena (SP) that are aversive uncomfortable sensations that accompany repetitive behaviors in OCD result in the hyperactivation of the insular (a primary area of interoceptive processing) (Brown et al., 2019). These mixed results may provide further evidence that the type of interoception (e.g., mindfully or anxiety-based) is more important than whether there is a direct increase or decrease in overall interoception. One study specifically focusing on ISen showed that the MAIA subscales were differentially associated with the different OCD symptom dimensions.

Central to interoception is the vagus nerve, which is the main cranial nerve in the human body known to primarily relay visceral (interoceptive) signals to the brain (Critchley and Harrison, 2013; Yoris et al., 2018; Quadt et al., 2019). The vagus nerve is the 10th cranial nerve (labeled CN X) and has a central role in transmitting interoceptive information to the brain, as well as being main anatomical component of the parasympathetic nervous system (PNS) (Walker, 1990). It has been largely acknowledged for its afferent neuron functions that make up 80% of the nerves which relay sensory information from viscero-somatic structures (Porges, 2007; Bonaz et al., 2017). It is assumed that the vagus nerve not only includes visceral homeostatic function, but also is involved in social, cognitive, and affective components (Membrilla et al., 2020). A recent systematic review of the literature showed that both indices of interoception along with more direct vagal activity were shown to be central to emotional regulation (Pinna and Edwards, 2020). For example, the study found that individuals with higher parasympathetic activity and interoception were associated with higher levels of emotional regulation. This, therefore, shows the important role of vagal function and interoception in emotional regulation and mental health.

Vagal tone can be measured in a variety of different ways, all of which involve an electrocardiograph (ECG). A commonly used measure is heart rate variability (HRV), which measures the variability between each consecutive heartbeat, and is described more formally as measuring sequential R-R peaks in the QRS complex of an ECG measure Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology (1996). HRV has been found to be a reliable indicator of psychosomatic functions that include emotional and

behavioral regulations (Laborde et al., 2018; Pinna and Edwards, 2020). The heart receives dual innervation from the ANS in the form of the sympathetic nervous system (SNS) and PNS. One of the common measures of this HRV construct is the frequency domain index, whereby the high frequency (HF) has been shown to provide a reliable index of vagal function (Thayer, 2009). In addition to the HF index, HRV can be measured using a time domain index called the root mean square successive difference (RMSSDD), as well as the respiratory sinus arrhythmia (RSA) index, which provides a value of HRV in synchrony with the respiratory cycle. A high HRV measure indicates increased parasympathetic activity whereas lower HRV indicates lower parasympathetic and greater sympathetic activity.

One important observation is that HRV has been found to positively correlate with ISen in healthy individuals (Owens et al., 2018). Interestingly, alexithymia has been found to negatively correlate with ISen but not IAc (Zamariola et al., 2018). This link has been supported by another study, which showed that alexithymia was significantly negatively correlated with the dimensions of ISen as recorded by MAIA-2 (noticing, not-distracting, attention regulation, emotional awareness, self-regulation, body listening, and trusting body) (Edwards and Lowe, 2021). Lower HF-HRV has also been found to be associated with higher alexithymia (Lischke et al., 2018), which is consistent with the ISen data, and indicates that these two indices are closely related (both abstracted from the vagal nerve).

In relation to autism, a recent meta-analysis showed that HRV in autism is lower at rest than healthy controls (Cheng et al., 2020); however, ISen (when using the Porges Body Perception Questionnaire) was found to be higher in those with higher autism. For OCD, the results are more mixed. One study has found that OCD showed no difference in HRV when comparing with healthy controls (Slaap et al., 2004); however, another study showed a decrease in HRV for patients with OCD compared to healthy controls (Pittig et al., 2013).

Some researchers have suggested that interoception is a complex and multi-faceted construct which requires continual refinement in conceptualization and operationalizing to fully understand how it can be used to explore psychopathology (Trevisan et al., 2021). Instead of simply concluding that higher or lower interoception is better or worse for mental health, rather a better distinction may be whether the interoceptive bodily awareness is adaptive or maladaptive (Mehling et al., 2018; Trevisan et al., 2021). To conceptually link interoception and vagal functioning (e.g., HRV) in a broader model which is inclusive of ASD, alexithymia, and OCD, existing models can be considered.

Several models exist that explain the biological and brain functions and pathways, such as neurovisceral integration model (NIM) (Thayer and Lane, 2009) and polyvagal theory (Porges, 2018, 2022). However, one very interesting model of cardiac interoception is called the predictive coding model (or active inference), which suggests that the brain makes sense of multiple interacting streams of physiological interoceptive information by predicting their causes and generating prediction errors (Seth, 2013; Barrett and Simmons, 2015; Barrett et al., 2016; Seth and Friston, 2016; Stephan et al., 2016; Owens et al., 2018). This idea of psychopathology as a result of interoceptive error has been further developed by predictive coding frameworks. For example, it has been used to explain major depressive disorder (MDD) (Kube et al., 2020), anxious hypervigilance (Cornwell et al., 2017), but also autism (van Laarhoven et al., 2019) and altered conscious states, such as explaining a placebo induced analgesia (Büchel et al., 2014).

In the case of MDD (Kube et al., 2020), predictive coding assumes that an individual does not perceive the world as it actually is but through a lens which corresponds to the brains best guess of it (Ongaro and Kaptchuk, 2019). The brain handles uncertainty (entropy) of new events and environments by integrating information and making rational use of it, through applying prior knowledge in the interpretation of new observations (O'Reilly et al., 2012). In this case, their perception of the world corresponds to a negative perception which is consistent with their predictive (predictive coding) beliefs relating to their prior knowledge about the world (Rief and Joormann, 2019). This can include reinforced and derived failures that they have experienced in the world, and corresponding derived feelings of failure that they have made about themselves (their own concept of themselves). So, this skewed pattern of predictions may explain why people with MDD perceive the world in a predominantly negative way, thus creating a self-reinforcing negative feedback loop (Kube et al., 2020).

Specifically, in relation to ASD, Pellicano and Burr's (2012) general Bayesian account suggests that attenuated Bayesian priors (called hypo-priors) may be responsible for the unique perceptual experience of individuals with ASD. It is assumed that as perceptual experience is shaped by the integration of stimulus information both incoming interoceptive and other sensory information and prior background information about the world, the ASD individuals' perception is modulated to perceive the world more biased through sensory information (i.e., in a more real way) and largely ignores prior information. This modulation of perception through sensory experience favors local (real world) perception over global (knowledge-based) perception. This view is consistent with the theories of over selectivity, which assume that autism results from an overly strong perceptual focus on certain local features and which ignore contextual and other global characteristics (Edwards et al., 2012).

In predictive coding higher brain areas, attempt to predict and explain lower brain areas and project these predictions down to lower levels where the predicted information is subtracted (discounted) from the input (environmental or bodily) sensory information. This feedback of predictions to lower brain levels represents the empirically driven prior contextual background knowledge (Feldman and Friston, 2010).

Conditions such as alexithymia could be related to high predictive errors, which could affect the shaping of a sense of embodied self (Seth and Friston, 2016), which may explain why individuals with alexithymia struggle to feel embodied emotions relating to themselves.

In relation to OCD, one review (Levy, 2018) suggested that in OCD, predictive coding errors were more weighted in a way (in the brain) that meant they were more costly for them than for healthy individuals. It is assumed that this added cost results in an upregulation of attention, which in turn leads to an overestimation of possible threats in the environment. Such an increase in perceived threat has been directly observed (Hezel and McNally, 2016).

Concepts such as selfhood are also important in therapeutic models, such as acceptance and commitment therapy (ACT) (Hayes et al., 2011; Hayes, 2019), a third wave behavioral therapy, which attempts to build psychological flexibility through six key processes: (1) present moment awareness; (2) openness and acceptance of painful feelings, thoughts, and memories; (3) cognitive defusion, the act of recognizing that thoughts are just thoughts and not to buy into them; (4) values orientation through identifying what is meaningful in your life; (5) commitment to values; (6) self-as-context (SAC), which is the awareness of thoughts and feelings but being an observer to these experience, i.e., the complete detachment of "self" from the literal meaning of thoughts.

Perhaps, the most relevant of these in relation to interception and selfhood is SAC (Zettle et al., 2018). In the ACT model, SAC relates to a "self" that once psychologically flexible is assumed not be a fixed state and instead a flexible and context dependent, as an observer to experience (i.e., the perspective-taking self) (McHugh and Stewart, 2012; McHugh et al., 2019). Some recent works have been conducted in the area of alexithymia, for instance through exploring the link between alexithymia and ISen, and within the context of mental health, psychological flexibility, and level of SAC (Edwards and Lowe, 2021). This found that SAC mediated the association between some of the ISen subconstructs and mental health, so clearly it is linked. This also means that it is potentially linked to the predictive coding account, whereby lower SAC, and perspective-taking skills likely means greater predictive errors.

Given the following problems: (1) the lack of clarity from the DSM which assumes latent syndromes should form discrete categories and cannot explain why there is co-morbidity between alexithymia, OCD, and autism; and (2) given that there seems to be a set of complex interactions between alexithymia, OCD, and autism in combination with SAC, psychological flexibility, and mental health, this study will seek to explore these in more detail. This study will therefore explore the complex causal sequences among ISen (interoception), mental health, psychological inflexibility, SAC, and how these relate to the conditions of OCD, alexithymia, and ASD.

This will be done through constructing a conceptual model which will explore direct and indirect sequential causality through a structural equation modeling (SEM). Previous studies have largely explored associations with the use of standard regression modeling and related statistical approaches (such as analysis of variance, ANOVA). However, regression analysis is not well-suited for describing causal sequences where there are potentially complex interactions between the variables. Many variables can be added in a multiple regression model, which can make it more comprehensive, but it still does not show causal sequences. Path models such as SEM allow the chains of conditional relations to be explore; therefore, it is ideal for representing causal models and it allows for both confirmatory and exploratory modeling.

However, before a conceptual model is constructed, it needs to be developed in stages. Questions that must be asked are (1) what potential confounds should be controlled for? (2) What should the structure of the conceptual model look like? (3) Which of the variables should mediate, if any? To answer these, standard statistical approaches (ANCOVA, regression, and simple mediation will be used) given that the literature provides less clues as to what the overall structure of such a conceptual model which captures such complex causal sequences should look like. For this approach, there will be four main stages in informing the development of a conceptual model and SEM of direct and indirect causality between these variables, and these include the following:

(1) Exploring potential confounds to a conceptual model through exploring how age effects vagal functioning when controlling for body mass index (BMI), gender, and comparing HRV at different age groups. Though there is evidence that age does affect vagal functioning is affected by age (Zhang, 2007), this phase will explore this while controlling for gender and BMI. This will lay the foundation for demonstrating how vagal function (which ISen interoception is based on) may deteriorate as a result of natural aging (it is hypothesized that participants in the older groups will have lower HRV than the younger groups). This will, therefore, provide useful knowledge about whether this should be controlled for in the SEM.

(2) Backwards stepwise regression models will explore which variables are most predictive of alexithymia, OCD, and autism to inform stage 3. It is hypothesized that all subconstructs and total values of ISen, alexithymia, OCD, alexithymia, and age would predict autism; all subconstructs and total values of mental health, ISen, alexithymia, autism, psychological flexibility, and age would predict OCD; and all subconstructs and total of values mental health, ISen, autism, and OCD would predict alexithymia. SAC is not hypothesized to directly predict these outcomes as will more likely act as an indirect effect.

(3) Five independent simple mediation analyses will be conducted, whereby some of the outcomes in the final regression models (of stage two) will inform the mediation analyses to be made. The mediation analyses will provide the conceptual

TABLE 1 Index of measurement score meaning.

Outcome measure/ variable	Meaning
AQ-10	Higher score indicates higher autism. Scoring sheet suggest referring yourself for a specialist diagnostic if the individual scores are >6 out of 10.
TAS-20	Higher score indicates higher alexithymia for the total. ≥ 61 = high alexithymia; ≤ 51 = low alexithymia (no alexithymia)
Y-BOCS-10	Higher score indicates higher OCD. Total score; 8–15 = Mild OCD; 16–23 = Moderate OCD; 24–31= Severe OCD; 32–40 = Extreme OCD
DAS-21	Higher scores indicates higher depression, anxiety, stress for the (three) relevant respective subsections.
AAQ-2	Higher score indicates higher inflexibility
SAC	Higher score indicates greater self-as-context
MAIA-2	Higher score indicates higher interoceptive awareness for the (eight) relevant respective subsections.

model with the details of what structure the conceptual model and SEM should take through both direct and indirect effects. It is hypothesized that ISen self-regulation will mediate the association between OCD and autism, as well as alexithymia and depression. SAC will mediate the association between autism and alexithymia. Psychological inflexibility will mediate the association between ISen self-regulation and SAC, as well as SAC and ISen trusting.

(4) Finally, exploratory factor analysis and confirmatory factor analysis will demonstrate which item variables are the best fit for each loading of a latent variable in the SEM. This will be followed by the direct model fit test of the SEM to confirm the conceptual model. Tentative hypotheses for the SEM include the following: there will be a positive association between alexithymia and psychological inflexibility, a negative association between psychological inflexibility and SAC as well as ISen self-regulation, but a positive association with depression. There will be a negative association between ISen self-regulation and autism. There will be no direct effects between alexithymia and autism or depression, or OCD autism or depression, but there will be indirect effects of these *via* psychological inflexibility and SAC.

Methods

Participants

For the questionnaire, the inclusion criteria for participation were listed as follows: (1) participants needed to be at least 18 years of age; (2) have good ability to read English; (3) have normal to corrected to normal vision; (4) have internet access; and (5) and needed to report that they had received a diagnosis of autism from a healthcare professional. Participants were excluded if they did not meet these inclusion criteria requirements. For the ECG data, participants must have been 18 years, otherwise healthy with no specific diagnosis (refer to PhysioNet database for full details[1].

In the first part of the study, 1,121 healthy participants were involved in ECG recordings, which measured healthy resting-state HRV and BMI. However, once missing data were removed (such as age), then 1,089 remained. In total, 242 participants took part in following survey and 18 withdrew without completing it, leaving 224 complete surveys recorded.

Materials

The ECG data[2] (Schumann and Bär, 2022) held on a publicly accessible database (PhysioNet) (Goldberger et al., 2000) were used for the baseline restful age-related cardiac change in HRV. Recordings were made through an ECG (lead II) at 1,000 Hz either by an MP150 (ECG100C, BIOPAC system inc., Golata, CA, USA) or Task Force Monitor system (CNSystems Medizintechnik GmbH, Graz AUT). These used pre-gelled Ag/AgCl electrodes (BlueSensor VL, Ambu BmbH, Bad Nauheim, GER) were attached according to an Einthoven triangle.

The survey section of data collection was conducted through Qualtrics[3], which was distributed on various autism support groups on Facebook. Table 1 shows a scoring index for the questionnaires used (i.e., what a high or low score indicates). The survey included demographic questions about age, gender, and the following seven questionnaires:

Autism spectrum quotient (AQ-10)

This is a 10 item scale and is a brief "red flag" assessment tool to help health professionals make a decision as to whether to make a referral for a full diagnostic assessment (Allison et al., 2012). The National Institute for Health Care Excellence (NICE, 2014) does not recommend any specific screening tool for adults and children with suspected moderate to severe autism; however, the AQ-10 is recommended in cases where there is not moderate to serve intellectual disabilities. This scale has four options to choose from "definitely agree" to "definitely disagree." As a threshold of score of 6 for adults, sensitivity was 0.88, specificity was 0.91, and positive predictive value (PPV) was

1 Full details can be found at: https://physionet.org/content/autonomic-aging-cardiovascular/1.0.0/.

2 Full details can be found at: https://physionet.org/content/autonomic-aging-cardiovascular/1.0.0/.

3 See here for Qualtrics: www.qualtrics.com.

0.85. Cronbach's alpha is also high on all measures (age groups) (>0.85) (Allison et al., 2012).

Yale-Brown obsessive compulsive scale (Y-BOCS)

This is a 10 item scale of OCD severity (Goodman et al., 1989) and is considered the gold standard for this measure and symptom severity (Storch et al., 2010). Participants can choose between five options, from 0 to 4 with varying answers, and include question such as "how much of your time is occupied by obsessive thoughts?" and "how much distress do your obsessive thoughts cause you?" It has five overall dimensions which questions are focused on: (1) time spent; (2) interference with functioning or relationships; (3) degree of distress; (4) resistance; and (5) control. Internal consistency of this measure is high, with a Cronbach's alpha of 0.89 and an interclass correlation >0.85 (Goodman et al., 1989).

Toronto alexithymia scale (TAS-20)

This is a 20 item scale of alexithymia, which specifically measures three constructs in addition to a total alexithymia score: (1) difficulty identifying feelings (DIF); (2) difficulty describing feelings (DDF); and (3) externally orientated thinking (EOT) (Bagby et al., 1994). Participants respond based on a five-point Likert scale, ranging from 1 = strongly disagree to 5 = strongly agree. The three subscales can also be combined to give a total alexithymia score, whereby scores of >61 indicate the presence of alexithymia, 52 to 60 indicate possible alexithymia, ≤51 indicate the absence of alexithymia. Construct validity of the scale (Pinaquy et al., 2003; Larsen et al., 2006; Pike, 2013) has been found to be high for DIF (Cronbach's alpha = 0.83) and DDF (Cronbach's alpha = 0.80), but not as high for EOT (Cronbach's alpha = 0.55).

Multi-dimensional assessment of interoceptive awareness (second version, MAIA-2)

This is a 32 item scale, with eight constructs (Mehling et al., 2018) of ISen (and not IAc). These constructs include the following: (1) noticing (noticing uncomfortable sensations in your body); (2) non-distracting (not ignoring painful bodily sensations); (3) not worrying (not worrying about bodily discomfort); (4) attention regulation (despite distractions, having the ability to place attention to one's body); (5) emotional awareness (noticing changes in one's body when your emotions change); (6) self-regulation (when one is feeling overwhelmed, being able to find a place of clam); (7) body listening (listening to one's body for emotional states); and (8) trusting (feeling at home in your body). These construct scales are rated from 0 to 5, whereby 0 = never and 5 = always. Higher scores indicate higher ISen for a particular subscale. Cronbach's alpha for all eight constructs ranged between 0.64 and 0.83. Only "noticing" (0.64) and "not worrying" (0.67) fell below the standard criterion of 0.7, indicating good overall construct validity.

The depression anxiety stress scales-21 (DAS-21, short-form)

This is a short version, which measures general ongoing (over the past week) psychological distress on three mental health subscales (anxiety, depression, and stress). The participant must enter a value between 0 and 3, which answers the degree to which a particular statement applied to them (0 = "did not apply to me at all" and 3 = "applied to me very much or most of the time"). Higher scores indicate higher levels of stress, anxiety, and depression. The measure has good construct validity, with a confirmatory factor analysis of 0.94. The measure also has good internal reliability as measured through Cronbach's alpha coefficients, which are 0.88 for depression, 0.82 for anxiety, 0.90 for stress, and 0.93 for the total scale (Henry and Crawford, 2005).

Acceptance and action questionnaire (second version; AAQ-2)

This is a seven item scale, which measures general psychological inflexibility (Bond et al., 2011). The questions ask the participant how they accept and open up to difficult thoughts and feelings, as well as how they engage in valued behavior when difficult thoughts and feelings are present. The participant must enter a value between 1 and 7, whereby 1 = never true and 7 = always true. Higher scores indicate higher psychological inflexibility. The measure has good construct validity with a Cronbach's alpha of 0.83 (Frewen et al., 2008).

Self-as-context (SAC) scale

This is an 11 item self-report scale, where participants must respond on a seven point Likert scale with responses ranging from 1= strongly agree to 7 = strongly disagree, where higher scores indicate higher self-as-context (Gird, 2013). The item statements include, for example, "I have a perspective on life that allows me to deal with life's disappointments without getting overwhelmed by them." and "Even though there have been many changes in my life, I'm aware of a part of me that has witnessed it all." The scale has good construct validity with a Cronbach's alpha of 0.82.

Procedure

For the ECG data, refer to their website[4] for full details, but the key points are summarized here. Participants were instructed to lie down on an examination tilt table in a temperature-controlled room of 22°C. During the recordings, it was quiet and fully shaded. For resting-state recordings, participants were instructed to avoid movement and the instructor waited a few minutes for the participants to relax while checking the quality of the signals (electrodes were repositioned if the signal was noisy). The length of the recordings averaged 19 min and was supervised at all times by the instructor.

For the questionnaire, an advertisement was placed on autism support groups on Facebook, which explained the study in some details and provided an email that interested individuals could respond to. Once participants responded to the advertisement, they were then given a Qualtrics link that contained full information about the study, ethical implications, and a consent form. On consent, participants were then provided with seven questionnaires (refer to Materials section) in addition to demographic questions *via* Qualtrics.

Ethical statement

Ethics were approved through Swansea University's Department of Psychology Research Ethics Council (REC). This was in accordance with the Declaration of Helsinki and included obtaining written informed consent from all participants, right to withdraw, and a full debriefing at the end of the study.

Data analysis

For the first phase of the study, ECG data[5] (Schumann and Bär, 2022) held on a publicly accessible database (PhysioNet) were analyzed using the Matlab PhysioNet tool, cardiovascular analysis toolbox to produce the HRV analysis, which included artifact removal of the data. IBM's SPSS, version 28.0. was used to conduct a general linear model, analysis of covariance (ANCOVA). Here, the data age groups were collapsed into three groups as follows: group one included ages 18 to 29, group two included ages 30 to 44, and group three included ages 45 and over. Gender and BMI were included as covariates in this model.

For the second phase of the study questionnaires, there were no missing data as the participants were required to complete all questions. For this, a rule was set in Qualtrics, which prevented participants from progression through the questionnaire without first completing the questions on each page (i.e., a reminder appeared if they missed a question), as in previous studies (Edwards, 2019; Edwards and Lowe, 2021).

Descriptive and inferential statistics (regression and correlations) were carried out using IBM's SPSS, version 28.0. As the associations among alexithymia, autism, and OCD are largely uncertain, assumptions about a predefined hierarchy as required for hierarchical regression models could not be achieved. So, instead, stepwise backwards regressions were chosen over a hierarchical regression as the hypothesis assumptions are much more tentative. This included 19 predictors: age, the two sub measures Y-BOCS (OCD), the three sub measures TAS-20 (alexithymia), the three sub measures of DAS-21 (mental health); AAQII (psychological inflexibility), SAC, the eight sub measures of MAIA-2 (IAw), and the dependent measure of autism (AQ10).

For the stepwise backwards regressions, the selection criteria determine which of the variables are retained at each step. This selection criteria only retains variables in each step if they improve the overall goodness of model fit as indexed by R^2, and minimize the complexity of the model as indexed by the Akaike information criterion (AIC) which is based on information theory) (Akaike, 1974).

A power calculation utilizing G*Power[6] version 3.1.9.7 (Faul et al., 2007) was conducted that determined whether there was sufficient power to input the 19 predictors into the stepwise backwards regression. For 19 predictors, with power set to 0.8, and a medium effect size specified by Cohen's criteria of 0.15 f^2 (Cohen, 1988) an a priori assumption of 153 participants was calculated. A larger sample size of 224 participants (who completed the survey), was obtained, whereby a *post hoc* analysis, assuming a medium effect size, calculated power of 0.96. Given this power, there is only 3% chance of making a type two error (failing to reject the null hypothesis when it should have been) (Cohen, 1988).

In addition to the regression analyses, as part of phase three of the study, further mediation analyses were conducted using the SPSS PROCESS macro (model 7) by Andrew Hayes (Hayes, 2013). Mediation (or indirect effects) is the effect of independent variable X_1 on dependent variable Y goes through a mediator X_2. This is commonly defined as the reduction of the regression coefficient of X_1 on Y, when X_2 is controlled for (Judd and Kenny, 1981; Baron and Kenny, 1986). Baron and Kenny (Baron and Kenny, 1986) proposed a four step approach for simple mediation, whereby all of these steps need to be significant. The first step is to conduct a simple regression with X predicting Y to test the coefficient of path c, expressed as, $Y = B_{0+} B_1 X + e$. The second step is to conduct a simple regression with X predicting M (the mediator), called path a, and expressed as $M = B_{0+} B_1 X + e$. The third step is to conduct a regression with M predicting

4 See here for full procedural details: https://physionet.org/content/autonomic-aging-cardiovascular/1.0.0/.

5 See here for full details: https://physionet.org/content/autonomic-aging-cardiovascular/1.0.0/.

6 See here for G*Power software: https://stats.idre.ucla.edu/other/gpower/.

TABLE 2 Descriptive statistics.

Variable	Mean (SD)
Age group 1 (18 to 29)	50.84 (25.05)
Age group 2 (30 to 44)	39.72 (28.65)
Age group 3 (45 +)	30.99 (33.57)

Y, called the b path and expressed as $Y = B_{0+}\ B_1\ M + e$. The final step is to conduct a regression whereby X and M predict Y (X controlled for, or mediated by M) and expressed as $Y = B_{0+}\ B_1\ X{+}B_2\ M + e$. Once mediated, if X no longer predicts Y, this is a full mediation (i.e., path c'), and if not, then this is instead considered a partial mediation (as long as the difference is significant between c and c', i.e., confidence intervals do not cross zero).

The regression outcomes, along with the literature, helped to inform the development of a conceptual model, which could be tested through an SEM. Regression analysis is not well-suited for describing causal sequences. Path models such as SEM allow the chains of conditional relations to be explored, and this includes mediation hypotheses, so helps with evaluating causal hypotheses. For the SEM of part of the study, IBM's AMOS version 28.0. was used.

Results

Baseline aging effects of the vagus nerve HRV functioning in healthy controls

Aging of the vagal nerve that modulates the sympathetic and parasympathetic functioning of the ANS was explored. Table 2 shows the descriptive statistics, whereby HRV is higher for the youngest age group (M = 50.84, SD = 25.05), followed by the second youngest age group (M = 39.72, SD = 28.65), and lowest for the oldest age group (M = 30.99, SD = 33.57). One-way analysis of covariance (ANCOVA) was utilized to explore the HRV differences across the four age groups (the data were compressed into four groups) whereas gender and BMI were included as control covariates. A Shapiro–Wilk test revealed the data to be non-normal; however, when sample size is >40, the violation to this assumption does not cause a problem (Pallant, 2020). Furthermore, in cases where there are hundreds of participants (as is the case with this sample), the distributions of data can be ignored (Altman and Bland, 1995) and the parametric test can be used (Elliott and Woodward, 2007). HRV differed according to BMI [$F_{(1,1087)} = 5.56$, $p < 0.05$, $\eta_p^2 = 0.005$] and age [$F_{(2,1087)} = 11.89$, $p < 0.001$, $\eta_p^2 = 0.021$], but not gender [$F_{(1,1087)} = 1.23$, $p = 0.27$, $\eta_p^2 = 0.001$]. Most importantly, age when controlling for gender and BMI was still highly significant [$F_{(2,1090)} = 26.41$, $p < 0.001$, $\eta_p^2 = 0.046$]. *Post hoc* Bonferroni adjusted tests indicated that HRV differences between all age groups were significant ($p < 0.001$).

TABLE 3 Descriptive statistics and normality scores of the variables.

Variable	Mean (SD)	Minimum–maximum	Skewness	Kurtosis
Age	31.61 (10.16)	18–73	1.14	1.34
ASQ-10	6.87 (2.37)	1–10	−0.58	−0.56
Y-BOCS	16.71 (6.91)	0–38	0.16	0.17
Y-BOCS Obsession	8.85 (3.61)	0–19	0.42	0.17
Y-BOCS Compulsion	7.85 (3.90)	0–19	0.43	−0.04
AAQ-2	33.56 (8.43)	7–49	−0.41	0.30
SAC	46.71 (12.06)	17–77	−0.20	−0.14
DAS-21 Stress	27.06 (10.87)	0–48	−0.28	−0.40
DAS-21 Anxiety	19.64 (10.09)	0–42	0.06	−0.70
DAS-21 Depression	23.43 (11.15)	0–42	−0.15	−0.92
TAS-20 Total	63.34 (11.04)	30–89	−0.34	−0.13
TAS-20 DIF	23.96 (5.98)	7–35	−0.51	−0.39
TAS-20 DDF	18.15 (4.17)	5–25	−0.78	0.37
TAS-20 EOT	21.23 (4.27)	11–33	−0.07	−0.19
MAIA-2 Not-noticing	2.89 (1.07)	0–5	−0.02	−0.39
MAIA-2 Not-distracting	2.12 (1.01)	0–4	0.02	−0.07
MAIA-2 Not worrying	2.04 (0.99)	0–5	−0.03	−0.43
MAIA-2 Attention regulation	1.97 (0.97)	0–5	0.40	0.04
MAIA-2 Emotional awareness	2.79 (1.09)	0–5	0.01	−0.31
MAIA-2 Self-regulation	1.83 (1.14)	0–5	0.46	−0.29
MAIA-2 Body listening	1.80 (1.18)	0–5	0.47	−0.19
MAIA-2 Trusting	2.10 (1.39)	0–5	0.39	−0.65

Questionnaire data of clinical sample

Table 3 shows the descriptive statistics, where mean ASQ-10 score was 6.87 (SD = 2.37) and this was within the range for suspected autism whereby the questionnaire criteria suggest that a referral to a specialist should be made. Y-BOCS-10 mean score for OCD was 16.71 (SD = 6.91) and this was within the range for moderate OCD. TAS-20 mean score was 63.34 (SD = 11.04), and this was in the range for high alexithymia. The skewness and kurtosis were all within a value of plus or minus two, indicating a normal distribution for each variable (George and Mallery, 1999). On inspection of the heteroskedasticity visual plot of the residuals, these were observed to be homoscedastic. Before regression analysis was conducted, preliminary analyses were conducted to ensure that there were no violations to the assumptions of multi-collinearity, normality, linearity, and homoscedasticity. The correlations showed that the predictors

TABLE 4 Correlations between variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
2	0.27**																				
3	0.08	0.24**																			
4	0.10	0.21**	0.92**																		
5	0.05	0.24**	0.93**	0.69**																	
6	−0.04	0.26**	0.47**	0.52**	0.36**																
7	0.07	−0.26**	−0.25**	−0.29**	−0.17**	-.51**															
8	0.04	0.29**	0.50**	−0.48**	−0.45**	0.61**	−0.34**														
9	−0.15*	0.13	0.56**	0.53**	0.51**	0.51**	−0.28**	0.70**													
10	−0.07	0.23**	0.41**	0.42**	0.34**	0.68**	−0.46**	0.72**	0.54**												
11	0.09	0.40**	0.29**	0.29**	0.25**	0.41**	−0.38**	0.44**	0.34**	0.36**											
12	0.06	0.39**	0.37**	0.39**	0.29**	0.50**	−0.37**	0.54**	0.46**	0.43**	0.86**										
13	0.08	0.35**	0.19**	0.18**	0.17*	0.29**	−0.14*	0.33**	0.24**	0.19**	0.81**	0.62**									
14	0.09	0.16*	0.05	0.01	0.08	0.07	−0.33**	0.07	0.01	0.13	0.59**	0.20**	0.26**								
15	−0.23**	−0.24**	0.19**	0.15*	0.19**	0.02	0.17*	0.09	0.29**	0.06	−0.13*	−0.06	−0.09	−0.16*							
16	0.46	−0.01	−0.04	−0.87	0.01	−0.14*	−0.01	−0.13	−0.17*	−0.17*	−0.26**	−0.22**	−0.24**	−0.12	0.02						
17	0.11	−0.07	−0.24**	−0.23**	−0.21**	−0.27**	−0.21**	−0.38**	−0.33**	−0.25**	−0.21**	−0.31**	−0.17*	0.06	−0.13*	−0.05*					
18	−0.22*	−0.45**	−0.19**	−0.22**	−0.15*	−0.29**	0.46**	−0.28**	−0.09	−0.25**	−0.44**	−0.42*	−0.36**	−0.19*	0.44**	−0.06	0.19**				
19	−0.16**	−0.21**	0.11	0.12	0.07	−0.01	0.27**	0.05	0.19**	−0.05	−0.08	0.02	−0.06	−0.18**	0.62**	−0.03	−0.24**	0.42**			
20	−0.19**	−0.38**	−0.22**	−0.22**	−0.19**	−0.29**	0.41**	−0.26**	−0.03	−0.26**	−0.27**	−0.25**	−0.14**	−0.21**	0.36**	−0.09	0.07	0.60**	0.50**		
21	−0.11	−0.33**	−0.07	−0.08	−0.04	−0.17**	0.37**	−0.09	0.01	−0.23**	−0.25**	−0.16*	−0.21**	−0.22**	0.39**	0.05	−0.06	0.54**	0.58**	0.61**	
22	−0.15*	−0.37**	−0.20**	−0.25**	−0.12	−0.46**	0.62**	−0.34**	−0.20**	−0.44**	−0.50**	−0.49**	−0.36**	−0.25**	0.35**	0.11	0.18**	0.60**	0.43**	0.57**	0.53**

1. Age; 2. AQ10; 3. Y-BOCS Total; 4. Y-BOCS Obsession; 5. Y-BOCS Compulsion; 6. AAQII; 7. SAC; 8. DAS-21 Stress; 9. DAS-21 Anxiety; 10. DAS-21 Depression; 11. TAS-20 total; 12. TAS-20 DIF; 13. TAS-20 DDF; 14. TAS-20 EOT; 15. MAIA-2 Not-noticing; 16. MAIA-2 Not-distracting; 17. MAIA-2 Not worrying; 18. MAIA-2 Attention regulation; 19. MAIA-2 Emotional awareness; 20. MAIA-2 Self-regulation; 21. MAIA-2 Body listening; 22. MAIA-2 Trusting. Sig, 2 tailed; *$p < 0.05$; **$p < 0.01$.

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TABLE 5 Regression model summary where autism is the DV.

Variable	Standardized β	S.E.	*t*-value	*P*-value
Age	0.18	0.01	3.18	<0.01
Gender	0.13	0.21	2.29	<0.05
OCD Compulsion	0.14	0.04	2.48	<0.05
Alexithymia DDF	0.19	0.03	3.28	<0.01
ISen attention regulation	−0.21	0.18	−2.75	<0.01
ISen self-regulation	−0.17	0.15	−2.36	<0.05

TABLE 6 Regression model summary where OCD is the DV.

Variable	Standardized β	S.E.	*t*-value	*P*-value
Age	0.12	0.04	2.10	<0.05
Gender	−0.15	0.57	−2.94	<0.01
Autism	0.12	0.17	1.96	=0.05
Psychological inflexibility	0.19	0.05	2.97	<0.01
Anxiety	0.42	0.04	6.69	<0.001
ISen self-regulation	−0.46	0.38	3.05	<0.01
ISen not noticing	0.18	0.36	−2.44	<0.05

were below 0.8 (refer to Table 4), with the VIF scores of the coefficients below 10, indicating that these were free from multi-collinearity.

Table 4 shows the correlations between the variables. There was a positive correlation between age and autism, but a negative correlation between age and anxiety. Autism was positively correlated with stress and depression. Age was also negatively correlated with several of the ISen indices but did not correlate with either the alexithymia scale or OCD, suggesting that it is related specifically to autism (i.e., the older individuals were more likely to be autistic in this sample). SAC was negatively correlated with OCD, autism, and alexithymia scales. There was also a positive correlation among psychological inflexibility and OCD, autism, and alexithymia scales. Autism, OCD, and alexithymia all were negatively correlated with several of the ISen subscales, suggesting that their interceptive sensibility was low for these conditions. Autism, OCD, and alexithymia all positively correlated with several mental health (DAS-21) dimensions, suggesting that mental health issues were high in these conditions.

Tables 5–7 show the outcomes of the three stepwise backwards regression models. Table 5 specifically shows all of the variables (subscales were chosen instead of total scores where they were available) entered as predictors and regressed against autism as the DV. Here, the adjusted $R^2 = 0.31$, and the model was significant [$F_{(6,217)} = 17.51$, $p < 0.001$]. In the final step of the model, age (standardized beta coefficients expressed here, $\beta = 0.18$), gender ($\beta = 0.13$), OCD compulsion ($\beta = 0.14$), alexithymia DFF ($\beta = 0.19$), ISen attention regulation ($\beta = -0.21$), and ISen self-regulation ($\beta = -0.17$) were all selected.

For the second regression model (refer to Table 6), all of the variables (subscales were chosen instead of total scores where they were available) were entered into the regression model except for the two OCD subscales (obsession and compulsion), which were excluded as total OCD was the DV. Here, the adjusted $R^2 = 0.43$, and the model was significant [$F_{(7,216)} = 24.61$, $p < 0.001$]. In the final step of this model, age ($\beta = 0.12$), gender ($\beta = -0.15$), autism ($\beta = 0.12$), psychological inflexibility ($\beta = 0.19$), anxiety ($\beta = 0.42$), ISen not noticing ($\beta = 0.18$), and ISen self-regulation ($\beta = -0.46$) were all selected.

TABLE 7 Regression model summary where alexithymia is the DV.

Variable	Standardized β	S.E.	*t*-value	*P*-value
Autism	0.17	0.27	2.89	<0.01
Stress	0.21	0.06	3.54	<0.01
ISen not distracting	−0.20	0.57	−3.87	<0.01
ISen attention regulation	−0.20	0.79	−2.86	<0.01
ISen emotion awareness	0.15	0.61	2.44	<0.05
ISen trusting	−0.29	0.55	−4.13	<0.01

For the third regression model (refer to Table 7), all of the variables (subscales were chosen instead of total scores where they were available) were entered into the regression model except for the three alexithymia subscales; DIF, DDF, and EOT which were excluded, whereby the DV was this time specified as total alexithymia. Here, the adjusted $R^2 = 0.42$, and the model was significant [$F_{(6,217)} = 27.49$, $p < 0.001$]. In the final step of this model, autism ($\beta = 0.17$), stress ($\beta = 0.21$), ISen not distracting ($\beta = -0.20$), ISen attention regulation ($\beta = -0.20$), ISen emotion awareness ($\beta = 0.15$), and ISen trusting ($\beta = -0.29$) were selected.

Mediation models

A number of five separate mediation models were conducted, and these are displayed in Figure 1 and stacked in a conceptual hierarchy. The structure of the mediation models was informed by both the literature and also the regression models performed previously. In the first, OCD (X) was explored as a predictor for autism (Y), and ISen self-regulation was chosen as a mediator (M). The direct association between OCD (X) and autism (Y) was significant [$c = t_{(221)} = 2.66$, $p < 0.01$, $\beta = 0.17$]. The direct association between OCD (X) and the mediator (M) ISen self-regulation was also significant [$a = t_{(222)} = -3.35$, $p < 0.01$, $\beta = -0.22$]. The direct association between the mediator (M) ISen self-regulation and autism (Y) was significant [$b =$

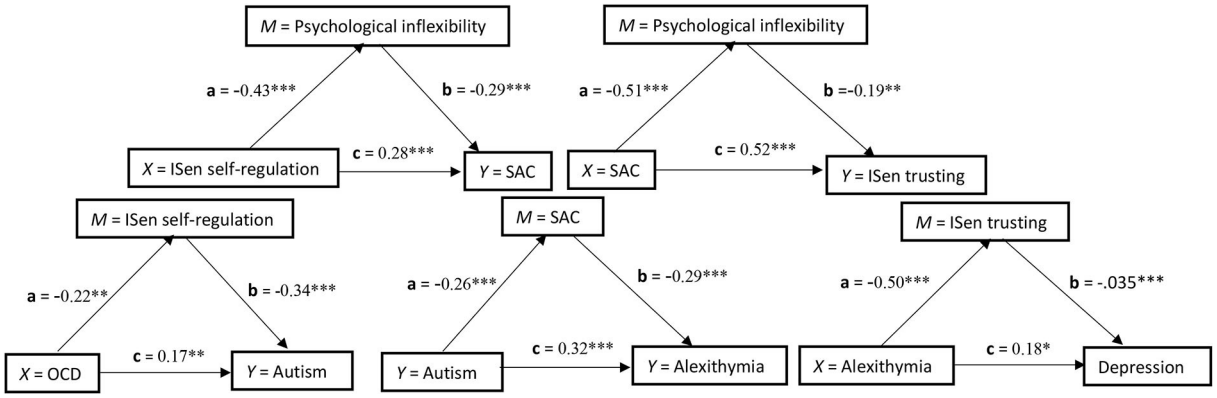

FIGURE 1
Five simple independent mediation models stacked in conceptual hierarchy and showing the standardized coefficients of each path. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

$t_{(221)} = -5.46$, $p < 0.001$, $\beta = -0.34$]. To indicate a mediation effect, the indirect association of X to Y *via* M was significant as confidence intervals at 95% did not cross zero [CI = 0.01, 0.05]. However, as the variance of the direct path of X to Y did not reduce to zero after the mediator was added (i.e., the c' path), this indicated a partial mediating effect.

In the second mediation analysis, autism (X) was explored as a predictor for alexithymia (Y) and SAC was chosen as a mediator (M). The direct association between autism (X) and alexithymia (Y) was significant [$c = t_{(221)} = 5.36$, $p < 0.001$, $\beta = 0.32$]. The a path association between autism (X) and the mediator (M) SAC was also significant [$t_{(222)} = -3.97$, $p < 0.001$, $\beta = -0.26$)]. The b path association between the mediator (M) SAC and alexithymia (Y) was significant [$b = t_{(221)} = -4.89$, $p < 0.001$, $\beta = -0.29$]. To indicate a mediation effect, the indirect path of X to Y *via* M was significant as confidence intervals at 95% did not cross zero [CI = 0.14, 0.59]. However, as the variance of the direct path of X to Y did not reduce to zero after the mediator was added (i.e., the c' path), this indicated a partial mediating effect.

In the third mediation analysis, alexithymia (X) was explored as a predictor for depression (Y) and ISen trusting was chosen as a mediator (M). The direct association between alexithymia (X) and depression (Y) was significant [$c = t_{(221)} = -5.15$, $p < 0.05$, $\beta = 0.18$]. The a path association between alexithymia (X) and the mediator (M) ISen trusting was also significant [$t_{(222)} = -8.67$, $p < 0.001$, $\beta = -0.50$]. The b path association between the mediator (M) ISen trusting and depression (Y) was significant [$t_{(221)} = -5.15$, $p < 0.001$, $\beta = -0.35$]. To indicate a mediation effect, the indirect path of X to Y *via* M was significant as confidence intervals at 95% did not cross zero [CI = 0.09 to 0.28]. However, this was a partial mediation as the variance of the direct path of X to Y did not reduce to zero after the mediator was added (i.e., the c' path).

In the fourth mediation analysis, ISen self-regulation (X) was explored as a predictor for SAC (Y) and psychological inflexibility was chosen as a mediator (M). The direct association between ISen self-regulation (X) and SAC (Y) was significant [$c = t_{(221)} = 4.94$, $p < 0.001$, $\beta = 0.28$]. The a path association between ISen self-regulation (X) and the mediator (M) psychological inflexibility was also significant [$t_{(222)} = -7.53$, $p < 0.001$, $\beta = -0.43$]. The b path association between the mediator (M) psychological inflexibility and SAC (Y) was significant [$b = t_{(221)} = -4.56$, $p < 0.001$, $\beta = -0.29$]. To indicate a mediation effect, the indirect path of X to Y *via* M was significant as confidence intervals at 95% did not cross zero [CI = 0.69 to 2.13]. However, this was a partial mediation as the variance of the direct path of X to Y did not reduce to zero after the mediator was added (i.e., the c' path).

In the fifth mediation analysis, SAC (X) was explored as a predictor for ISen trusting (Y) and psychological inflexibility was chosen as a mediator (M). The direct association between SAC (X) and ISen trusting (Y) was significant [$c = t_{(221)} = 8.65$, $p < 0.001$, $\beta = 0.52$]. The a path association between SAC (X) and the mediator (M) psychological inflexibility was also significant [$a = t_{(222)} = -8.92$, $p < 0.001$, $\beta = -0.51$]. The b path association between the mediator (M) psychological inflexibility and ISen trusting (Y) was significant [$b = t_{(221)} = -3.28$, $p < 0.01$, $\beta = -0.19$]. To indicate a mediation effect, the indirect path of X to Y *via* M was significant as confidence intervals at 95% did not cross zero [CI = 0.004 to 0.02]. However, this was a partial mediation as the variance of the direct path of X to Y did not reduce to zero after the mediator was added (i.e., the c' path).

SEM analysis

The first SEM was conducted to explore autism and mental health as two separate DVs. The first step in the process was to identify applicable latent variables. This was done first through exploratory factor analysis (EFA), whereby the

TABLE 8 Pattern matrix of four groups as identified through EFA.

Variable	Factor 1	Factor 2	Factor 3	Factor 4
Obsession			0.77	
Compulsion			0.93	
DAS21-Stress		0.87		
DAS21-Anxiety		0.62		
DAS21-Depression		0.91		
DIF				0.80
DDF				0.78
ISen Not noticing	0.64			
ISen Attention regulation	0.65			
ISen Emotion awareness	0.81			
ISen Self-regulation	0.76			
ISen Bodily listening	0.77			
ISen Trusting	0.61			

Kaiser–Mayer–Olkin (KMO) measure of sampling adequacy (KMO = 0.81) exceeded the desired cutoff score of 0.70 (Kaiser, 1974), indicating the data represented high sampling adequacy. Bartlett's test of sphericity [$\chi^2_{(120)} = 1677.08$, $p < 0.001$] was significant, indicating that the matrix was not an identity matrix, which means the variables are sufficiently related to one another, therefore, indicating that it is acceptable to use EFA. The communalities table which utilized maximum likelihood as the extraction method revealed that three items were smaller than 0.3, and these were EOT = 0.11, ISen not distracting = 0.09, and ISen not worrying = 0.19. Total variance loaded onto four factors, whereby the cumulative value of four factors equaled 54.79% of the variance, and goodness of fit was at an acceptable level and significant [$\chi^2_{(62)} = 158.01$, $p < 0.001$].

The pattern matrix demonstrated that EOT, ISen not distracting, and ISen not worrying were removed from the factor loading (as their communality extraction values were below 0.3 and therefore deemed too low). There were no cross-loadings, and the pattern matrix is illustrated in Table 8. The factor correlation matrix indicated that no factor loadings were >0.7 and were, therefore, within an acceptable range.

Following the EFA, a confirmatory factor analysis (CFA) was conducted whereby the four variables groups created by EFA were converted into latent variables called mental health, alexithymia, OCD, and ISen. Covariance was then added between all latent variables and combinations (threshold for modification indices was set to 10 and the number of bootstrap samples was set to 1000). However, the initial CFA did not indicate a good model fit, root mean square error of approximation (RMSEA) was >0.1, and comparative fit index (CFI) and Tucker–Lewis index (TLI) were lower than 0.9. As a result of this, modification indices were checked and was the standardized residual covariance matrix table. Several ISen items were above a standardized residual covariance value of two and were removed with RMSEA, CFI, and TLI retested for fitness of model. Once high values were removed, only the item ISen self-regulation was maintained from the ISen latent variable and kept as a standalone direct measure of itself. "Anxiety" and "stress" were removed from the latent variable "mental health," leaving depression as standalone direct measure of itself. All other items within the latent variables "alexithymia" and "OCD" were maintained. The final model fit indicated RMSEA = 0.30, CFI= 0.99, and TLI = 0.99 indicating an excellent fit. CFI and TLI values ≥0.95 and RMSEA values ≤0.08 indicate the data which are well fitting (Hu and Bentler, 1998, 1999). The acceptable range for the standardized root mean squared residual (SRMR) index is between 0 and 0.08 (Hu and Bentler, 1999).

The remaining conceptual model was tested within a SEM (refer to Figure 2) (with 1000 bootstrap samples). SEM fits (through RMSEA, CFI, TLI, and SRMR) were explored. This model produced a model fit: [$X^2(df = 13) = 15.19$, $p = 0.29$], whereby this X^2 test indicates the extent to which the model covariance matrix deviates from the sample covariance matrix and tests that deviation against a null hypothesis of zero (i.e., it is not significantly different) (Peugh and Feldon, 2020). So, a non-significant finding here indicates that the proposed model is a good fit of the data (it is not significantly different from the representation of the data). In addition to this, RMSEA = 0.03, comparative fit index (CFI) = 0.99; Tucker–Lewis index (TLI) = 0.99, GFI = 0.99, SRMR = 0.03. Alexithymia covaried with OCD (correlation values given, $r = 0.39$), with age ($r = 0.06$), with gender ($r = 0.17$); OCD covaried with age ($r = 0.10$), with gender ($r = -0.09$); and age covaried with gender (r = -0.11).

For direct effects, alexithymia was significantly positively associated with psychological inflexibility (reporting standardized beta coefficients) ($\beta = 0.36$, CI = [0.21, 0.52], $p < 0.001$); alexithymia was also significantly positively associated with autism ($\beta = 0.27$, CI = [0.10, 0.49], $p < 0.001$); alexithymia was not significantly associated with ISen self-regulation ($\beta = -0.13$, CI = [−0.31, 0.05], $p = 0.11$); OCD was significantly positively associated with psychological inflexibility ($\beta = 0.39$, CI = [0.24, 0.53], $p < 0.001$); psychological inflexibility was significantly negatively associated with ISen self-regulation ($\beta = -0.24$, CI = [−0.41, −0.07], $p < 0.01$). ISen self-regulation was significantly negatively associated with autism ($\beta = -0.26$, CI = [−0.39, −0.11], $p < 0.001$). For control measures, age was significantly negatively associated with ISen self-regulation ($\beta = -0.19$, CI = [−0.29, −0.07], $p < 0.01$]. Age was also significantly associated with autism ($\beta = 0.22$, CI = [0.12, 0.32], $p < 0.001$). However, age was not significantly associated with psychological inflexibility ($\beta = -0.10$, CI = [−0.19, −0.00], $p = 0.06$. Gender was not significantly associated with neither ISen self-regulation ($\beta = 0.03$, CI = [−0.02, 0.03], $p = 0.89$), autism ($\beta = 0.11$, CI = [0.00, 0.21], $p = 0.05$), nor psychological inflexibility ($\beta = -0.01$, CI = [−0.11, 0.09], $p = 0.89$).

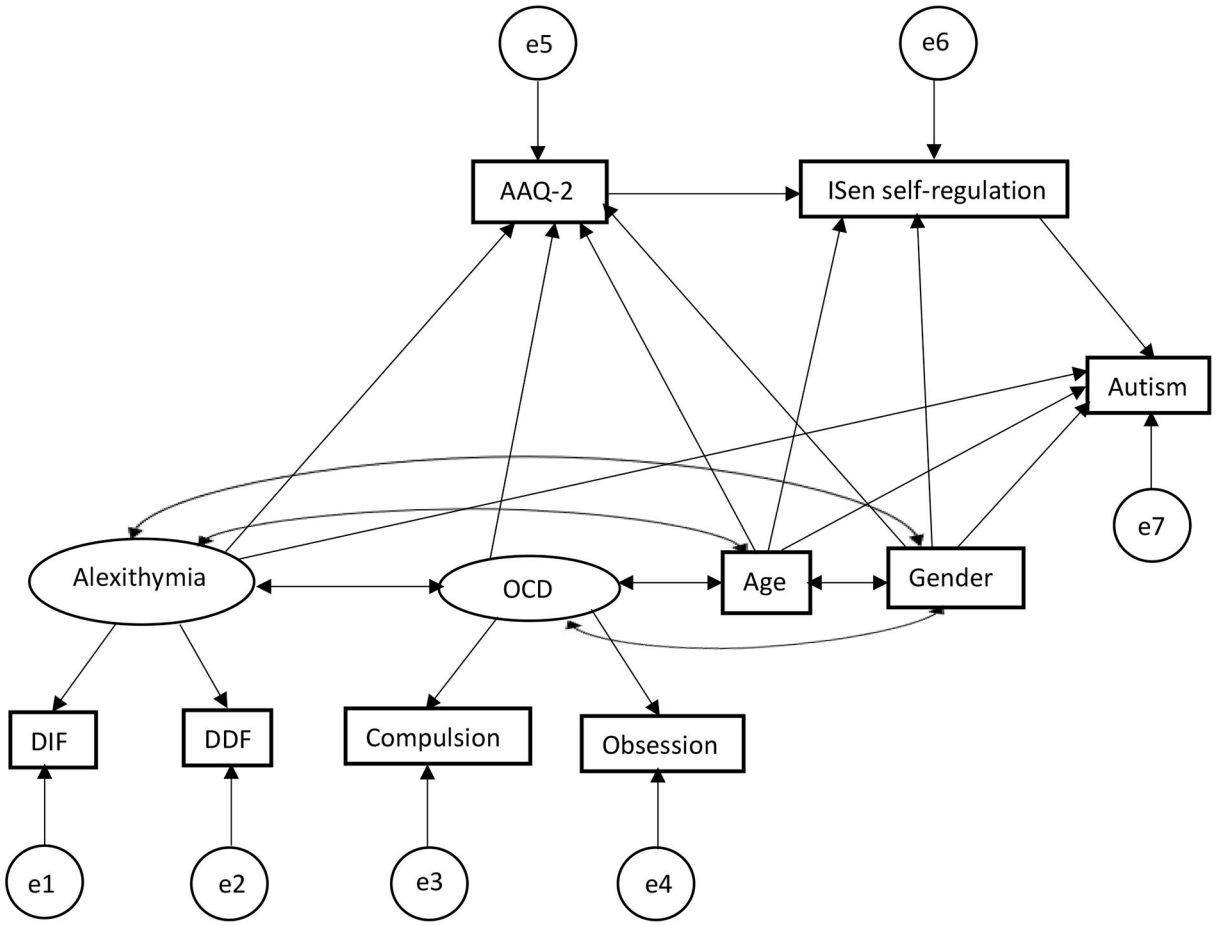

FIGURE 2
SEM first output predictors for autism, showing alexithymia and OCD are related indirectly (alexithymia *via* serial mediation) through psychological inflexibility and ISen self-regulation in predictively causing autism.

In terms of mediating indirect effects, age was indirectly associated with ISen self-regulation *via* psychological inflexibility ($\beta = 0.02$, CI = [0.00, 0.06], $p < 0.05$); alexithymia was indirectly associated with ISen self-regulation *via* psychological inflexibility ($\beta = -0.09$, CI = [−0.19, −0.03], $p < 0.01$). OCD was indirectly associated with ISen self-regulation *via* psychological inflexibility ($\beta = -0.09$, CI = [−0.18, −0.03], $p < 0.01$). Psychological inflexibility was indirectly associated with autism *via* ISen self-regulation ($\beta = 0.06$, CI = [0.02, 0.15], $p < 0.01$).

In the second SEM (refer to Figure 3), depression was added as a second DV in addition to autism, which also included adding SAC into the model to account for this. This model produced again a good model fit: [$X^2(df = 24) = 34.75$, $p = 0.07$], RMSEA = 0.04, CFI = 0.99; TLI = 0.97. GFI = 0.97, SRMR = 0.03. Some of the beta coefficients change as a result of the new variables added while others remained the same. Alexithymia covaried with OCD (correlational values given, $r = 0.39$), with age ($r = 0.06$), with gender ($r = 0.17$); OCD covaried with age ($r = 0.10$), with gender ($r = -0.09$); and age covaried with gender ($r = -0.11$).

The standardized beta coefficients can be seen in Figure 4 in the graph model, sharing many of the same associations as the first SEM but with the addition of the SAC and depression scales (note that the addition of new variables resulted in different associations than the first SEM in some cases with different corresponding coefficients and confidence intervals). As such, for direct effects, alexithymia was significantly positively associated with psychological inflexibility (reporting standardized beta coefficients) ($\beta = 0.36$, CI = [0.21, 0.52], $p < 0.001$); alexithymia was also significantly positively associated with autism ($\beta = 0.27$, CI = [0.10, 0.51], $p < 0.001$); alexithymia was not significantly associated with ISen self-regulation ($\beta = -0.08$, CI = [−0.26, 0.11], $p = 0.29$). OCD was significantly positively associated with psychological inflexibility ($\beta = 0.39$, CI = [0.24, 0.53], $p < 0.001$). Psychological inflexibility was

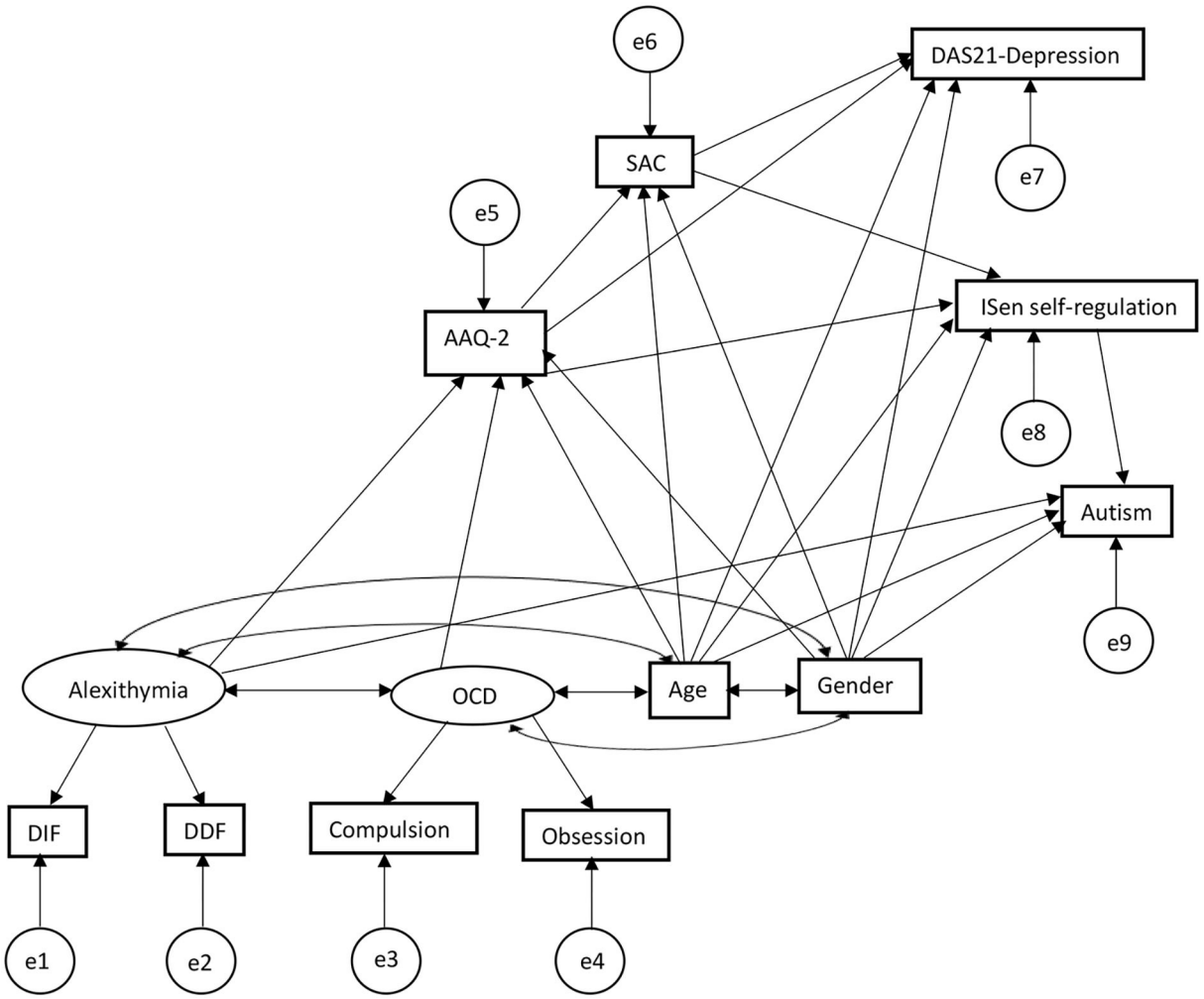

FIGURE 3
SEM second output extended the first SEM in Figure 2 adding SAC and depression scale, showing a second and third mediation of SAC mediating the relationship between AAQ-2 and ISen self-regulation, and the relation between AAQ-2 and DAS-21 depression.

no longer significantly negatively associated with ISen self-regulation ($\beta = -0.08$, CI = [−0.27, 0.08], $p = 0.32$) (this has been significantly associated in the first SEM, indicating indirect mediation effect of SAC). ISen self-regulation was significantly negatively associated with autism ($\beta = -0.26$, CI = [−0.39, −0.11], $p < 0.001$). Novel to this SEM was the introduction of an association between psychological inflexibility and SAC which was significant ($\beta = -0.51$, CI = [−0.61, −0.39], $p < 0.001$). Also, there was an association between psychological inflexibility and depression which was also significant ($\beta = 0.60$, CI = [0.51, 0.70], $p < 0.001$); a significant association between SAC and depression ($\beta = -0.14$, CI = [−0.26, −0.01], $p < 0.05$); and a significant association between SAC and ISen self-regulation ($\beta = 0.36$, CI = [0.21, 0.49], $p < 0.001$). For control measures (age and gender), age was significantly negatively associated with ISen self-regulation ($\beta = -0.21$, CI = [−0.31, −0.09], $p < 0.001$) and autism ($\beta = 0.22$, CI = [0.12, 0.32], $p < 0.001$). However, age was not significantly associated with neither psychological inflexibility ($\beta = -0.10$, CI = [−0.19, −0.00], $p = 0.06$) nor SAC ($\beta = 0.04$, CI = [−0.07, 0.13], $p = 0.52$), nor depression ($\beta = -0.03$, CI = [−0.13, 0.07], $p = 0.51$). Gender was not significantly associated with neither ISen self-regulation ($\beta = 0.06$, CI = [−0.04, 0.17], $p = 0.32$), nor autism ($\beta = 0.11$, CI = [0.00, 0.21], $p = 0.05$), nor psychological inflexibility ($\beta = -0.01$, CI = [−0.11, 0.09], $p = 0.88$), SAC ($\beta = -0.10$, CI = [−0.23, 0.01], $p = 0.08$, nor depression ($\beta = 0.05$, CI = [−0.06, 0.12], $p = 0.36$).

In terms of mediating indirect effects, age was not indirectly associated with ISen self-regulation ($\beta = 0.04$, CI = [−0.01, 0.09], $p = 0.09$) (this had been a significant indirect effect in the first SEM). However, age was significantly indirectly associated with SAC *via* psychological inflexibility ($\beta = 0.05$, CI = [0.00,

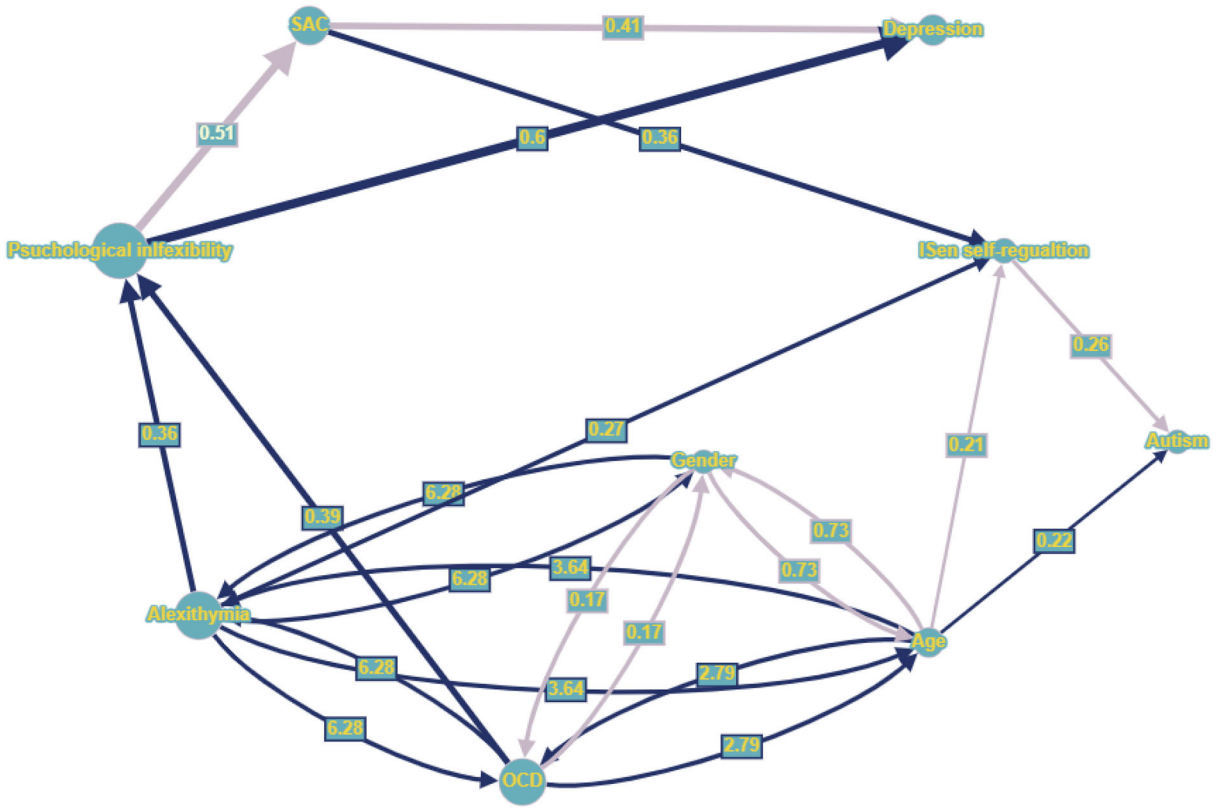

FIGURE 4
Graph nodes and edges representation (larger nodes and wider lines indicates those with greater effect within the network), whereby dark blue directed lines indicate positive standardized regression coefficients (only significant coefficients presented), light purple directed line represent negative regression coefficients. Dark blue bidirectional lines represent positive covariance (line width given by correlational value), while light purple bidirectional lines represent negative covariance. Numbers centered on directed lines indicate standardized beta coefficients and bidirectional lines indicate covariance estimate values.

0.10], $p < 0.05$) and depression *via* psychological inflexibility and SAC ($\beta = -0.07$, CI = [−0.14, −0.01], $p < 0.05$). There were significant indirect effects between alexithymia and SAC *via* psychological inflexibility ($\beta = -0.19$, CI = [−0.28, −0.10], $p < 0.01$), alexithymia and ISen self-regulation *via* psychological inflexibility ($\beta = -0.10$, CI = [−0.21, −0.03], $p < 0.01$), and alexithymia and depression *via* psychological inflexibility and SAC ($\beta = 0.14$, CI = [0.14, 0.36], $p < 0.01$). There were also indirect effects between OCD and SAC *via* psychological inflexibility ($\beta = -0.19$, CI = [−0.29, −0.12], $p < 0.01$), OCD and ISen self-regulation *via* psychological inflexibility ($\beta = -0.10$, CI = [−0.19, −0.04], $p < 0.01$), and OCD and depression *via* psychological inflexibility and SAC ($\beta = 0.26$, CI = [0.15, 0.37], $p < 0.01$). There were also indirect effects between psychological inflexibility and ISen self-regulation *via* SAC ($\beta = -0.19$, CI = [−0.28, −0.10], $p < 0.01$), psychological inflexibility and depression *via* SAC ($\beta = 0.07$, CI = [0.01, 0.14], $p < 0.05$), and psychological inflexibility and autism *via* ISen self-regulation ($\beta = 0.07$, CI = [0.02, 0.16], $p < 0.01$. Additionally, there were indirect effects between SAC and autism *via* ISen self-regulation ($\beta = -0.09$, CI = [−0.17, −0.14], $p < 0.01$).

Visualizing SEM in graph theory networks

A graph of nodes and edges utilizing graph theory can represent an SEM and can be modeled through available R packages, such as SEMgraph (Palluzzi and Grassi, 2021). Within a graph theory approach, an exogenous parent variable is a source node with incoming connectivity equal to 0. They are also two types of endogenous variables called "connectors" with non-zero outgoing connectivity, and another called "sinks" which have no outgoing connections. There are three types of path diagrams in graph theory: (1) directed acrylic graphs (DAG) which use beta coefficients β_{jk}, to give a magnitude to directed edges ($k \rightarrow j$) within the graph., but all covariances are assumed null ($\psi_{jk} = 0$); (2) covariance models in which only covariances have non-zero values and coefficients can only equal to zero

($\beta_{jk} = 0$); (3) bow-free acrylic graphs (BAPs), which have acrylic directed edges ($k \rightarrow j$), and bidirectional covariance relations ($k \leftrightarrow j$) only when the k-th and j-th variable do not share a directed edge, therefore, if $\beta_{jk} \neq 0$ then $\psi_{jk} = 0$. Through this graph approach, latent variables are marginalized out and instead are represented as correlations among unobserved latent confounders (Pearl, 1998).

Structural equation modeling is based on a system of structural (typically linear) regression equations that defines a path diagram that can be represented as a graph $G = (V, E)$, whereby V is a set of nodes (the variables) and E is a set of edges that can be both directional ($k \rightarrow j$) if $k \in pa_{(j)}$ or bidirectional edges ($k \leftrightarrow j$) if $k \in sib_{(j)}$, where the parent set $pa_{(j)}$ and the sibling set $sib_{(j)}$ determine the linear equations in the following way:

$$Y_j = \sum_{k \in pa_{(j)}} \beta_{jk} Y_k + U_j \quad j \in V \tag{2}$$

$$Cov\left(U_j; U_k\right) = \begin{cases} \psi_{jk} & if\ j = k\ or\ k \in sib_{(j)} \\ 0 & otherwise \end{cases} \tag{3}$$

Where Y_j and U_j are, respectively, an unobserved variable and unobserved error term. β_{jk} represents a regression coefficient, and ψ_{jk} denotes a covariance (Cov) which indicates the errors are dependent when there is a latent unobserved confounder between k and j.

This is a simple graph, which has at most one edge between a pair of nodes, which are identifiable whereby parameters β and ψ can be estimated from a population covariance matrix of the observed variables (Pearl, 1998; Brito and Pearl, 2002). For the graph implementation of the second SEM with DVs of autism and depression, refer to Figure 4[7].

Cluster networks of SEM in graph theory to expand functional contextual properties

It is also possible to define topological communities through network clustering, and this can be done through existing R packages, such as igraph (Csardi and Nepusz, 2006). For example, there is the walktrap community detection algorithm based on random walks (Pons and Latapy, 2005), which generates as many clusters as is needed to cover the whole network. There is also the edge betweenness clustering (Newman and Girvan, 2004) that produces one large network and several other subnetworks. In addition, there is also tree agglomerative hierarchical clustering (Yu et al., 2015) for complex networks that include hierarchical properties. These algorithms are useful particularly when scaling up the network, to include additional dimensions and levels defined in the EEMM. For example, tree agglomerative hierarchical may be useful when dealing with complex multi-level networks, such as incorporating individual factors plus societal factors.

Several measures in this study were ACT consistent, such as psychological inflexibility and SAC. However, at more basic behavioral functional analytic level, relational frame theory (RFT) underpins these processes of change (Hayes et al., 2001; Blackledge, 2003; Barnes-Holmes et al., 2015). This is a post-Skinnerian behavioral model for higher cognition, related to symbolic reasoning, and based on functional contextualism. It assumes that language can be thought of as patterns of generalized contextually controlled derived relational responding. It focuses on the role of context *via* contextual cues in facilitating the emergence of patterns of relating in which functions of stimuli become connected to these patterns (Hayes et al., 2001). It assumes that relational responding can either be arbitrary or non-arbitrary. Non-arbitrary responding relates to basing responding on physical and actual features of the environment, whereas arbitrary applicable responding relates to responding being controlled by historical contextual cues. There are several patterns of arbitrary applicable responding, which include the following: coordination (e.g., stimuli x is equivalent to stimulus y), causation (IF, THEN), comparison (A is bigger than B), opposition (e.g., up is the opposite of down), distinction (e.g., C is not the same as D), hierarchy (e.g., a Labrador is a type of dog), and perspective-taking (deictic) involving the interpersonal (I vs. YOU), spatial (HERE vs. THERE) and temporal relations (NOW vs. THEN).

In total, three essential properties are important for relational frames to develop and to organize a network (Torneke, 2010): (1) mutual entailment (ME), relating one stimulus entails relating to a second stimulus; (2) combinatorial entailment (CE), relating a first stimulus to a second, and the second to a third, facilitates entailment between the first stimulus and the third; (3) the last one is the transfer (or transformation) of stimulus function (ToF) whereby the functions (e.g., fear) of any stimulus that participates within a relational frame may be transferred or transformed in line with the relations that the stimulus shares with other stimuli also participating in that frame. The individual frames can network, forming complex networks of relational frames, and can even be relationally framed with other relationally framed networks (relating relational networks) (Barnes-Holmes et al., 2017) becoming infinitely complex. Idiographic approaches of PBT such as when collecting EMA data, longitudinally, are ideal for capturing such complexity of these relational networks and how they transform (ToF) over time.

This functional analytic level of RFT applied at an ideographic level in line with EEMM and PBT could further expand the graphs (depicted in Figure 5) utilizing community cluster networks. This could allow for basic level relational frame process of change properties, such as ToF to be mapped onto a

7 Graph developed with software found at: https://graphonline.ru/.

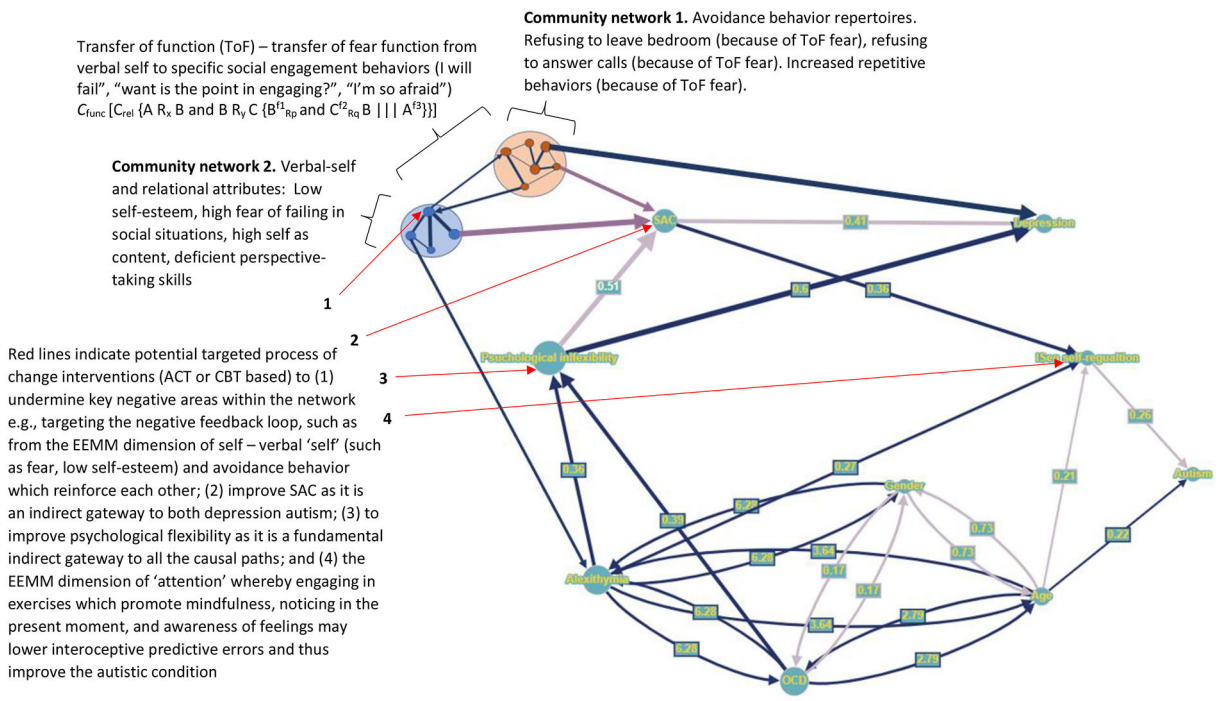

FIGURE 5
A conceptual extension of the graph nodes and edges representation in Figure 4, when extending ideographically and implemented through a more dynamic RFT PBT approach which include additional community cluster networks.

PBT graph. Some works (Smith and Hayes, 2022) have already explored this level of analysis with graphs, such as through implementing a graph model specific to RFT properties, such as ME bidirectionality. Such an approach could also allow for complex community networks (relations of relational frames) to be explored along with the traditional middle level ACT constructs of psychological flexibility and SAC. This may allow for an implementation of RFT community graphs as discussed in recent work (Edwards et al., 2022) and conceptually illustrated in Figure 5. Each node represented as a set, and therefore giving graphs the ability to represent and update in real time ME or ToF from one community set to the next, could be possible and beneficial. For example, ToF can be represented as a combination of two sets as follows:

$$C_{\text{func}}[C_{\text{rel}}\{AR_{\text{x}}B \; and \; BR_{\text{y}}C\{B^{\text{f1}}_{\text{Rp}} \; and \; C^{\text{f2}}_{\text{Rq}}B|||A^{\text{f3}}\}\}] \quad (4)$$

Here → is used to show the direction of the ToF from one stimulus to another.

Where C_{func} is a context that controls the ToF, C_{rel} is a contextual relation, and $^{\text{f}}$ is a function, in this case "fear." Here, "A" is a neutral socializing event and is related to (R_x) you ("B") as you try to decide will attend the socializing event, and you ("B") are also related to (R_y) your own verbal-self ("C," a community network in itself which relationally frames many thoughts and feelings about yourself, and its dominated by fear, thoughts about failure, and low self-esteem). THEN you (B) become fearful ($^{\text{f1}}_{\text{Rp}}$) of the social event (A) as the function of A (A^{f3}) transforms from neutral to fear ($^{\text{f2}}_{\text{Rq}}$) (C→A ToF) as your feelings of failure about yourself, and fear, become mutually entailed (|||) with the social event, (as you think about failing in socializing at this event, and how scared you will be) which now shares the fear function A^{f3} of your verbal self (C^{f2}). This leads the individual to decide to avoid the social situation (A), to prevent further pain of fear and failure thus causing the individual to isolate further.

These community networks of verbal self and the resultant avoidance behaviors (and their associated relational frames) not only act to transfer a fear function, but they act to reinforce one another. Low self-esteem and fear of the verbal self lead to a greater probability of avoidance (isolation from others due to ToF), and the resultant avoidance then further reinforces low self-esteem and fear of the verbal self (as you may tell yourself that you have again failed), which then increases the chances of further avoiding social events (and communicating more generally) in the future. This is called a negative feedback loop (or a self-reinforcing loop of maladaptation) in PBT (Hayes and Hofmann, 2020; Hofmann et al., 2021). It is suggested that these should be identified and targeted with the correct interventions

(ACT or CBT) (as seen in Figure 5 for an example) to undermine this negative feedback loop.

Such modeling at the level of the relational frame could ultimately give the PBT therapist very strong influence over the entire network, thus making them more able to influence processes of change at a basic functional contextual level, in a dynamic way which is consistent with EEMM. This approach is more relevant at the ideographic level as individuals each form their own unique relational networks through their unique learning histories. It could also be extended even further with an RFT implemented reinforcement machine learning interpretation through discrete time series Markov chains (Edwards, 2021) to analyze reinforced behavior (and any other EMA data) through time in a complex distributed system (i.e., the real-world environment, and outside of the laboratory) (Dabrowski and Hunt, 2011).

General discussion

This study aimed to identify and confirm two conceptual models through two corresponding SEMs, which maps the causal pathways between alexithymia and OCD (as exogenous IVs) with autism and autistic-related depression (as endogenous DVs) *via* the variables bodily interoception, psychological inflexibility, and SAC (with age and gender as controls).

To do this, the first part of this study explored through ANCOVA whether age had an effect on autonomic nervous functioning in healthy controls. The measure for this was HRV (HRV is closely correlated with the ISen interoceptive measures used in the questionnaires), and BMI and gender were added as covariates. There was a significant decrease in HRV given age, and this finding highlighted the importance of controlling the SEM for age, as it would likely be a significant control in the SEMs and having a direct effect on autonomic functioning (ISen interoception) within the network regardless of the autistic condition. Within the SEM, age was found to significantly affect both ISen self-regulation interoception and autism directly as expected, though the indirect effect between age and autism *via* ISen self-regulation interoception was non-significant.

The second part of the study's goal was to develop a conceptual SEM. However, the literature gave limited clues as to what the structure of the SEM should consist of (other than demonstrating there was much covariation between OCD, alexithymia, and autism). Recent work (Edwards and Lowe, 2021) had given some clues in how alexithymia relates to psychological inflexibility and SAC, but not in the cases of covarying OCD and autism. So, to explore this further, three linear (backward) regressions were explored, to first (in the first regression model) determine whether the measures of mental health, OCD, interoception (ISen), alexithymia, psychological inflexibility, and self-as-context predicted ASD as an outcome. The second regression model was used to determine whether the measures of mental health, OCD, interoception (ISen), autism, psychological inflexibility, and self-as-context predicted alexithymia. The third regression model was used to determine whether the measures of mental health, alexithymia, interoception, autism, psychological inflexibility, and self-as-context predicted OCD. The outcomes in the final regression step models informed the third part of the study in terms of which variables were most likely to directly predict each of the three variables (OCD, alexithymia, and autism).

One problem with the regression models is that they only show direct associations and give no clues how the variables may indirectly associate with one another. In the third part of the study, five independent simple mediation analyses were conducted to give some clues about how these variables indirectly relate to one another. Here, some of the outcomes in the final regression models (of part two) informed the mediation analyses to be made. The first mediation analysis showed that ISen attention regulation partially mediated the relation between OCD and autism. The second mediation analysis showed that SAC partially mediated the relation between autism and alexithymia. The third showed that ISen trusting partially mediated the relation between alexithymia and depression. The fourth showed that psychological inflexibility partially mediated the relation between ISen attention regulation and SAC. The fifth showed that psychological inflexibility partially mediated the relation between SAC and ISen trusting. What is interesting about these mediation analyses is that at a hierarchical level (as depicted in Figure 1), psychological inflexibility seems to at least partially mediate all of the different relations at the highest hierarchical level. This provided some insights into a conceptual model, indicating that psychological inflexibility should be a key indirect pathway between the IVs (OCD and alexithymia) and DVs (autism and autistic-related depression).

In the fourth part of the study, the conceptual models for causal pathways were developed concretely, whereby IVs were identified as OCD and covarying alexithymia, while the DVs were autism (in model one) and autistic-related depression (in model two, with autism as a DV). These were tested through two SEMs, but before this could happen, the first steps were to utilize EFA and CFA to assign (explore then confirm) item variables to latent constructs where possible. However, when utilizing these factor analysis approaches items within the same questionnaire constructs did not always load well together. Items variables were removed from the latent variables when the standardized residual covariances were significantly different from the data to improve the overall SEM fit. This meant that items such as the many subsections of the ISen questionnaire did not fit well together in the context of the data and conceptual model and were removed when they did not. Once these were removed, the final first SEM that included autism only as a DV showed that alexithymia was directly significantly positively associated with autism and psychological inflexibility, but it (alexithymia) was not directly significantly

associated with ISen self-regulation. Alexithymia was instead indirectly associated with ISen self-regulation *via* psychological inflexibility. OCD was not directly or indirectly associated with autism, but it was indirectly associated with ISen self-regulation mediated by psychological inflexibility. Psychological inflexibility was not directly associated with autism, but it was indirectly associated with it *via* ISen self-regulation. Gender was not a significant control, but age was a strong controlling variable (as expected given the data from the ANCOVAs). Age was directly associated (a direct control) to autism and was significantly negatively associated with ISen self-regulation directly and indirectly *via* psychological flexibility. Age was marginally outside of significance in its association (control) with psychological inflexibility directly.

In the second SEM, these findings were extended further, by including a second DV in the form of depression. Psychological inflexibility was directly associated with depression and indirectly associated with it *via* SAC, while SAC was directly associated with depression. Neither age nor gender has any direct associations with SAC or depression. Age was significantly indirectly associated with SAC *via* psychological inflexibility and depression *via* psychological inflexibility and SAC. There were also indirect effects between alexithymia and SAC *via* psychological inflexibility, alexithymia and ISen self-regulation *via* psychological inflexibility, and alexithymia and depression *via* psychological inflexibility and SAC. There was an indirect effect between OCD and SAC *via* psychological inflexibility, OCD and ISen self-regulation *via* psychological inflexibility, and OCD and depression *via* psychological inflexibility. There were indirect effects between psychological inflexibility and ISen self-regulation *via* SAC, psychological inflexibility, and depression *via* SAC, and between SAC and autism *via* ISen self-regulation.

Perhaps, the most important findings in this study are that the SEMs show the clear indirect causal association relation between alexithymia and OCD with autism. Though alexithymia and OCD shared a strong correlation with autism, the model confirmed that the best fit of the data were through an indirect causal association with autism, indirectly through psychological inflexibility and SAC and then indirectly through ISen self-regulation interoception. This indicates that there exists a complex relation between psychological flexibility and vagal nerve related interoception, and this is supported by an increasing number of evidence (Pinna and Edwards, 2020; Edwards and Lowe, 2021; O'Brien et al., 2021). This could even include connections with embodied knowledge of psychological flexibility (Falletta-Cowden et al., 2022) as the ISen interoceptive measure used relates to confidence in embodied interoceptive signals. The findings also suggest that these complex associations are causally related to autism, and this is not captured in the current diagnostic DSM protocol. The SEMs show causally how alexithymia and OCD are comorbidly showing up with autism.

The findings also show that autistic-related depression is caused indirectly through psychological inflexibility and SAC, and there was no direct causal path between depression and autism (despite there being a strong correlation between depression and autism). Much of the causal pathway traffic in the associations between alexithymia and autism and its associated depression was *via* psychological inflexibility. The causal diagram shows psychological inflexibility to be a central gateway to the link between alexithymia and OCD with autism (which was predicted from the results of the mediational analysis, in the third part of the study given its hierarchical position), whereby ISen self-regulation bodily interoception is a secondary gateway for the link between alexithymia and OCD with autism severity specifically. SAC association with psychological inflexibility and autistic-related depression also seems a key secondary causal path gateway for the depression specifically. As SAC relates to perspective-taking skills, it seems likely that the onset of depression is linked to the lack of ability of ASD individuals to connect and communicate with others (for which perspective-taking skills is crucial). Building such perspective-taking skills may be a key and useful intervention in reducing depression in autism, given this nomothetic model.

This SEM path analysis helps to delineate the associations between alexithymia, OCD, and ASD more concretely. This highlights why these conditions cannot be taken as singular discrete categorical syndromes with an independent set of symptoms and underlying etiology which is treatable through a static protocol for treatment as specified by the DSM (American Psychiatric Association, 2013a). Instead, this study results support the claim that there is great comorbidity between these conditions (Kupfer et al., 2008) whether direct or indirectly. They also support the claim that any specified singular treatment protocol (such as what is specified by the DSM) would lack treatment specificity (Kupfer et al., 2008; Insel et al., 2010). Given such comorbidity, as seen in the casual diagram, any individual changes, or differences at any of the intersecting indirect pathways, could lead to quite different outcomes and have cascading effects. Therefore, a more dynamic and ideographic (individual level) process-based approach is likely to be more effective to access and initiate processes of change within then complexity, rather than a strict and rigid DSM protocol from treatment in treating individuals with autism.

This work supports the conclusions made by PBT and EEMM research advocates that suggest dynamic, longitudinal, and multi-level (e.g., biological and psychological) approaches are required to identify important change processes rather than singular protocols for syndromes (Hayes and Hofmann, 2017, 2018; Hofmann and Hayes, 2019; Hofmann et al., 2021). The SEM presented here (though nomothetic data) fits well with the EEMM as it emphasizes that autism is a multi-level condition. For example, it identifies that interoception (ISen self-regulation) fits well with both the individual level dimension of "attention" as it relates to noticing bodily

feelings and the level of "physiology" as the vagal nerve carries bodily information to the brain and is processed in the insular cortex. SAC fits with the "self" dimension and psychological flexibility with the "cognitive" dimension at the individual level.

In relation to the theories of interoception more generally, interoception defined as a predicting coding error (Seth, 2013; Barrett and Simmons, 2015; Barrett et al., 2016; Seth and Friston, 2016; Stephan et al., 2016; Owens et al., 2018) overcomes some of the issues with directional predictions typically associated with interoception. Higher ISen self-regulation interoception represents high confidence in the interoceptive signals, and therefore, this is consistent with the predictive coding theory, as low confidence should mean high prediction errors. This interpretation of interoception suggests that autism is a condition whereby there are high bodily prediction errors. To lower these predictive errors using the PBT EEMM approach, the "attentional" dimension may be an important domain (as illustrated in intervention point 4 of Figure 5), whereby engaging in exercises which promote mindfulness, noticing in the present moment, and awareness of feelings may lower interoceptive predictive errors and thus improve the autistic condition. Again, this would be most accurately done through ideographic assessments, such as EMA longitudinally overt time giving precise ever-changing interoceptive predictive coding data within the complex network.

In relation to ASD, the predictive coding model explains why autistic individuals tend to focus on local information (ignoring contextual prior background knowledge) as it suggests that the predictive priors of contextual background information are weaker in ASD individuals when compared to healthy individuals, as observed in previous studies (Happé and Frith, 2006; Mottron et al., 2006). As such when developing a longitudinal EMA PBT study, we would expect to see contextual relational frame community clusters (as conceptually illustrated in Figure 5) more heavily weighed to recent events. This would mean, for example, something recently learned, i.e., whereby a function in the network transfers from one stimuli of a cluster to the next (through ToF), then the impact would be greater for more local recent events than something learned further back in time. This would perhaps mean targeting the verbal self with a cognitive defusion intervention to undermine the negative feedback loop of avoidance (as illustrated in intervention point 1 of Figure 5) resultant from destructive verbal self-language (e.g., "I will fail"), thus preventing such negative transformations of functions. It could also mean targeting SAC with perspective-taking building skills to help the individual communicate and see others perspective (as illustrated in intervention point 2 of Figure 5). Crucially, it should mean targeting the key gateway of the network, psychological inflexibility such as through values orientation, mindfulness, openness to pain exercises, and cognitive defusion (as illustrated in intervention point 3 of Figure 5).

The advantage of the longitudinal approach advocated by the PBT developers (Hayes and Hofmann, 2017, 2018; Hofmann and Hayes, 2019; Hofmann et al., 2021) is that this longitudinal and ideographic approach would allow therapists and researchers enough detail (data) to model these types of transformations of functions in real time and ideographically for each individual. Existing graph approach such as group iterative multiple model estimation (GIMME) approach (Gates and Molenaar, 2012; Beltz and Gates, 2017; Weigard et al., 2021), which combines the elements of graph theory with SEM, is useful for modeling ideographic longitudinal EMA type data and is advocated by PBT researchers (Hayes et al., 2019). However, these may be further developed in line with an ideographic version of what is proposed in Figure 5, which would help to account for dynamic and ongoing relational frame processes, such as ToF. This may be further helpful for clinicians and researchers alike and would allow for interventions to target and undermine these negative functions directly and affect the overall network at the level of the relational frame.

All studies include limitations. Questionnaire data in this study required participants to answer all questions, so this may have impacted attrition rates as some may have dropped out of the study due to frustration. Another limitation was that the data used here were solely cross-sectional nomothetic (population-based). However, PBT approaches are optimized when exploring longitudinal ideographic data, such as through EMA, therefore, it would be useful to explore this SEM in a longitudinal and ideographic way to see whether the model is still supported by the data. Finally, ideally, a physiological measure such as HRV would have supplemented the interoceptive measure greatly, though these are related.

In conclusion, this study demonstrated that autism is a complex and dynamic condition, which is not easily definable and is in part caused by alexithymia and OCD indirectly through psychological inflexibility, SAC, and interoception (ISen self-regulation). Though some of these associations are quite predictable such as covarying OCD with alexithymia, the novelty of this study was to capture the complex processes (psychological inflexibility, SAC, and interoception) that indirectly related to OCD, alexithymia, and autism. Further studies exploring the ideographic level and longitudinally may be able to generate more complex graphs that can model specific relational frame processes, such as ToF and dynamically in real time, which may greatly benefit both researchers interested in PBT and therapists utilizing this approach to support autistic individuals.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Swansea University Psychology Ethics. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DE completed all aspects of this manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Adolescence between biology and culture a perspective on the crisis of symbolization

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One way to conceptualize human life is to describe it as a process through which the biological body is progressively transformed into a psychological one through its mentalization and symbolization. This process occurs through the relational field, which begins with caregiver-infant proto-conversations and develops through adolescence into the ongoing complex interpersonal relational network we call society and culture. The essence and the problems of adolescents are intricately tied to the social and cultural contexts in which they experience life. Therefore, adolescence cannot be understood if all the levels that it expresses (biological, psychological cultural/social) are not taken into consideration. We identify three psycho-historical phases through which adolescence has changed in the past century: (1) Oedipal; (2) Narcissistic; and (3) Post-narcissistic. In this last phase due to the psychological and historical failure of the narcissistic ideals, the ideal is mingling with the real in a wholly new way. This process has overturned Erikson's paradigm: identity, opposed and defined by a dichotomic otherness, must be transformed into a fluid integration of similarities and differences negotiated and developed through empirical interpersonal intersubjective experiences. This, in our perspective, is a possible key to understand the rapid change in the nature of consciousness, selfhood, and gendering in today's western world, together with some important psychopathological disorders which describe the new creative challenges of today's adolescents.

KEYWORDS

adolescence, identity, psychopathological disorders, crisis, Oedipus complex, narcissism, anthropology, ethnology

Introduction

It is possible to say that human life is a process through which the biological body is progressively transformed into a psychological one through its mentalization and symbolization (Bion, 1962). This process occurs through the relational field, which begins with caregiver–infant proto-conversations and develops through adolescence into the ongoing, complex, and interpersonal relational network we call society and culture. In this sense, Anthropology is the *complementary* side of a whole in which the other aspect is Psychology (Devereux, 1978). Within this perspective, the essence and the problems of adolescents are tied to the social and cultural contexts in which they experience life (Erikson, 1959; Coleman, 1974; Lerner and Foch, 1987; Dahl et al., 2018; Hurrelmann and Quenzel, 2018; Israel et al., 2021).

Therefore, adolescence cannot be understood if all the levels that it expresses (biological and psychological cultural/social) are not taken into consideration (Sawyer et al., 2018; Worthman and Trang, 2018).

Adolescence's developmental tasks (Lancini, 2019; Lancini et al., 2020), as highly complex as they are, define adolescence as a real-time of transformation, so pervasive as to be described as a second birth (Blos, 1962, 1967). Erikson (1968) somehow considered adolescence the barycenter of the subject's development, from the beginning of postnatal life (the Freudian "primary narcissism" and the "oral stage") to old age and the completion of the life cycle by finding meaning in its very finitude. Erikson also theorized that adolescence was essentially a critical process–i.e., somehow a de-integration of the previous infantile state of the self–to obtain a more mature self, now integrated into a developed self-reflective awareness, and subject/object constancy (Mahler et al., 1975)–a self-provided with what Erikson called "identity." The critical nature of this process and its challenges, for many aspects such as the deeply ambiguous and disconcerting nature of the middle phase of the anthropological rites of passages as described by Van Gennep (1961), are described by Erikson as a "crisis" which may be resolved at the positive end of the process, or which may end in a fragmented psycho-social organization (confusion and diffusion of identity).

We would like to re-formulate Erikson's view. In fact, we think that today both concepts of crisis and identity have become critical themselves. From the consideration that the child at the end of adolescence will become an active agent of his/her cultural (symbolic), social, economic, and historical world, we maintain that adolescence is not only a process that happens through interpersonal time (and that, therefore, may be studied through a purely psychological lens) but that it also takes place within a social, economic, anthropological, and *historical* time (and that, therefore, needs an ethno-psychological perspective). The point is that the same applies to Erikson's theory itself, as we think that today—at least in the capitalistic West—the contemporary empirical form of "identity" is profoundly different from Erikson's time and that this difference implies also a revision of the concept of "crisis," as Erikson conceptualized it. In a few words, identity and crisis themselves might be a historically determined form of the many ways the structural and representational self is organized.

In our opinion, from the middle of the 1960s to the present time adolescence and, therefore, "identity" and "crisis" have undergone a very deep transformation. A point of reference for this is Deleuze and Guattari's *Anti-Oedipus* (Deleuze and Guattari, 1977), in which the authors analyzed the reformulation of the organization of the personality in the West as wholly embedded within history and, therefore, capitalism. In fact, capitalism is the form of the most pervasive contemporary *mythology* that organizes the totality of human life in post-modernity (for an interpretation of mythology see, for instance, Jung, 1951), and which encompasses narratives that symbolize and organize all levels of life from its embodied forms—such as sex, genders, and procreation—all the way to the social, religious, and cultural levels. Under this perspective, Deleuze and Guattari's position seems very pertinent, indeed.

Within a psycho-historical perspective we individuate three main phases: (1) Oedipal; (2) Narcissistic; and (3) Post-Narcissistic.

The Oedipal phase

Before the 1960s, the main organizing mental–and therefore social and anthropological (hence mythical) structure, at least for the western's mind, was the Oedipus complex. Just to sketch our argument: in the Oedipus complex, history is (a) conservative, as the child must identify with the Father and therefore carry his value-system, under the form of Super-Ego, toward the next generation; and (b) repressive, as the polymorphic and "perverse" (Freud, 1905) nature of the unconscious (the infinitely creative and alive *body without organs*, as defined by Deleuze and Guattari (1977) is confined within rigid norms under the threat of castration—i.e., the absolute loss of psychic life. Erikson was writing precisely during this time when *historical* identity was under huge attack (a crisis) by the "Beat generation." In fact, during the revolution of the 60s, we notice a migration of the ideal from the Father to the Child. Before the 1960s, the empirical representation of the self could provide *stability and recognition* to the personality by granting not only its *regulative* function but because of its transgenerational stability derived from the identification with the Father, also the illusion of its *constitutive* reality (Kant, 1967), which psychoanalysis (Freud, 1905) and analytical psychology (Jung, 1951) had already definitively dismantled by proving the intrinsic dissociability of the psyche. For Erikson (1950, 1968), the synthetic and regulative function of the ego would grant stability, and recognition together with a highly stable—apparently constitutive—*identity*, which means: the possibility to constitutively belong to a specific psycho-social category, *stable* in biographical, social and historical time—a category whose borders, once established—had to remain very well defined and fixed. Such an identity would automatically define the other as a wholly Other. Erikson's world was a world based on static and well-defined identities express by nouns, and not on fluid relationships expressed by adjectives and verbs, a world destined to change under a complex set of historical conditions, among which: the two world wars, the ever-increasing pace of capitalism, materialism, individualism, and the subordination of every possible difference to that of the relationship between the subject as a consumer and his objects as commodities, and the logarithmic acceleration of time.

The narcissistic phase

The revolution of the 60s demolished the super-egoic authority of the Father and therefore, broke transgenerational continuity, while historical changes dramatically accelerated (Lévi-Strauss, 1967). This meant the *migration of the ideal from the Father to the Child*, and the subsequent birth of psycho-social mythology whose essential feature was narcissism (Sobo, 1977). For this myth, the Child, and with-it youth, consumption, creativity, change, manic-like lifestyles, and transgression become the basic organizers of identity. A narcissistic identity for which the adolescent has the illusion that he/she must be a uniquely precious being (who he/she is, indeed. The question is what the adolescent will do with the *opposite* values: his/her "normality"). In this phase, the Western adolescent (and hence the future adult) believes that he/she may fabricate his/her own values; that he/she is *already* mature before any painstaking process of learning. The fact that learning is necessary to pursue an ideal that, differently from what the subject believes, is *not yet real, and will never be,* is negated. In Freudian terms, this is due to the unresolved Oedipal complex and the impossibility to enter into latency. The Child has the illusion to be already an adult. The ideal seems real.

In this narcissistic historical phase, sexuality is liberated; the myths of "authenticity" and creativity are claimed, although the tragic illusion (which will be progressively clear in the next phase) of the *right* to be adored and admired (by the Oedipal mother) remains an illusion; an illusion which the fundamental capitalistic myth will use for its own structural purposes: consumption and commodification. In this scene, while the adolescent tries to realize his/her "identity," more than getting to love an exogamic—a real—object, he/she wishes to be loved by the object. Ethics—which was a central feature of the previous Oedipal/Superegoic phase—is now substituted by a narcissistic exhibitionism and, therefore, with esthetics. This is the time in which bulimia comes into the world scene for the first time ever, probably as an ethno-psychological tragic cry that something, in the liberation of women from the phallic domination is failing and should be re-thought in much more radical terms (Anderson-Fye, 2018).

This narcissistic historical phase was bound to fail, together with its cocky and yet extremely fragile, insecure "identity," which had lost its symbolic reference to the Father. In fact, this phase-specific form of identity formation cannot mark the completion of adolescence, as it was with Erikson, but will actually infinitely *prolong* it by transforming adolescence itself in a permanent, positive pseudo-value for every age. Instead of a child becoming an adult through adolescence, we witness an eternally pseudo-adolescent ideal adult. Within this sense of identity, everyone wishes to remain young and "creative"; everyone will claim an enslaving and impossible hyper-sexuality (which, in the capitalistic myth will be soon pornographically commodified and used as a form of consumption), an eternal youth, together with the "right" to affirm the subject's opinions even if they have no real ground, logic, rationality, or sophistication. In this context, social media are the places in which everyone may *tell without ever listening* (McCain and Campbell, 2018). Even if there is no real knowledge, expertise, or ground to justify these assertions. Once again: talent is narcissistically given for granted, even if it does not exist, and the process of learning (i.e., living, growing up) is ignored. Within this psycho-anthropological milieu, how can an adolescent realize the tasks of such a complex process? Within this picture, how can we define "crisis" as referred to as adolescence if the whole ideal regarding how life should be has become adolescent-like? The crisis of what once was adolescence becomes the existential crisis of every age for everyone.

The post-narcissistic phase

The third phase is the present one. As with all developmental cycles, the end of the previous narcissistic phase is the result of its own acme, for which, paradoxically, it is the adults who have absorbed many values of adolescence. In this historical phase, a large multiplicity of factors, which involve the structure of the western self, disrupt the very core of what we so far called "identity." Among these factors we may remember: the hyper fragmentation of social life and the transgenerational discontinuity, which entails the idealization of present and future and the de-idealization of the past (which carries a sense of being uprooted from the "world of the ancestors" and makes it much harder to recognize the pervasive transgenerational nature of psychological conflicts); globalization—i.e., the infinite flow of equivalent commodities, among which we include humans, neutralized by their being measured exclusively by their economic value as producers/consumers; the possibility to live *apparently* infinite lives in what we now know as the "virtual world" (unknown in history before today), while these lives risk to remain virtual anyway and, therefore, are an obstacle to the fundamental goal of adolescence of *realizing* (knowing / making real) its ideals; the compulsive, desperate way to try to exist as socialized individuals (i.e., to stably exist through compulsive requests of mirroring the adolescent's idealized narcissism by others) as we may notice from the explosion of the phenomenon of the *selfie*; the progressive empirical realization that the idealized Child actually lives a *less* creative and meaningful life, bound to commodification and consumption (hence, that the subject of experience is actually subjected *to* his/her commodified objects); the looming realization that he/she will *not* be admired as he/she needs, since everyone—as it always happens in adolescence—is looking for the same recognition by the others (Chopik and Grimm, 2019).

To this progressive realization of the betrayed promises that the idealized narcissistic Child pursued is the realization of the climate crises and, generally, of the catastrophic results of the last decades of the Anthropocene. The world is not the oyster in which the narcissistic Child will shine. An anomic trait of this historical phase is the hiatus between an illusion of being an ideal Child and the absurd cutthroat competitiveness which children, adolescents, and post-adolescents must face throughout their schooling, and where cooperation (which, again, promotes social fragmentation, and intrinsic solitude) seems not to be convenient. Here we see the covert, hugely destructive revenge of the Father toward his children.

In fact, the previous narcissistic investment of the idealized Child had created the conditions for a structural shrinking of the former psychosocial categories of identity, which were able to clearly and stably define "how to be what." This phenomenon, for which identity categories become less and less inclusive, is very coherent with the progressive molecularization and fragmentation of the social world (which carries with itself a fragmentation of the nuclear family itself). Now, the adolescent becomes always more and more a self-defined, nuclear subject, while the identity categories, without the organizing role of the Father, become extremely fluid.

In this phase–the present post-narcissistic one—the "identity" of this atomized subject, based on his/her narcissistic idealization (I am special) *cannot be considered an identity in the old sense anymore*. In fact, in this psycho-historical phase, we witness the end of identity as Erikson had envisioned. The social and psychological fluidity (Bauman, 2000, 2009) coupled with the extreme narcissistic individualism (a sort of ego-centrism) cannot any longer resort to already given categories (destroyed together with the Oedipal Father) into which identify. Now, identity refers not to belonging to an already given social, personal, or sexual top–down category (as it happened in the Oedipal historical phase), but to *an empirical bottom–up cluster*. If the Oedipal category of the pre-narcissistic phase was a psycho-social formation derived from the idealized Father, now the adolescent's "identity" resembles the aggregation of specific, empirical features that the individual—the subject—collects bottom–up through his/her own intersubjective, interpersonal, and social life. Through this path, he/she will aggregate into a cluster of his/her characteristics *and only at this point* look around to see who could be defined in the same way, and who could belong to the same cluster. This process is producing enormous stress on language, its nouns, and pronouns (She, He, It, … How many pronouns will be needed? What will the balance between the narcissistic atomized identity and the fluidity of belonging to clusters be?).

We are witnessing a powerful process of hybridization and creolization, in which differences and similarities mingle and form *fluid identities*, which, paradoxically deconstruct what is identical and do not denote anything as identical anymore (Remotti, 2019). As highlighted by Lemma (2015, 2018) freedom of choice and the right to self-realization emerge as guiding principles. Indeed, it could be argued that nowadays we are expected to present ourselves as biographically flexible and open to change. This freedom of choice finds its synthesis in the ability to customize one's body—a trend modeled on consumer choices under the dominance of the neo-liberal consumerist concept with the attendant risk that identity is based on what the author herself defines as "acquisitive imitations" where imitation trumps identification. It seems that today, what Erikson called "crisis" has actually become the immanent device of this fluidity. What was critical then, is normal and constitutive now. Obviously, the challenges of this peculiar nature of adolescence are, as usual, very great. Yet, they seem to be very different from those of the Erikson's Oedipal phase, and even those of the previous narcissistic phase. The possibility to find and in dwell within these multiple, changing clusters may not only produce a less difference, but also less polarized and conflictual personality structure and society. It may also produce identity disorders and a feeling of non-continuity of one's personal biography (something that we have witnessed in the progressive transformation of psycho-pathologies in the last 60 years), or dangerous potential phenomena of superficial forms of identification in search for a more stable identity definition.

One thing is evident among all: what for Freud was the fundamental, essential, oppositional difference—the difference that granted identity and, therefore, also conflict, scapegoating, and splitting—the *difference between the sexes*—is now about to explode under the phenomenal deconstruction of identity and crisis and the multiplication of psycho-socio *genders*. Especially, this phenomenon of gender fluidity seems to represent the multiplication of identity clusters and the wholly new way to build bottom-up, a (fluid) identity through biographical time.

Clinical conclusions

Through our perspective, we tried to analyze the historical transformation of adolescence—itself a psychological developmental process embedded in socio-cultural history. The pivotal psychological constructs that we have identified are as follows: (a) the transformation of the ideal and its "migration" from the Father to the Child; (b) the deconstruction of what we usually call "identity," together with; and (c) the conceptualization of the adolescent process as a passage that needs to be structured by rituals as those of the anthropological rites of passage.

This view of ours implies some corollary considerations: (1) the fate of the transformations of adolescence, its ideals and identity, as we have described it, may produce defensive movements of retreat from interpersonal involvement, which may produce phenomena such as that of the so-called hikikomori; (2) the increase of internalized symptoms involving the self, and the body (self), where aggressivity may be conveyed,

with or without acting outs (such as self-harming), instead of the frequent externalizing symptoms (or just manifestations) of the adolescent's protest against society; (3) the difficulty to balance the idealizing ideals toward the object world (such as falling in love) and the narcissistic idealization of one's self (wanting to be admired), which may produce a difficult harmonization of sexual and attachment motivations and the decrease of genital sexual involvement; and (4) the progressive increase of the once (illusory) unity of identity at all levels, from the social/professional one, to those aspects that involve gender.

Referring to the Jungian point of view, we think that within the adolescent's clinical setting not only it is undesirable to promote a transference related to the adolescent's infantile history, but that this would go against the very essence of his/her psychological development (this is also the position of Pietropolli-Charmet et al., 2010). In fact, never as in adolescence is it clear that (all) psychological processes are teleological and that it is useful to consider memories and past events only if we frame them as causes-for-intrinsic aims. The past, infancy, and childhood must be seen as preparatory conditions for something *future*. This "future"—the temporal place where the self will realize itself in the world—happens, in its purest form, within adolescence. Seen this way, the process of adolescence *needs* not parents, or "experts," who, already "knowing" do not express any future anymore, but figures such as *mentors*, who are called to initiate the adolescent into the adult world and a coherent psychological organization. This mentor might be called to perform the same functions that through the rites of passage initiate the person into a renewed and more encompassing form of life. Not transference, but the therapeutic alliance is therefore pivotal. Under this respect, the role of the psychotherapist (or also of the non-parental adult) acquires in adolescence a fundamental transitional role, for which knowledge of anthropology and ethnology might be a necessary requisite.

Such a tension toward the future describes the adolescent as the subject engrossed with the quintessential human need: to symbolize effects. It should be obvious that "symbolization" cannot but refer to a psychological activity of the mind which expresses what we call "culture" at any level we may describe it—from the interpersonal way a caregiver interacts with her/his child, to social life within history. Such a perspective, which joins symbolization, relationship, culture, and teleology, involves the adult, but in its purest and most intense form, especially the adolescent. It is adolescence's fundamental nature. This makes it imperative that the psychotherapist acquires an anthropological lens through which he/she may look at the patient, who is wholly engrossed in the very human attempt to symbolize, actualize within the relational world, and dialectically fit within his/her anthropological world his/her emotional (hence also bodily) experience of himself/herself. No reductive psychological theories or clinical approaches, which purely psychologize or biologize the adolescent's challenges, or which reduce the intrinsic creative and open-ended nature of symbolization, can really help the adolescent. Actually, he/she will rightfully resist them.

In the present times more than ever—times in which the Father must be recreated often through what we may call the *inversion of the Shadow*—for which the "positive" traits of kindness, sensibility, love, curiosity, etc., are hidden under "negative" traits, the adolescent will challenge his/her therapist in order to check whether he/she is taking his/her matter as seriously as he/she is: the matters being nothing less than extracting meaning out of life and transcending its tragic, conflictual aspects.

A last clinical issue involved with the present historical situation has to do with "identity," and therefore, the sense of one's continuity in time and space. Today more than ever, the clinician must not confuse the specific forms within which the adolescent tries to recognize his/her own selfhood with the synthetic activity of the mind. In the past, it was possible to conflate the synthetic activity of the mind with the specific contents and identification that the mind tries to synthesize. In fact, it was possible for someone to be continually, personally, and socially sure "to coherently be a layer," or even "a man/woman." Today this is not so, as the plural, possible personal/social contents of one's identity are much more fluid and, often, fragmented. Therefore, the clinician is called to *never conflate the synthesizing ego with its contents, while recognizing, holding, and validating its activity and continuity.* The stabilization of the adolescent's identifications, and therefore of an *implicit, yet impossible to make explicit sense of identity,* will come with time.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Physiological reactivity at rest and in response to social or emotional stimuli after a traumatic brain injury: A systematic review

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Numerous studies have shown that alterations in physiological reactivity (PR) after traumatic brain injury (TBI) are possibly associated with emotional deficits. We conducted a systematic review of these studies that evaluated PR in adults with moderate-to-severe TBI, either at rest or in response to emotional, stressful, or social stimuli. We focused on the most common measures of physiological response, including heart rate (HR), heart rate variability (HRV), respiratory sinus arrhythmia (RSA), electrodermal activity (EDA), salivary cortisol, facial electromyography (EMG), and blink reflex.

Methods: A systematic literature search was conducted across six databases (PsycINFO, Psycarticles, SciencDirect, Cochrane Library, PubMed, and Scopus). The search returned 286 articles and 18 studies met the inclusion criteria.

Results: Discrepancies were observed according to the type of physiological measure. Reduced physiological responses in patients with TBI have been reported in most EDA studies, which were also overrepresented in the review. In terms of facial EMG, patients with TBI appear to exhibit reduced activity of the corrugator muscle and diminished blink reflex, while in most studies, zygomaticus contraction did not show significant differences between TBI and controls. Interestingly, most studies measuring cardiac activity did not find significant differences between TBI and controls. Finally, one study measured salivary cortisol levels and reported no difference between patients with TBI and controls.

Conclusion: Although disturbed EDA responses were frequently reported in patients with TBI, other measures did not consistently indicate an impairment in PR. These discrepancies could be due to the lesion pattern resulting from TBI, which could affect the PR to aversive stimuli. In addition, methodological differences concerning the measurements and their standardization as well as the characteristics of the patients may also be involved in these discrepancies. We propose methodological recommendations for the use of multiple and simultaneous PR measurements and standardization. Future research should converge toward a common methodology in terms of physiological data analysis to improve inter-study comparisons.

KEYWORDS

traumatic brain injury, brain injury, physiological reactivity, autonomic reactivity, emotion, social stimuli

1. Introduction

Moderate to severe traumatic brain injury (TBI) can cause focal injuries at the site of the impact or in tissues opposite to the impact. Moreover, rapid acceleration and deceleration of the brain within the skull produces diffuse brain injuries characterized by widely distributed damage to axons, diffuse vascular injury, hypoxic–ischemic injury, and brain swelling (oedema; Andriessen et al., 2010). These injuries have a propensity to cause damage to the ventral frontal and temporal cortices (Stuss, 2011). The major sequelae of the damage are persistent emotional and behavioral disorders present in 62% of patients one year after TBI (Deb et al., 1999; Stéfan and Mathé, 2016). This damage is, in part, responsible for persistent emotional and behavioral disorders that disturb daily functioning, socio-professional reintegration, and quality of life (Milders et al., 2003). Among these difficulties, emotion regulation disorders result in emotional lability, indifference, and irritability (McDonald, 2013). Patients also report a decrease in their ability to experience emotional states, such as sadness or fear (Croker and McDonald, 2005), and the degree of impairment in subjective emotional experience is correlated with the severity of social behavioral problems (Hornak et al., 1996). Compared with motor and cognitive sequelae, emotional disorders have a greater impact on social reintegration (Milders et al., 2003). As these disorders are among the most frequent sequelae, it is crucial to investigate their etiology and propose ways to remedy them.

Multilevel models of emotional response postulate that its adequate expression is based on the awareness of the emotion experienced, which in turn is based on the ability to become aware of the bodily changes associated with the emotion (Lane, 2000). These responses refer to physiological reactivity (PR). The implications of PR in emotions have been discussed for more than a century. The first major peripheralist theory of James and Lange (James, 1884) postulated that physiological changes [including facial expressions (crying, smiling, blinking) and peripheral visceral responses (heart rate, emotional sweating, etc.)] elicited by the stimulus are at the origin of the emotional subjective feeling. This theory was strongly criticized by Cannon (1931), who postulated independence between PR and emotion. Modern theories posit that the role of PR in emotional processes lies at the intersection of these two theories (Scherer, 2005). Indeed, PR should be considered a cue, among others, on which the formation of emotion is based (Christopoulos et al., 2019). Damasio's somatic marker hypothesis places the perception of somatic states at the center of emotional reasoning and interpersonal relationships (Damasio et al., 1996). According to this hypothesis, the prefrontal cortex records somatic states experienced during each emotional experience in the form of internal representations called somatic markers. These markers are reactivated upon subsequent confrontations with similar situations/stimuli to adapt behavior for predictable consequences. This hypothesis is based on the famous case of Phineas Gage who, following a severe TBI with prefrontal lesions, developed emotional behavioral disorders similar to an 'acquired sociopathy'. Therefore, this theory supports the involvement of PR in emotional processes.

The PR reflects the electrical and hormonal expression of autonomic activity under the control of the autonomic nervous system (ANS) and limbic–hypothalamic–pituitary–adrenal axis (LHPA). The ANS is part of the nervous system which controls the automatic functions of the body, such as smooth muscles, cardiovascular tissues (heart, blood vessels), sensory systems (eyes, skin), and glands (endocrine and exocrine), to maintain internal homeostasis and adapt it to environmental changes (see Figure 1). The ANS comprises two branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). The SNS is an activating system for mobilization and activation of the body to facilitate attention, fight, or flight. The PNS is an inhibiting system that allows the restoration and recovery of the body. The ANS activation in response to stimulation produces changes in the heart rate (HR), heart rate variability (HRV), and electrodermal activity (EDA), whereas limbic–hypothalamic–pituitary–adrenal axis (LHPA) activation produces the stress hormone cortisol. The ANS is controlled by a neuronal system composed of the hypothalamus, limbic system, and frontal lobe areas (Christopoulos et al., 2019). Accordingly, impairments in PR are frequently reported following TBI and are not surprising given the location of the lesions. Several studies have reported reduced startle blinks, skin conductance activity, and facial reactivity to emotional pictures and movies (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011). Several researchers have hypothesized that abnormalities in PR may underlie the emotional issues in TBI (de Sousa et al., 2010; Rushby et al., 2013b; Francis et al., 2016). In addition to research on TBI populations, other research and reviews have reported links between PR abnormalities and different psychiatric disorders, such as anxiety (Hyde et al., 2019), depression (Sarchiapone et al., 2018), and behavioral disorders, such as aggression, psychopathy, and conduct problems (Lorber, 2004).

Given the role of PR in emotional processes, PR abnormalities may play a major role in the etiology of emotional difficulties after TBI. These difficulties manifest as emotional regulation disorders, such as emotional lability, indifference, or irritability (McDonald, 2013). Patients also report a decrease in their ability to experience emotional states such as sadness or fear (Croker and McDonald, 2005), with the degree of impairment in subjective emotional experience correlating with the severity of social behavioral problems (Hornak et al., 1996). Although these disorders are known to exist, to date, no systematic review of the literature on physiological reactivity abnormalities in TBI has been conducted. Therefore, this review will focus on potential physiological disturbances at rest or in response to emotional, social, and stressful stimuli in adults with moderate-to-severe TBI compared to healthy controls. Social and emotional stimuli refer to all stimuli and tasks involving other people, elements of social interactions (gaze or speech), or human emotions. Stressors refer to all situations that may induce stress in the participants. This review includes the most common measures of physiological responses, including HR, HRV, RSA, EDA, EMG, and blink reflex. For research involving resting physiological data collection, only studies linking physiological data to psychological variables measured using cognitive tasks, self-report, or hetero-report psychometric scales were selected.

2. Methods

2.1. Protocol and registration

Before starting the research procedures, the protocol for this review was submitted to the PROSPERO International Prospective Register of Systematic Reviews in July 2021 (registration number CRD42021266886). This protocol details the complete methodology of this review, and no changes were made during the review.

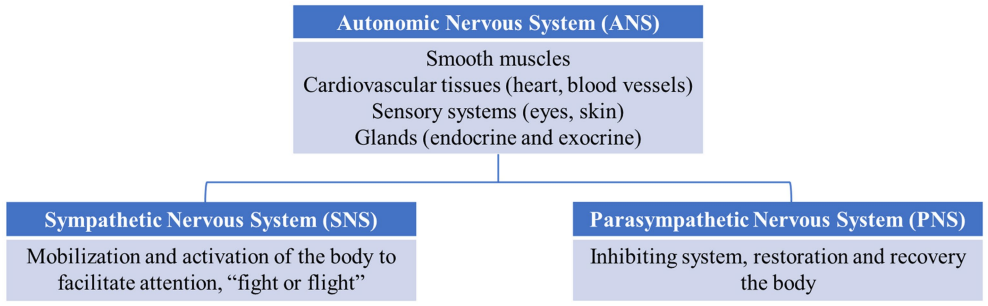

FIGURE 1
Autonomic nervous system divisions.

2.2. Search procedure

We conducted a systematic review of the literature in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) guidelines. The research was conducted using PsycINFO, Psycarticles, SciencDirect, Cochrane Library, PubMed, and Scopus. The search was limited to peer-reviewed articles in French and English from 2000 to 2021. Keywords in the title or abstract were "*traumatic brain injury" OR "chronic brain injury" OR "brain injury" OR "head injury" OR "head trauma*" in combination with the following keywords: *"physiological" OR "physiological reactivity" OR "physiological change" OR "physiological response" OR "arousal" OR "skin conductance" OR "heart rate" OR "heart rate variability" OR "facial reactivity" OR "electrodermal" OR "galvanic skin response" OR "arousal" OR "hyperarousal" OR "hypoarousal" OR "autonomic" OR "eyeblink startle"* and "emotion" OR "stimuli" OR "emotional responses" OR "emotional reactivity" OR "rest" OR "stress" OR "habituation."

2.2.1. Inclusion and exclusion criterion

We included studies that (1) had at least one participant with moderate to severe TBI; (2) compared the physiological data of participants with TBI to a group of healthy participants without TBI or other psychiatric or neurologic histories; (3) measured at least one of HR, HRV, RSA, EDA, facial EMG, startle blink, or cortisol; (4) used research designs that exposed participant(s) to at least one stimulus condition different from baseline; or (5) involved resting physiological data collection, linking physiological data to psychological variables measured using cognitive tasks, self-report, or hetero-report psychometric scales. We excluded studies if they (1) are animal studies; (2) utilized physiological measures to assess the efficiency of a pharmacological intervention; (3) included participants under 18 or over 80; (4) included patients in a persistent vegetative state; (5) targeted pathologies other than moderate to severe TBI (post-traumatic stress disorder, mild TBI,TBI without brain lesion or cognitive and emotional sequelae, other neurological, post-traumatic stress disorder); (6) had no control group; (7) involved no physiological measures; and (8) are conference papers because they are not always peer-reviewed or are preliminary data for future publications, abstracts, posters, reviews, or meta-analyzes.

The research returned 286 articles from the six databases. We excluded 39 duplicates and screened 247 articles. Figure 2 summarizes the selection process and details of the reasons for articles' exclusion. The first screening stage for titles and abstracts excluded 220 articles. The main reason for exclusion was the fact that the articles focused on mild TBI. A second screening stage on the full article excluded nine articles because of the absence of a control group. Eighteen articles were included in this review. Study selection was performed with two reviewers independently and was cross-checked by the two reviewers, and all disagreements in the team were unanimously resolved. For data extraction, a standardized data collection form was used by two independent researchers.

2.3. Quality assessment

To our knowledge, no evaluation criteria exist for non-randomized, non-interventional, and psychophysiological studies. We used Farrington's suggestions for the assessment of methodological quality standards (Farrington, 2003) to develop our own criteria for the quality of the studies included in our review [see also the systematic review on PR in autism by Lydon et al., 2016]. We established 12 criteria (see Table 1), all of which were fulfilled by the 18 selected studies.

3. Results

First, we present the sample characteristic, followed by physiological measures and stimuli. Second, studies' results are presented according to the type of physiological measurement and stimuli used. Table 2 lists the characteristics of the participants, stimuli used, types of physiological measures, main results, and potential link with psychological assessment for each of the 18 studies.

3.1. Sample characteristics

The sample size ranged from 11 to 128 participants, with a total of 386 patients with TBI, 5 patients with ischaemic stroke, and 431 control participants. The mean age of patients was 42.58 and 36.62 for control participants. We analyzed the pooled effect of age using the mean and standard deviation of both groups for 16 studies. Two studies were not included in this analysis because the authors did not specify the mean age and standard deviation (Saunders et al., 2006; McDonald et al., 2011). The pooled effect was medium ($d = -0.34$, SE = 0.0752, 95% CI 0.4841–0.189) and the heterogeneity between studies moderate (Cochran's Q, $df = 15$, $p = 0.0004$, $I^2 = 40.2\%$; Hedges and Olkin, 1985). The patient sample included 290 men (74.17%) and 101 women (25.83%), and the control sample included 285 men (6.13%) and 146

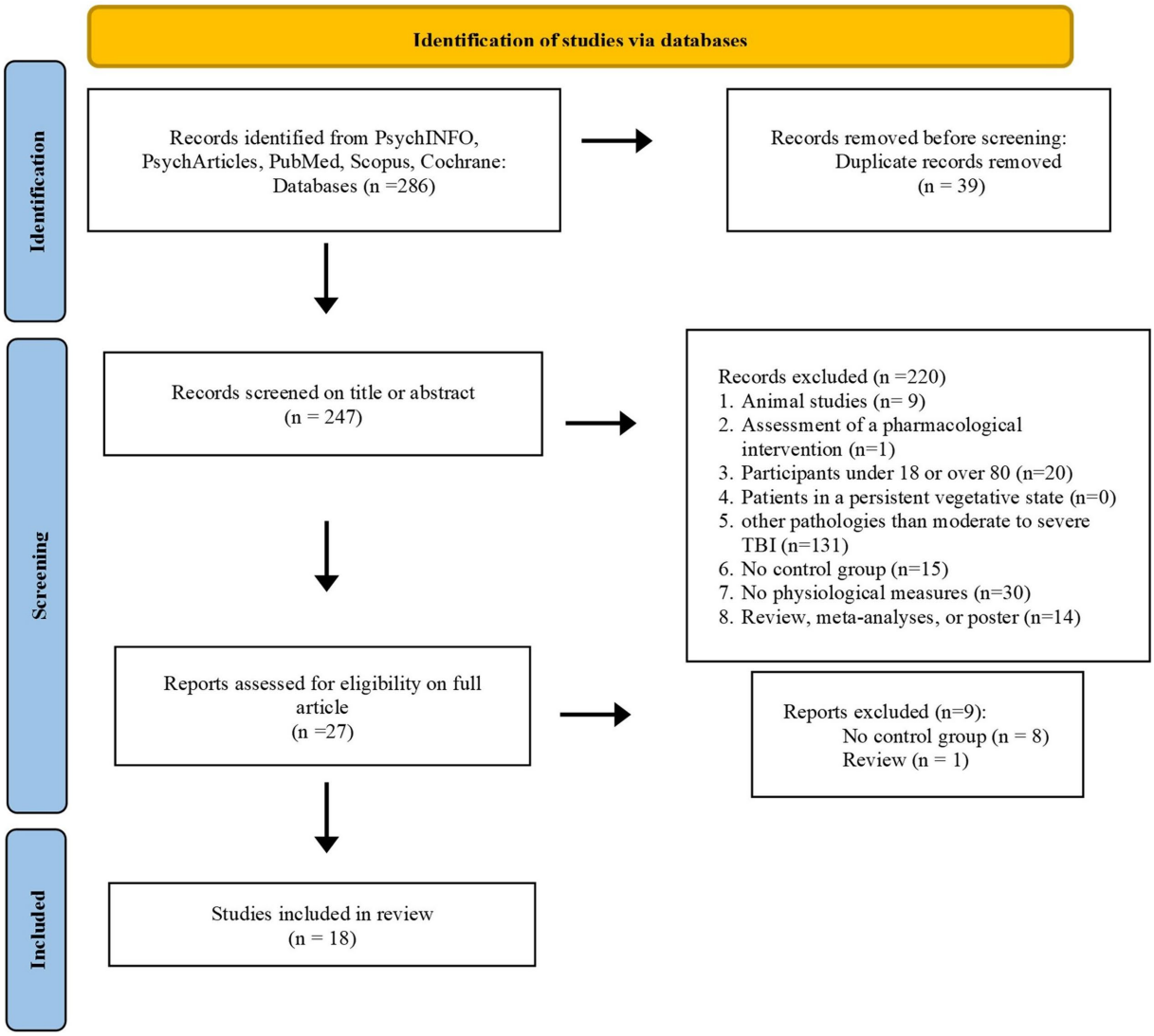

FIGURE 2
Flow diagram showing inclusion/exclusion of studies identified during database search process.

women (33.87%). The percentage of women in the TBI sample was significantly lower than in the control group ($M_{TBI} = 23.77\%$, SD = 12.59, $M_{controls}$: 32.34%, SD = 15.66; W = 92, $p = 0.028$). Conversely, the percentage of men was significantly higher in TBI sample ($M_{TBI} = 78.22\%$, SD = 15.47, $M_{controls} = 67.66\%$, SD = 15.66; W = 88, $p = 0.019$).

Concerning the injury severity, 15 studies included only moderate to severe TBI (Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011, 2012; Krpan et al., 2011; McDonald et al., 2011; Williams and Wood, 2012; Rushby et al., 2013a, 2013b, 2016; Fisher et al., 2015; Francis et al., 2016; Kelly et al., 2017; Osborne-Crowley et al., 2020), one study included mild to severe TBI (Aboulafia-Brakha et al., 2016). Sánchez-Navarro et al. (2005) included patients with frontal brain damage, and Amorapanth et al. (2016) included patients with TBI with cognitive or emotional disorders, but these two studies did not specify the severity of brain injuries. Finally, the mean time post-injury was 10.42 years, the shortest post-injury period was 3 months (Aboulafia-Brakha et al., 2016) and the longest was 40 years (de Sousa et al., 2012). Kelly et al. (2017) did not specify the average post-injury time and only mentioned a minimum time of 24 months post-injury.

3.2. Physiological measures

Table 3 summaries the physiological measures contained in each study. Most studies used several physiological measures (82.35%). The most commonly used measure was EDA in 14 studies (Soussignan et al., 2005; de Sousa et al., 2010, 2011, 2012; Krpan et al., 2011; McDonald et al., 2011; Rushby et al., 2013a, 2013b, 2016; Fisher et al., 2015; Aboulafia-Brakha et al., 2016; Kelly et al., 2017; Osborne-Crowley et al., 2020), followed by cardiac activity in 7 studies (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Krpan et al., 2011; McDonald et al., 2011; Rushby et al., 2013b; Amorapanth et al., 2016; Francis et al., 2016), and facial EMG in 8 studies (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011, 2012; Williams and Wood, 2012; Rushby et al., 2013b). Krpan et al. (2011) measured cortisol levels, and Amorapanth et al. (2016) recorded the respiratory rate. As this respiratory measurement is used in combination with cardiac data to calculate the respiratory sinus arrhythmia (RSA), the last study will be discussed in Section 3.

TABLE 1 Quality criteria.

Descriptive validity:	1. The design of the study is stated.
	2. The sample size is stated.
	3. Participant characteristics concerning age, gender, TBI severity and time post-injury are outlined.
	4. The physiological response, and any behavioral responses being measured, are operationally defined.
	5. The stimulus/stimuli are described in detail including information on their emotional content and duration.
	6. The study contained a physiological data baseline, and its duration is specified.
	7. If standardized measures are used, their psychometric properties are stated.
	8. Statistical methods employed are described.
Internal validity:	1. The study included a control group.
	2. Baseline physiological activity is considered during analyzes.
Statistical conclusion validity:	1. Statistical analyzes are appropriate for the research question and are performed with parametric tests.
	2. The statistical significance of the findings is stated.

3.3. Stimuli

The types of stimuli used to elicit PR vary between studies. Eight studies used emotional pictures (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011; McDonald et al., 2011; Williams and Wood, 2012; Fisher et al., 2015), three of which presented pictures of emotional faces (de Sousa et al., 2011; McDonald et al., 2011; Fisher et al., 2015), four others presented emotional pictures (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010; Williams and Wood, 2012) from the standardized International Affective Picture System (IAPS, Lang et al., 1997), and the last one presented both types of pictures (Saunders et al., 2006). One study used short video clips of emotional faces (Aboulafia-Brakha et al., 2016). Three studies were extracted from famous movies (de Sousa et al., 2012; Rushby et al., 2013b; Amorapanth et al., 2016), two asked participants to report an event (Aboulafia-Brakha et al., 2016; Osborne-Crowley et al., 2020), two simulated social stress situations (Krpan et al., 2011; Kelly et al., 2017), three contained acoustic startle probes (Sánchez-Navarro et al., 2005; Saunders et al., 2006; Williams and Wood, 2012), and one used odor (Soussignan et al., 2005). Five studies included different types of stimuli (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Saunders et al., 2006; Williams and Wood, 2012; Aboulafia-Brakha et al., 2016), whereas the remaining studies included only one type of stimulus (de Sousa et al., 2010, 2011, 2012; Krpan et al., 2011; McDonald et al., 2011; Rushby et al., 2013a, 2013b, 2016; Fisher et al., 2015; Amorapanth et al., 2016; Francis et al., 2016; Kelly et al., 2017; Osborne-Crowley et al., 2020). Finally, three studies used measures at rest as the main measure (Rushby et al., 2013a, 2016; Francis et al., 2016) and seven others reported physiological data during the baseline (Sánchez-Navarro et al., 2005; Krpan et al., 2011; McDonald et al., 2011; Rushby et al., 2013b; Fisher et al., 2015; Aboulafia-Brakha et al., 2016; Kelly et al., 2017). In the following sections, studies are presented according to the type of physiological measurement and stimuli used.

3.4. Electrodermal activity

Two different indices were used to assess EDA in the reviewed studies: first, the skin conductance response (SCR) refers to a phasic change in the electrical conductivity of the skin in response to a change in an environment, such as emotional stimuli presentation. SCR is measured by the maximum amplitude change of the signal occurring in seconds following stimulation (usually between 1 and 3 s; Grapperon et al., 2012). SCR is used, for example, to measure habituation to repeated stimulus presentations. Second, the skin conductance level (SCL) refers to the tonic level of the electrical conductivity of the skin. This reflects general changes in autonomic arousal. It is characterized by slow and long-lasting state changes related to the accumulation or resorption of sweat in the surface layers. SCL increases (sensitisation) after stimuli presentation but rapidly decreases (habituation) when participants are attending passively. However, when participants are actively engaged in a task, habituation does not occur (Barry, 2004; Nagai et al., 2004). Among the 14 studies measuring EDA, 11 studies reported statistically significant differences between the responses of TBI and control participants (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010, 2011, 2012; McDonald et al., 2011; Rushby et al., 2013a, 2016; Fisher et al., 2015; Aboulafia-Brakha et al., 2016; Osborne-Crowley et al., 2020). For 9 of them, TBI participants showed a reduction in EDA compared to controls. Conversely, in the study by Aboulafia-Brakha et al. (2016), patients with TBI showed higher SCL during uninstructed anger recall than the control group. Finally, Kelly et al. (2017), Krpan et al. (2011), and Rushby et al. (2013b) did not report significant differences between TBI and control groups.

3.4.1. Pictures

Seven studies measured EDA during image presentation; three used stimuli from the IAPS (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010), and the other used pictures or short video clips of facial expressions (Sánchez-Navarro et al., 2005; de Sousa et al., 2011; McDonald et al., 2011; Aboulafia-Brakha et al., 2016).

3.4.1.1. International affective picture system pictures

In three IAPS studies, TBI participants displayed reduced SCR across pleasant, unpleasant, and neutral pictures compared to control participants (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010). However, the observed power of the group effect on SCR is only mentioned by de Sousa et al. (2010): the partial eta squared (η^2p) was 0.35, which corresponds to a small effect (Cohen, 1988). Concerning a possible valence effect in patients with TBI, no differences were observed between pleasant, unpleasant, and neutral pictures in the studies by de Sousa et al. (2010) and Soussignan et al. (2005). However, Sánchez-Navarro et al. (2005) reported a

valence × group effect: healthy participants produced greater SCR for pleasant and unpleasant pictures as compared to neutral pictures, while the TBI group showed larger SCR for pleasant pictures only, without any difference between unpleasant and neutral conditions. Moreover, de Sousa et al. (2010) found a significant positive correlation between SCR amplitude and cognitive empathy levels. Similarly, a marginally significant positive correlation was observed with affective empathy. Taken together, these results suggest that after TBI, image valence has less influence on SCR, which is instead predicted by empathy abilities.

Although these findings are interesting, variability also existed in the results of the control groups. Hence, compared to neutral images, control participants produced greater SCRs for positive images (de Sousa et al., 2010), negative images (Soussignan et al., 2005), or both (Sánchez-Navarro et al., 2005). However, these studies differed in at least three dimensions. First, stimuli were presented for 6 s in all three studies, but their number differed between the studies: de Sousa et al.'s (2010) study used 18 pictures (6 per category), while Sánchez-Navarro et al. (2005) and Soussignan et al.'s (2005) studies contained 54 (18 per category) and 90 pictures (30 per category),

TABLE 2 Summary of studies.

Author's name	n	Age mean (± SD)	Severity of TBI	Time post injury mean (± SD)	Stimuli/ task	Physiological measure(s)	Findings	Link with psychological assessment
Aboulafia-Brakha et al. (2016)	20 TBI, 22 controls	TBI: 37.4 (±12.6); Controls: 33.4 (± 8.5)	12 severe, 3, moderate, 5 mild	18.8 months (±12.01 months)	Verbal reports; Emotion faces on video clips	EDA; SCL	Anger regulation task: Only in the TBI group was mean SCL higher during uninstructed compared to neutral recall. Emotion recognition task: No difference between groups was observed	/
Amorapanth et al. (2016)	16 TBI, 10 controls	TBI: 51.9(±15.0); Controls: 38.0 (± 14.4)	/	5.9 years (± 8.6 years)	Emotional film clips	ECG; HRV	TBI group exhibited lower LFA HRV during amusement films compared to controls. Conversely, the TBI group showed higher LFA HRV during sad films than the control group.	This increase in sympathetic activity for sad films was correlated with self-reported attentional difficulties and impairment in visual attention.
de Sousa et al. (2012)	21 TBI, 25 controls	TBI: 41.2 (±13.1); Controls: 29.0 (±11.1)	Severe	14.3 years (±10.4 years)	Emotional film clips	EMG; ZM and CM; EDA: SCL	ZM: Greater activity for pleasant films than neutral or unpleasant in controls, little differentiation between the type of films for TBI. Activity increased over time in the control group, especially for pleasant films, this activation decreased in the TBI group, especially for unpleasant films. CM: Greater activation for unpleasant films compared to pleasant and neutral films in controls, no effect valence in TBI. SCL: Lower SCL during unpleasant films in TBI compared to controls. Habituation during unpleasant films and sensitisation during pleasant films only in controls.	

(Continued)

TABLE 2 (Continued)

Author's name	n	Age mean (± SD)	Severity of TBI	Time post injury mean (± SD)	Stimuli/ task	Physiological measure(s)	Findings	Link with psychological assessment
de Sousa et al. (2010)	20 TBI, 22 controls	TBI: 47.4 (±10.0); Controls: 36.1 (± 12.6)	Severe	13.4 years (± 6.9 years)	IAPS pictures	EMG; ZM and CM; EDA: SCR	ZM: No difference between groups. CM: TBI showed reduced responses to unpleasant pictures. SCR: TBI group exhibited reduced SCR in pleasant, unpleasant, and neutral pictures compared to control participants.	ZM: No significant correlations with emotional or cognitive empathy for both groups. CM: Positive correlations with emotional and cognitive empathy scores for controls during unpleasant pictures. SCR: Positive correlation with cognitive empathy and with emotional empathy (trend toward significance) for TBI during pleasant pictures
de Sousa et al. (2011)	21 TBI, 22 controls	TBI: 48.4 (±8.8) Controls: 36.1 (± 12.6)	Severe	11.9 years (± 7.8 years)	Facial expressions pictures	EMG: ZM and CM; EDA: SCR and SCL	SCL: Reduced SCL to anger faces in TBI. SCR: Greater SCR to angry faces compared to happy faces in controls, larger SCR to happy faces.in TBI. ZM: No difference between groups. CM: produced greater activity for angry faces compared to happy faces in controls, with no emotional effect in TBI.	SCR: Same SCR to angry and happy faces for TBI and controls with higher emotional empathy level, participants with a lower level of empathy presented higher SCR for happy faces compared to angry faces. ZM: Larger ZM for happy faces than angry for the higher emotional empathy TBI and controls groups. No emotion effect for the low empathy TBI and control group. CM: Group effect with higher CM for TBI group comparing their control counterparts. Emotion effect and group effect in low empathy group: greater CM for angry faces compared to happy faces, inverse pattern in TBI group

(Continued)

TABLE 2 (Continued)

Author's name	n	Age mean (± SD)	Severity of TBI	Time post injury mean (± SD)	Stimuli/ task	Physiological measure(s)	Findings	Link with psychological assessment
Fisher et al. (2015)	19 TBI, 19 controls	TBI:44.89 (±13.76); Controls: 43.95 (±15.15)	Severe	12.37 years (±7.99 years)	Facial expressions pictures	EDA: SCL	Lower SCL in TBI not emotional effect	
Francis et al. (2016)	30 TBI, 30 controls	TBI: 45,73 (±13,68) Controls: 46,9 (±12,91)	Severe	14.03 years (± 8.74 years)	Resting state and one session of HRV biofeedback	ECG: HRV	No difference between groups at rest and during the biofeedback session	Positive correlation between HRV and social cognition and emotional empathy, negatively correlation with alexithymia in the TBI group.
Kelly et al. (2017)	21 TBI, 17 controls	TBI: 49.81 (±11.81); Controls: 46.29 (±16.22)	Moderate severe	at least 24 months post-injury.	Cyberball game	EDA: SCL	No difference	No correlation between SCLs and self-reported emotional experience in both groups
Krpan et al. (2011)	18 TBI, 24 controls	TBI: 38.8 (±13.6); Controls: 38.7 (± 17.4)	Moderate–severe	153 months (±117 months)	Simulated real-world stress test	EDA: SCL, ECG: HR, cortisol	SCL: No significant difference between groups. HR: No significant difference between groups Cortisol: No significant difference between groups	/
McDonald et al. (2011)	18 TBI, 18 controls	TBI: 49.0 (range 31 to63 years); Controls: 35.9 (range 20 to59 years)	Moderate severe	mean time since injury 13.0 (± 7.0 years)	Emotional faces pictures, passive and identification task	EDA: SCR and SCL, ECG: ECD	SCR: No difference between groups SCL: Passive task: increasing of SCL over trials for angry faces and decreasing for happy faces in controls Habituation and no emotion effect in TBI. Identification task: no habituation for either expression for either the control or TBI participants. ECD: Increasing for the identification condition compared to the passive condition in both groups. Identification task: magnitude increasing across repetition higher in controls relative to TBI. Increasing for the happy face across the repetition and decreasing for the angry face in controls, no emotional effect on TBI	No correlation between physiological measures and accuracy in recognizing tasks in both groups

(Continued)

TABLE 2 (Continued)

Author's name	n	Age mean (± SD)	Severity of TBI	Time post injury mean (± SD)	Stimuli/ task	Physiological measure(s)	Findings	Link with psychological assessment
Osborne-Crowley et al. (2020)	30 TBI, 30 controls	TBI: 44.47 (±15.32); Controls: 41.70 (±14.97)	Moderate Severe	13.63 years (±13.08 years)	Verbal report; Listening stories	EDA: SCL	Greater SCL across the emotional conditions in controls compared to TBI.	
(Rushby et al., 2013a)	17 TBI, 22 controls	TBI: 46.47 (±13.30); Controls: 41.23 (± 14.86)	Severe	12.59 years (± 8.05 years)	Resting state eyes open, eyes closed	EDA: SCL	Lower SCLs across both conditions in TBI compared to controls	
Rushby et al. (2016)	24 TBI, 24 controls	TBI: 43.3 years (± 14.96); Controls: 42.4 (±14.9)	Severe	12.63 years (±8.81 years)	Resting state	EDA: SCL	Lower SCL for the TBI compared to controls	
Rushby et al. (2013b)	19 TBI, 25 controls	TBI: 41.5 (±13.8); Controls: 31.0 (±11.1)	Severe	13.21 years (±10.3 years)	Emotional film clips	EMG: ZM and CM; EDA: SCL, ECG: HR	SCL: Increasing across films repetition in both groups. No emotion effect ZM: No difference between groups CM: Greater activity across all film types in TBI compared to controls. Emotion effect with higher activation for unpleasant films compared to neutral and pleasant films in both groups HR: Increasing across films repetition in controls, deceleration in TBI	SCL: Positive correlation with emotional empathy only in TBI ZM: Larger response in TBI for the low emotional empathy group compared to the higher empathy TBI group.
Sánchez-Navarro et al. (2005)	19 ABI* (14 TBI, 5 ischemic stroke), 23 controls	ABI: 31.63 (±13.05); control: 20.78 (±2.45)	Frontal damage	24.17 years (±2,01 years)	IPAS pictures	EDA: SCL and SCR; Startle blink, ECG: HR	SCL: No significant difference between groups SCR: Lower responses in TBI than in controls Startle blink: Lower responses in TBI for unpleasant pictures and higher ones to pleasant pictures compared to controls HR: No difference between group	
Saunders et al. (2006)	13 TBI, 24 controls	Adults	Severe	Mean: 6 years 9 months (range 1–17 years).	IAPS pictures, emotional faces pictures	Startle blink	IAPS pictures: Attenuation for pleasant pictures and potentiation for unpleasant ones in controls, attenuation for pleasant and unpleasant pictures in TBI. Slower to reach peak eyeblink response for positive and negative pictures in TBI compared to controls Faces pictures: no emotion and group effects	No correlation between subjective valence ratings and eyeblink peak, latency, or subjective arousal ratings in both groups

(Continued)

TABLE 2 (Continued)

Author's name	n	Age mean (± SD)	Severity of TBI	Time post injury mean (± SD)	Stimuli/ task	Physiological measure(s)	Findings	Link with psychological assessment
Soussignan et al. (2005)	1 TBI, 10 controls	TBI: 30, Controls: 26.4 (±4.87)	Severe	11 years	IAPS pictures	EMG: ZM and CM; ECG: HR; EDA:SCR	Pictures: SCR: Lower responses for all pictures in TBI. No emotion effect in TBI contrary to controls.ZM and CM: no emotional effect only in TBI Odors: SCL: No valence effect in TBI, greater SCL for unpleasant odors than pleasant or neutral ones in the control group. HR: No group and valence effect ZM and CM: no valence effect on TBI.	
Williams and Wood (2012)	64 TBI, 64 controls	TBI: 32.05 (±12.60); Controls 34.73 (± 12.14)	Moderate to severe	2.52 years (± 1.422 years)	IAPS pictures acoustic stimulus	Startle blink	Reduce effect of valence in TBI compared to controls	No correlation between with performance on europsychological measures in TBI

ABI, Acquired brain injury.

respectively. Second, the data transformation methods differed between the studies. Sánchez-Navarro et al. (2005) used a log transformation [log (SCR-1)] without a pre-stimulus baseline. Soussignan et al. (2005) subtracted the 2-s baseline pre-stimuli from the largest value averaged in the 2-s window after stimulation, and de Sousa et al. (2010) used a similar method but with a 1-s prepicture baseline. Finally, sample sizes differed, ranging from 10 in Soussignan et al.'s (2005) study to over 20 participants in the two other studies. Moreover, Sánchez-Navarro et al. (2005) included patients with frontal stroke in their TBI group. These methodological discrepancies may have led to inconsistencies in the results of the three control groups as well as in the TBI groups.

3.4.1.2. Facial expressions

Four studies used facial expressions: de Sousa et al. (2011) and McDonald et al. (2011) included happy and angry faces; Fisher et al. (2015) added neutral faces; and Aboulafia-Brakha et al. (2016) used short clips in which actors portrayed anger, surprise, disgust, happiness, sadness, and fear or neutral faces. The type of task also varied between studies. In de Sousa et al.'s (2011) and Fisher et al.'s (2015) studies, participants passively viewed pictures. The task of McDonald et al. (2011) contained two conditions: first, participants passively viewed the pictures; then, they had to identify the emotion among the six other emotions. Aboulafia-Brakha et al. (2016) also proposed an emotional recognition task in which participants identified the emotion portrayed in a clip from a list of seven emotional labels. In the passive viewing condition, the TBI group of de Sousa et al. (2011) exhibited lower SCR for angry faces than the control group. Indeed, while the control group showed greater SCR to angry faces than happy faces, the opposite effect was observed in the TBI group with larger responses to happy faces. However, when emotional empathy was considered, this response pattern was only observed among participants with low emotional empathy. The TBI and control participants with normal emotional empathy levels presented the same SCR to angry and happy faces, suggesting that emotional empathy played a role in SCR to angry faces after TBI. However, during a passive viewing task, the TBI group of Fisher et al. (2015) presented a lower SCL for angry, happy, and neutral faces than the control group; however, no effect of the type of emotion was observed in either group. Conversely, Aboulafia-Brakha et al. (2016) reported an emotional effect on the SCL mean, but no difference between groups during active emotional recognition. In their passive task, McDonald et al. (2011) did not report differences involving group, condition, or emotion in SCR. However, the SCL trial mean exhibited a greater level for happy faces than for angry faces in the TBI group. Moreover, while control participants showed sensitisation (increasing SCL) for angry faces and habituation (decreasing SCL) for happy faces, TBI participants rapidly habituated to both emotions. Habituation effects disappeared in both groups during the attend condition, suggesting the influence of attention on emotional arousal. Taken together, these results suggest that increasing attentional demand allows the EDA to be normalized in TBI, and that the level of empathy may influence electrodermal reactivity. However, the methods of data transformation were not consistent between the studies. Indeed, de Sousa et al. (2011) and McDonald et al. (2011) first subtracted the 1,000 msec prepicture baseline from the 1,000 and 4,000 msec of the picture onset, and then used a log transformation [Log (SCR – skin conductance response +1)] to standardize the data. In contrast, Aboulafia-Brakha et al. (2016) and Fisher et al. (2015) did not use any data transformation methods.

3.4.2. Films

de Sousa et al. (2012) and Rushby et al. (2013b) measured the EDA during pleasant, unpleasant, and neutral scenes from six movies. The data collection of these two studies occurred concurrently, and the first

TABLE 3 Summary of physiological measurements by study.

Author's name	Table 1			EDA		EMG			Cortisol
	HR	HRV	RSA	SCL	SCR	ZM	CM	Blink reflex	
Aboulafia-Brakha et al. (2016)				X					
Amorapanth et al. (2016)		X	X						
de Sousa et al. (2012)				X		X	X		
de Sousa et al. (2010)					X	X	X		
de Sousa et al. (2011)				X	X	X	X		
Fisher et al. (2015)				X					
Francis et al. (2016)		X							
Kelly et al. (2017)				X					
Krpan et al. (2011)	X			X					X
McDonald et al. (2011)	X			X	X				
Osborne-Crowley et al. (2020)				X					
Rushby et al. (2013a)				X					
Rushby et al. (2016)				X					
Rushby et al. (2013b)	X			X		X	X		
Sánchez-Navarro et al. (2005)	X			X	X			X	
Saunders et al. (2006)								X	

report focused on physiological responses to the first viewing of each film clip, while the second examined physiological patterns across five separate viewings of each film. de Sousa et al. (2012) analyzed the SCL data by dividing 90 s of film into 3-time intervals (0–30 s, 30–60 s, 60–90 s). For each interval, TBI participants exhibited less SCL during unpleasant films compared to control participants, while neutral clips produced similar SCL between groups. In addition, habituation to unpleasant films and sensitization to pleasant films were observed in the control group but not in the TBI group which had the same SCL across time. In Rushby et al. (2013b), the SCL increased across five film repetitions (sensitization) in both groups, but no significant effect of group or valence was observed. Moreover, in the TBI group, higher SCL correlated with higher self-reported emotional empathy. Separated analyzes according to emotional empathy levels in TBI groups revealed that increasing SCL across film repetition appeared only in TBI participants with normal to elevated self-report empathy scores, whereas TBI participants with low empathy scores maintained a low level of SCL across repetitions. Like de Sousa et al. (2011), the authors suggested a causal relationship between the loss of emotional contagion and loss of empathy for people after TBI. Finally, note that the data standardization methods used in these two studies were similar. In both studies, the 2 min resting baseline period was subtracted from the first 90 s time interval of each of the film clips presented. However, de Sousa et al. (2012) divided 90 s into three 30-s time intervals (0–30 s, 30–60 s, and 60–90 s). The SCL was calculated by subtracting the mean activity in the resting baseline period from the activity at each time interval.

3.4.3. Emotion induction

Aboulafia-Brakha et al. (2016) and Osborne-Crowley et al. (2020) elicited emotions through the recall of emotional memories. Aboulafia-Brakha et al. (2016) investigated SCL during an anger regulation task. In this task, participants were asked to recall a self-experienced neutral and angering event aloud. In the latter, participants had to recall the same event in three different conditions, (1) without instruction, (2) while focusing on the emotional aspects and (3) while focusing on the perspective of the other involved person. The authors found that the mean SCL was higher during uninstructed anger recall than during neutral recall only in the TBI group. However, these results have not been replicated by Osborne-Crowley et al. (2020). In this study, participants first recounted emotional self-experienced events that evoked anger, happiness, and sadness. The second time, they heard three stories like their own and three stories based on the stories of other participants. Healthy participants exhibited greater SCL than TBI participants under all conditions. An effect of condition was observed

in both groups with higher SCL for telling their story compared to listening to a similar or dissimilar story. However, no interaction between the group and emotion was observed. Note that Aboulafia-Brakha et al. (2016) included mild TBI whereas the Osborne-Crowley et al.'s (2020) sample contained only moderate to severe TBI. Contrary to de Sousa et al. (2010, 2011), who linked abnormal SCL for emotional expressions of anger and pleasant pictures after TBI with low self-reported empathy, Osborne-Crowley et al. (2020) found no difference between the self-reported emotional empathy of patients with TBI and controls. These authors suggest that after TBI, empathy is preserved despite reduced autonomic arousal. Finally, note that the data standardization of these two studies differed: Osborne-Crowley et al. (2020) took a baseline 10 s before the start of the recall which they subtracted from the first minute of the recall, while Aboulafia-Brakha et al. (2016) did not standardize the data with the baseline and used the SCL mean during 3 minutes of verbal reports.

3.4.4. Social stress situation

Two studies used social situation paradigms to obtain more ecological data (Krpan et al., 2011; Kelly et al., 2017). Kelly et al. (2017) measured the SCL during a cyberball game. This internet-based social exclusion paradigm involves an inclusion condition in which the ball is equally shared with the participant and an ostracism condition in which the participant is ignored by the other (fictive) players and does not receive the ball tosses. The results showed different patterns of SCL between the TBI and control groups. Whereas the SCL increased during the ostracism condition in the control group, the SCL was higher during the inclusion condition in the TBI group. However, the difference was not statistically significant. However, the self-reported emotional experience of ostracism significantly differed between the groups; TBI participants felt less included in the inclusion condition than in the control group and similarly excluded in the exclusion condition. Given that these self-reported behavioral results were not correlated with SCL, these authors postulated a dissociation of self-report and physiological arousal after TBI. Krpan et al., 2011 measured SCL during a psychosocial stress test in which participants had to prepare and give a speech to an expert in communications and perform mental arithmetic while being video recorded. The video recordings during the speech preparation were then analyzed to compare the number of avoidance behaviors (e.g., reading magazines, playing puzzles, text messaging, staring into space) and planful behaviors (e.g. writing, reviewing the speech or writing, and appearing to think). The groups did not differ in SCL or self-reported stress levels during the psychosocial stress test. However, the TBI group exhibited more avoidant than planful behaviors, whereas the opposite was true for the control group. Therefore, contrary to Kelly et al. (2017), there was no dissociation between SCL and self-reported emotional experience, but the authors found a dissociation between behaviors and PR induced by stress. Finally, Kelly et al. (2017) reduced the SCL data with the difference between the mean value of the 2-min baseline period and the mean value for each 10-s epoch across the game; then, the data were standardized with a log transformation. However, Krpan et al. (2011) did not mention the reduction or standardization of the data.

3.4.5. Startle acoustic

Only one study, by Sánchez-Navarro et al. (2005), measured SCR during an acoustic startle stimulus. The authors did not report any SCR difference between TBI and control participants during an acoustic stimulus of a 50-ms burst of white noise.

3.4.6. Olfactory stimuli

In Soussignan et al.'s (2005) case study, participants smelt five pleasant, five unpleasant, and five neutral odors before rating the level of pleasure and intensity of the smell. Analyzes showed greater SCR for unpleasant odors than for pleasant and neutral odors only in the control group. Moreover, unpleasant odors produced higher SC changes in controls than in participants with TBI. However, pleasure and intensity ratings differed between participants with TBI and controls. Finally, SCR correlated with pleasure and intensity ratings in control participants, but SCR did not correlate with rating scores in patients with TBI. These results suggest a dissociation between PR and self-reported measures. Concerning the data standardization method, the authors subtracted the SCR at the 2 s SC level immediately preceding the stimulus onset from the largest value averaged in the 2-s window after stimulation.

3.4.7. Resting state

Among the eight studies examining resting-state SCL (Sánchez-Navarro et al., 2005; Krpan et al., 2011; McDonald et al., 2011; Rushby et al., 2013b, 2016; Fisher et al., 2015; Aboulafia-Brakha et al., 2016; Kelly et al., 2017), half reported a lower level of SCL in the TBI group compared to the control group. Indeed, Rushby et al. (2013b) and Fisher et al. (2015) found a marginally significant lower SCL in their TBI groups during a 2 min resting condition. This difference was significant in studies by Rushby et al. (2016) and McDonald et al. (2011). The duration of Rushby et al.'s (2016) resting condition was 2 min. The resting data of McDonald et al. (2011) were derived in the 500 ms period immediately before stimulus onset. It is noteworthy that for this last study, baseline data were taken between two stimuli, while for the three other studies, data were taken at rest. Conversely, several studies showed no difference in SCL between controls and patients with TBI during baselines of 5 min (Krpan et al. (2011), 3 min (Sánchez-Navarro et al., 2005; Aboulafia-Brakha et al., 2016), or 2 min (Kelly et al., 2017).

3.5. Facial electromyography

The study of emotional reactivity by facial EMG is mainly based on the measurement of the contraction of the brow muscles, namely the corrugator supercilia (CR), the cheek muscles, namely the zygomaticus major (ZM), and the startle blink. Whereas the ZM contraction produces smiling expressions, the CR is the muscle above the eyebrows that brings them together and contracts during negative emotions such as grief or anger (Ekman and Friesen, 1978). The measure of the startle blink is based on a biphasic emotional theory, as negative stimuli activate the defence system, and positive stimuli activate the appetitive system (Lang et al., 1990). As blinking is an aversive reflex, it is potentiated for unpleasant stimuli and decreased for pleasant stimuli. Usually, an acoustic startle probe is presented together with the stimuli. It often consists of short bursts of white noise. Among the five studies measuring ZM and CM (Soussignan et al., 2005; de Sousa et al., 2010, 2011, 2012; Rushby et al., 2013b), only one reported a difference between the ZM responses of TBI and control participants (de Sousa et al., 2012). Conversely, regarding CR, only one study observed a similar response between groups (de Sousa et al., 2012). Finally, three studies investigating startle blinks found differences between groups (Sánchez-Navarro et al., 2005; Saunders et al., 2006; Williams and Wood, 2012).

3.5.1. Pictures

3.5.1.1. International affective picture system pictures

Among the five studies using IAPS pictures, de Sousa et al. (2010) and Soussignan et al. (2005) measured ZM and CR activity, whereas Sánchez-Navarro et al. (2005), Williams and Wood (2012), and Saunders et al. (2006) measured startle blinks.

3.5.1.1.1. Corrugator supercilia and zygomaticus major activity

de Sousa et al. (2010) reported higher ZM activity for pleasant pictures than for unpleasant and neutral pictures in both groups. A main effect of valence was also observed for CR, with higher activity for unpleasant pictures than for pleasant and neutral pictures. Moreover, an interaction between valence and group emerged, with significantly lower responses to unpleasant versus neutral pictures and marginally reduced activity to unpleasant versus pleasant pictures in the TBI group compared to controls. Interestingly, TBI participants self-rated these unpleasant pictures as less unpleasant and arousing than controls. Finally, while a positive correlation was observed between emotional and cognitive empathy scores and CR to unpleasant pictures in the control group, no correlation was observed in the TBI group. According to the authors, impaired emotional responsivity is associated with the impairment of the empathy network. In a study by Soussignan et al. (2005), a valence effect was observed in the control group with higher CR activation for unpleasant pictures and higher ZM activation for pleasant pictures. In contrast, participants with TBI's ZM and CM activity did not differ according to the valence of the picture. Notably, Soussignan et al. (2005) study examined only one patient with TBI, but it contained three times more pictures (54) than de Sousa et al.'s (2010) study. However, the data reduction methods used in these two studies were similar (see above).

3.5.1.1.2. Startle blink

Sánchez-Navarro et al. (2005) found a main effect of valence on blink magnitude in both groups, with larger blinks for unpleasant pictures than pleasant ones. In the control group, the blinks were larger during unpleasant than neutral pictures and lower during pleasant than neutral pictures. In contrast, in the TBI group, the difference between the unpleasant and neutral pictures did not reach statistical significance, and no difference between the pleasant and neutral pictures was observed. Finally, the intergroup comparison revealed that TBI participants showed lower startle blinks to unpleasant pictures and higher responses to pleasant pictures compared with the control group. Williams and Wood (2012) also found a valence effect in the control group, with linear amplitude increasing for pleasant, neutral, and unpleasant pictures. This linear pattern was also observed in the TBI group, but the differences among the three conditions were not significant. Moreover, like Sánchez-Navarro et al.'s (2005) results, unpleasant pictures produced larger startle responses in the control group than in the TBI group; however, no group effect was observed for neutral pictures. However, unlike in the latter study, no group effect was observed for pleasant pictures. Finally, Saunders et al. (2006) showed a trend of increasing blink amplitude from pleasant to neutral and unpleasant pictures in the control group. However, the TBI group produced higher blinks for neutral pictures than for pleasant and unpleasant pictures. Owing to this unusual and unexplained result, the authors compared blinks to pleasant and unpleasant pictures in TBI and control participants. The control group displayed an attenuation of the startle eyeblink response for pleasant pictures and potentiation for unpleasant pictures, whereas TBI participants demonstrated an attenuated startle eyeblink for both pleasant and unpleasant pictures. Saunders et al. (2006) also measured eyeblink latency as an index of interest in pictures. The TBI group was significantly slower to reach peak eyeblink response for both positive and negative pictures than the control group. In conclusion, these three studies show that blink reflexes are less differentiated according to the valence of the pictures after TBI and are attenuated for unpleasant pictures. Note that Sánchez-Navarro et al.'s (2005) study contained five patients with stroke and used 54 pictures (18 per category), whereas Williams and Wood (2012) and Saunders et al. (2006) included only TBI patients and used only 15 pictures (5 per category) and 18 pictures (6 per category), respectively. Williams and Wood (2012) and Sánchez-Navarro et al. (2005) also present startle probes in the absence of pictures. Williams and Wood (2012) found no significant differences across groups during the baseline of 12 startle probes before the presentation of the pictures. Sánchez-Navarro et al. (2005) reported significantly larger startle blinks in the control group than in the TBI group; however, these measurements were taken during the interstimulus phases between two pictures. For data reduction, the three studies standardized the raw amplitude in *z* scores and transformed them to *t* scores.

3.5.1.2. Facial expressions

Two studies measured EMG in response to the passive viewing of pictures of angry and happy faces (Saunders et al., 2006; de Sousa et al., 2011). First, de Sousa et al. (2011) measured the contraction of the ZM and CR muscles and observed that happy faces elicited greater ZM activity than angry faces in both groups. However, the control group exhibited greater CR activity for angry faces than for happy faces, whereas no emotional effect was observed in the TBI group. Analyzes according to the level of emotional empathy showed similar ZM responses for the higher empathy TBI group and the control group, with happy faces evoking larger ZM responses than angry faces. In contrast, no group or emotional effects emerged in the low-emotional-empathy group. Concerning CR activity, responses were higher for both faces in the normal emotional empathy TBI group than in their control counterparts. However, in the low emotional empathy group, whereas control participants exhibited greater CR activity in response to angry faces compared to happy faces, the TBI group demonstrated an inverse pattern, with higher CR activity in response to happy faces compared to angry faces. These authors concluded that the loss of emotional empathy after TBI could contribute to the lack of CR reactivity in response to angry faces. Second, Saunders et al. (2006) measured eyeblink startles and showed no group or emotional effects.

3.5.2. Films

de Sousa et al. (2012) and Rushby et al. (2013b) studied facial reactivity during the same movie clips. As mentioned in the previous section, the data collection of these two studies occurred concurrently; the first paper focused on physiological responses to the first viewing of each film clip, while the second examined physiological patterns across five separate viewings of each film. de Sousa et al. (2012) reported a reduced facial response in the TBI group. Indeed, the control group exhibited greater ZM activity for pleasant films than for neutral or unpleasant films, whereas the TBI group showed no emotion effect. The same pattern was observed for CR: the control group displayed greater activation for unpleasant films than for pleasant and neutral films, while there was no valence effect in the TBI group. Interestingly, a different pattern in the two groups was observed for the mean change in ZM activation during the clips. While ZM activity increased over time in the

control group, especially for pleasant films, it decreased in the TBI group, especially for unpleasant films. Unlike ZM, the same effect over time of increasing CR for unpleasant films and decreasing CR for pleasant films was observed in both groups. These authors suggest that the "contagion" effect was amplified with time, especially in the control group. Contrary to the results of de Sousa et al. (2012) and Rushby et al. (2013a) reported no changes in ZM activity in patients with TBI, as both groups exhibited greater ZM activity for pleasant clips than for neural and unpleasant clips. Contrary to expectations, separate analyzes according to the self-reported level of emotional empathy of TBI participants showed a larger ZM response for the group with low empathy scores than for those with normal to elevated self-reported empathy scores. Moreover, the TBI group exhibited greater CR activity across all film types than the control group. Finally, the valence effect, characterized by a higher CR activation for unpleasant films than for neutral and pleasant films, was observed in both groups. In their discussion, Rushby et al. (2013a) explained the contradiction of their results with those of de Sousa et al. (2012) by the fact that repeated watching might normalize the ZM reactivity in TBI participants. Moreover, repeated watching requires more attention after TBI, which is marked by a higher CR activity in this group. As mentioned in the EDA section, the data standardization methods were similar in both studies.

3.5.3. Odors

In addition to the IAPS pictures task, Soussignan et al. (2005) measured facial reactivity during the olfactory task described above. Control participants exhibited a main effect of valence with higher CR activity for unpleasant odors and greater ZM activity for pleasant odors, but participants with TBI showed no difference between these conditions, consistent with their picture task results.

3.6. Cardiac measures

Across seven studies on cardiac measures, four measured HR (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Krpan et al., 2011; Rushby et al., 2013b), two measured HRV (Amorapanth et al., 2016; Francis et al., 2016) and one measured evoked cardiac deceleration (ECD; McDonald et al., 2011). HRV refers to the variation in the time interval between heartbeats. This is an interesting index of the influence of the ANS on HR (Laborde et al., 2017). The ANS comprises an activating sympathetic branch and inhibiting parasympathetic branch. These two branches are responsible for the acceleration and deceleration of the HR, respectively. HRV can be quantified using time-domain and frequency-domain methods. In time-domain methods, the standard deviation of interbeat intervals (SDNN) and the root-mean-square of interbeat intervals (rMSSD) are often used as a global measure of temporal variability. Frequency-domain methods disentangle the influence of the parasympathetic and sympathetic systems on HRV. The low frequency (LF) component of HRV reflects both parasympathetic and sympathetic influences while the high frequency (HF) component reflects the parasympathetic influence (Shaffer and Ginsberg, 2017). Respiratory sinus arrhythmia (RSA), which refers to the phenomenon of HR acceleration on inspiration and HR deceleration on expiration, is also an indication of the influence of the parasympathetic system on HRV. Finally, ECD reflects the orienting attentional reflex toward new stimuli. This is the difference between the pre-stimulus baseline period and the slowest HR obtained during the post-stimulus period of the epoch (Graham and Clifton, 1966). A small majority of the cardiac studies in this review found similar responses for participants with TBI and controls. Indeed, across the four HR and ECD studies, two reported statistical differences between groups (McDonald et al., 2011; Rushby et al., 2013b) while the rest found no significant differences (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Krpan et al., 2011). In the two HRV studies, significant differences were found in the frequency domain for LF and HF (Amorapanth et al., 2016). Another study reported high inter-individual differences in the TBI group, but no statistical difference between the groups (Francis et al., 2016).

3.6.1. Pictures

3.6.1.1. International affective picture system pictures

Two articles reported HR during the presentation of IAPS pictures. First, Sánchez-Navarro et al. (2005) reported no difference between groups, as unpleasant and pleasant pictures produced higher HR deceleration than neural ones in both groups. Moreover, no difference was observed between the HR deceleration elicited by pleasant and unpleasant pictures. However, in Soussignan et al.'s (2005) study, for both groups, only the unpleasant pictures produced higher deceleration than the pleasant and neutral ones. Like Sánchez-Navarro et al.'s (2005) findings, no statistical difference was observed between the TBI and control groups. As discussed, these studies both contained 54 pictures (18 per category), but de Sousa et al.'s (2010) data reduction method subtracted the baseline pre-stimuli, whereas Sánchez-Navarro et al. (2005) used a log transformation [log (SCR-1)]. Finally, as mentioned above, Sánchez-Navarro et al. (2005) included patients with frontal stroke.

3.6.1.2. Facial expressions

McDonald et al. (2011) were interested in ECD that occurs after angry and happy face presentations in a passive viewing condition and an attended emotional recognition condition. In both groups, a conditioning effect was observed, with higher ECD in the attended condition than in the passive condition. The control and TBI participants exhibited ECD to the emotional faces, with no difference between angry and happy expressions in either group. However, in the attended condition, ECD magnitude increased across repetitions. This increase was greater in the control group than that in the TBI group. *Post hoc* analyzes revealed that the control group exhibited an ECD increase for happy faces across repetition and a decrease for angry faces, whereas no difference between faces over trials was observed in the TBI group. Finally, no correlation between ECD and emotion recognition accuracy was found in either the group or condition. The authors concluded that there was an improvement in the orientation reflex due to increased attentional demand after TBI. However, the relationship between this and the emotion recognition accuracy remains unclear.

3.6.2. Movies

Amorapanth et al. (2016) measured HRV during clips that elicited amusement, sexual amusement, sadness, or fear, compared to neutral films. No difference between the groups was observed for parasympathetic activity during RFA. However, for sympathetic activity, participants with TBI exhibited lower LF during amusement films than control participants. Conversely, TBI participants showed a higher LF during sad films than the control group. This increase in sympathetic activity for the sad film was correlated with self-reported attentional

difficulties and impairment in visual attention shifting during the rapid number naming test. The authors concluded that attentional difficulties may contribute to abnormal reactivity to sad stimuli. In Rushby et al.'s (2013b) study, participants viewed five repetitions of six 2-min film clip segments containing pleasant, unpleasant, and neutral content. In the control group, the average HR over time showed a small increase across film repetitions, whereas a large deceleration was observed in the TBI group. The authors explained this HR deceleration over time by the attentional effort involved in sustaining attention to repetitions. Taken together, these two studies seem to link cardiac reactivity and attentional difficulties following TBI. However, the comparability of patients in these two studies cannot be guaranteed. Indeed, the Rushby et al. (2013b) patient group contained only severe TBIs, but Amorapanth et al. (2016) did not specify the severity of the TBI and included patients with cognitive or emotional impairment. Moreover, the type and number of film clips used differed between the two studies. Indeed, both studies contained films from similar validated and normed sets; however, Rushby et al. (2013b) also included films used in previous research, not from validated sets. In addition, Amorapanth et al. (2016) used 11 different clips (two per emotional category and one neutral), whereas Rushby et al.'s (2013b) study only contained six clips (two per category). Finally, the data reduction methods used were different. Rushby et al. (2013b) computed the HR signals by subtracting the mean activity at baseline prior to that occurring in the first 90 s of each film. Amorapanth et al. (2016) first determined an interval of interest (IOI) which was the 30 s of the film clip that most strongly elicited the target emotion (the authors did not specify whether this IOI was determined based on self-reported data or physiological data). Second, RFA and LFA were standardized by dividing the baseline activity 30 s before IOI. Third, logarithmic transformation was performed for each variable.

3.6.3. Odors

The study by Soussignan et al. (2005) did not show HR modulations in response to odors according to valence or group.

3.6.4. Social stress situation

Krpan et al. (2011) measured HR during psychosocial test stress (see description above) and did not report differences between the groups. As expected, controls and participants with TBI exhibited increased HR when performing the psychosocial stress test compared with the 5 min' baseline.

3.6.5. Resting state

Three studies reported the cardiac data at rest. First, Francis et al. (2016) measured HRV at rest and during an HRV biofeedback session in which participants reduced their breathing to six breaths per minute. Concerning HRV at rest, the TBI group showed higher within-group variability in the temporal and frequency domains, especially for HF and LF/HF ratio. The authors presented this LF/HR ratio as an index of sympatho-vagal balance, but the accuracy of this measure has been questioned (Billman, 2013). After a log transformation value, no difference between the groups was observed in the time and frequency domains. In the TBI group, HRV at rest was correlated with self-reported measurements of alexithymia, empathy, emotion perception, and social cognition abilities. Specifically, SDNN, rMSSd, LF, and HF positively correlated with self-reported empathy and social cognition performance. SDNN and LF negatively correlated with self-reported alexithymia. The authors did not specify the values of these correlations for the control group. Finally, the HRV changes for the time and frequency domains during biofeedback were similar in both groups. Second, for HR data, Sánchez-Navarro et al. (2005) and Krpan et al. (2011) did not observe any difference between control and TBI during their 3- and 5-min baseline.

3.7. Cortisol

A single study, led by Krpan et al. (2011), measured cortisol levels and reported no difference between the groups before and after the psychosocial stress test (described above).

4. Discussion

This systematic review aimed to detail the main findings of 18 studies published between 2000 and 2021 and examine electrodermal, facial, cardiac, and cortisol reactivity to emotional stimuli, odors, social stressors, and at rest among individuals with moderate to severe TBI. The findings showed discrepancies depending on the type of physiological measures and stimuli. First, patients with TBI often showed reduced electrodermal responses compared to controls. Across the 14 studies measuring EDA, 11 studies reported lower EDA after TBI during picture presentations, movies, participants' verbal report (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010, 2011, 2012; McDonald et al., 2011; Rushby et al., 2013a, 2016; Fisher et al., 2015; Aboulafia-Brakha et al., 2016; Osborne-Crowley et al., 2020), two studies using a social stress situation paradigm found no difference between groups (Krpan et al., 2011; Kelly et al., 2017) and one reported higher SCL in the TBI group during a verbal report task of anger event recall (Aboulafia-Brakha et al., 2016). Lower reactivity was also observed for CR contraction and blink reflex in EMG studies. Across five studies measuring CM, four reported lower CM activation in the TBI group during film or picture presentation (Soussignan et al., 2005; de Sousa et al., 2010, 2011, 2012). Concerning the startle blink, three studies showed that responses of patients with TBI were less differentiated according to picture valence and attenuated for unpleasant pictures (Sánchez-Navarro et al., 2005; Saunders et al., 2006; Williams and Wood, 2012). In contrast, patients with TBI displayed significantly reduced ZM activity in only one of four studies (Soussignan et al., 2005). Similarly, the impact of TBI on PR was not so clear in ECG studies; among the seven reviewed studies, only two reported lower HRV or ECD in the TBI groups (McDonald et al., 2011; Amorapanth et al., 2016), four found no difference (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Krpan et al., 2011; Francis et al., 2016) and one reported higher HR deceleration across film repetitions (Rushby et al., 2013b). Finally, the only study measuring cortisol levels did not show abnormalities in the TBI group (Krpan et al., 2011). To explain these PR inconsistencies, we will discuss the role of neurophysiological factors as well as emotional, sociodemographic, and methodological factors.

The defense system reduced activation in TBI patients is our first hypothesis, as they may experience reduced affective responsivity, particularly to aversive and unpleasant-negative stimuli (Saunders et al., 2006; de Sousa et al., 2010; McDonald et al., 2011; Williams and Wood, 2012). According to motivational theory, two dimensions of motivation compose emotional responses: defensive for aversive stimuli and appetitive for attractive stimuli (Lazarus, 1991). The physiological pattern of defensive reactions reflecting sympathetic activation to provide energy and facilitate adaptive behaviors such as attack or escape,

involves limbic brain structures, including the amygdala (Adolphs, 2001). This last interpret signals from the environment as a threat that triggers an alarm signal, induced by specific ascending systems of the brainstem. First, through the hypothalamus, it activates the functions of sweat glands, resulting in EDA (Christopoulos et al., 2019). Although EDA is not exclusively related to the defence network, studies have reported that the direct stimulation of the amygdala generates an immediate increase in EDA (Lang et al., 1964; Inman et al., 2020). Second, facial motoneurons of the brain stem activate cranial nerve VII which produces contraction of the orbicularis muscle, resulting in a blink startle reflex (Kettle et al., 2006). Third, fibers descending from the brainstem innervate the preganglionic neurones of the sympathetic system. The activation of sympathetic fibers results from an increase in adrenaline in the bloodstream and causes the release of noradrenaline at sympathetic nerve endings. This produces measurable physiological responses, such as an increase in cardiorespiratory rate. Finally, the amygdala is involved in CR contraction. Indeed, electrical stimulation induces an increase in the EMG activity of the CR (Lanteaume et al., 2007). Moreover, increases in CR activity during negative picture viewing are associated with greater amygdala activity (Heller et al., 2014).

Although the TBI population is heterogeneous in terms of the location and severity of the injury, the frontal and temporal areas (including important limbic structures such as the amygdala) are particularly vulnerable to brain damage. The hypothesis of reduced affective responsivity in TBI could explain the lower CR activation and startle blinking together with the absence of ZM activity differences (Sánchez-Navarro et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011; Williams and Wood, 2012; Rushby et al., 2013b). CR and startle blinks are activated in response to unpleasant aversive stimuli. The ZM is activated in response to pleasant stimuli. Finally, the lower EDA observed in most TBI groups in the reviewed EDA studies is consistent with this aversive defence system disturbance.

The lack of difference between the groups in ECG studies could be explained by the implication of processes other than the aversive system in the cardiac reflex. Like EDA, CM activation, or the startle reflex, some cardiac reactions are implicated in the aversive defence system (i.e., the defence reflex). The defence reflex is characterized by heart acceleration to provide energy to facilitate adaptive behaviors such as attack or escape (Lang et al., 2000). However, other cardiac reflexes are also correlated with the attentional process, such as the orienting reflex. This orienting reflex causes heart deceleration. It is elicited by a novel stimulation to facilitate the attention and perception of the stimulus (Vila et al., 2007). Cardiac deceleration reflects the processing of new perceptual information. This type of reflex is less affected by the valence of the stimulus than is the defence reflex (Bradley, 2009). According to Phillips et al.'s (2003) neural model of emotional perception, attentional processes during emotional perception are mediated by the dorsal system. The identification of the emotional significance of stimuli and the production of the affective state are mediated by the ventral system which includes the amygdala. These reflexes depend on two different processes and the neural system. This dissociation between the orienting and defence reflexes could explain the discrepancy between the cardiac studies in our review. The orienting reflex was preserved after the TBI. This is consistent with the HR deceleration in both groups after the presentation of the pleasant and unpleasant pictures reported by Sánchez-Navarro et al. (2005). In McDonald et al. (2011), both groups demonstrated an increase in heart rate deceleration in the attend condition relative to the passive condition. However, in Soussignan et al.'s (2005) study, deceleration was not affected by the valence of emotion in the TBI group. Rushby et al. (2013b) observed HR acceleration and deceleration in the control and TBI groups, respectively.

However, given the unequal distribution between the study measures, these interpretations should be considered with caution. Indeed, across the 18 studies included in this review, 13 examined EDA measures, whereas only eight measured ECG or EMG and only one cortisol. It would be important to gather more data to identify a clear trend. Moreover, as a given emotional stimulus did not have the same effect on all physiological measures, future studies should take several measures simultaneously (Lydon et al., 2016). This refers to the directional fractionation phenomenon as described by Lacey (1967). Accordingly, a specific stimulation gives rise to a particular multidimensional activation pattern. For example, the orientation reflex results in an increase in EDA together with a deceleration of HR. In contrast, the increase in EDA is associated with an acceleration of HR during a defence reflex.

A second hypothesis would concern the level of empathy of the TBI participants involved in the studies. Empathy is crucial to understand and respond appropriately to the emotional experience of others (Decety and Ickes, 2011). Cognitive empathy refers to the ability to adopt another person's point of view, while emotional empathy refers to the ability to experience affective reactions to the emotional displays of others. Emotional empathy implies a mimicry of the physiological reactions of the others and, accordingly, PR to emotional stimuli is an important component of emotional empathy (de Wied et al., 2006; Nummenmaa et al., 2008; Bogdanov et al., 2013; Sonnby-Borgström, 2002). The literature has shown a decrease of emotional empathy after a TBI (de Sousa et al., 2010, 2011; Williams and Wood, 2012) contributing to the behavioral disorders frequently reported in this population (Milders, 2019). Several studies in this review investigated the link between PR and empathy (de Sousa et al., 2010, 2011, 2012; Rushby et al., 2013b; Francis et al., 2016; Osborne-Crowley et al., 2020). However, the results differed between studies according to the group of participants. Indeed, de Sousa et al. (2011) and Rushby et al. (2013b) found a positive correlation between EDA and emotional empathy in TBI group only. In addition, de Sousa et al. (2011) revealed the same SCR pattern in the "normal" level of empathy group for both controls and TBI participants, while in the low level of empathy group, this pattern differed between control and TBI participant. These results suggested that a loss of empathy after TBI leads to abnormal PR. There would be two subgroups across the TBI population: one with a preserved level of empathy and PR and another with reduced empathy affecting their PR. The abnormal EMG responses found in the lower empathy TBI groups of Rushby et al. (2013b) and de Sousa et al. (2011) support this assumption that a loss of empathy after TBI impacts the PR. But some results contradicted the idea that TBI participants with higher emotional empathy have preserved PR like those of control groups. Indeed, the TBI participants of de Sousa et al. (2011) with "normal" levels of emotional empathy demonstrated higher CM contraction than controls. In addition, Osbourne did not find a difference in self-reported emotional empathy between TBI participants and controls, while the TBI participants exhibited reduced EDA. This intact emotional empathy in the TBI group highlights the heterogeneity of emotional profiles after a TBI. In their discussion, de Sousa et al. (2012) suggested that two profiles of emotional disorder can be found in the TBI population. One is characterized by a loss of emotional control and higher emotional empathy levels, the other by an impaired drive (or motivation) and lower levels of emotional empathy. The loss of emotional control can correspond to impulsive profiles while the loss of drive corresponds to

apathetic profiles (Tate, 1999). Indeed, TBI can lead to various behavioral disorders that can range from general hypoactivity with apathy, abulia and loss of psychic self-activation to general hyperactivity with impulsivity, distractibility, and disinhibition (Godefroy, 2004). Apathy after TBI has been linked with lower PR (Andersson et al., 1999). Beyond the level of empathy, apathy and this involvement with PR should be more investigated. The decrease of empathy after a TBI could be the consequence of a general lack of interest and loss of motivation. The study of the relation between PR and apathetic profiles could contribute to understanding the discrepancies observed across the studies reviewed.

Related to this idea of the influence of apathy on PR after TBI, one explanatory factor for PR inconsistency across studies is the attentional demands of the tasks. Overall, the physiological differences between TBI and controls are more pronounced in studies involving passive tasks (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010, 2011, 2012; McDonald et al., 2011; Williams and Wood, 2012; Rushby et al., 2013a, 2016; Fisher et al., 2015; Amorapanth et al., 2016). These differences tend to diminish for studies in which participants are active (Krpan et al., 2011; McDonald et al., 2011; Aboulafia-Brakha et al., 2016; Francis et al., 2016; Kelly et al., 2017). This trend suggests that attend tasks could overcome the hypo reactivity induced by apathy in TBI participants. Future research should consider the effect of attentional demand of the task on PR after TBI.

In parallel, the presence of psychopathological disorders in patients with TBI may also influence PR. For instance, brain lesions often result from a traumatic experience (fall, traffic accident, interpersonal violence, war injury) and post-traumatic stress disorder (PTSD) is particularly frequent in TBI patients (Williams et al., 2002). In the general population, PTSD affects 27% of patients with severe TBI (Bryant et al., 2000) but the frequency of PTSD may reach 89% in war veterans with mild TBI (Carlson et al., 2011). As this review is the first to focus on PR after TBI, we have chosen not to include studies focusing on PTSD. However, PTSD has been associated with hyperarousal (Weston, 2014) and future studies should consider PTSD symptoms and their impact on PR in TBI participants.

In addition, demographic factors, like age and gender, also have an impact on PR. Indeed, PR declines with age (Neiss et al., 2009) and women exhibited higher PR for emotional stimuli than men (Bianchin and Angrilli, 2012). In this review, we noticed differences in age and gender distribution across the TBI participants and control samples. First, TBI patients were generally older than control participants. The mean age was 43 years old for TBI and 37 for control participants. Since PR to emotional stimuli declines with age (Gavazzeni et al., 2008), future studies should further match their samples by age and control the influence of age on their PR results. Secondly, the number of men was higher in TBI samples than in the control samples. This difference is not surprising as TBI occurs more frequently in men. Indeed, TBI usually results from risk-taking behaviors (traffic accidents, contact and extreme sports) or accidents at work in male-dominated professions (i.e., construction, military occupations; Iverson et al., 2011; Colantonio, 2016). In Europe, the prevalence of TBI is significantly higher in men than in women (independently of age, severity, and mechanism of injury), ranging from 55% in Sweden in 2001 to 80% in Ireland in 2005–2007 (Peeters et al., 2015). In The United States, men are approximately 40% more likely to suffer a TBI than women (Coronado et al., 2012). But in our case, these gender-based differences could contribute to the lower PR observed in TBI participants, as men exhibited lower PR than women (Bianchin and Angrilli, 2012; Bari, 2020). Therefore, this lack of gender matching in the samples limits the interpretation of several studies. Accordingly, we recommend considering the effect of gender on emotional responses in future research. Specifically, the persistence of the gender effect on PR after moderate to severe TBI should be investigated.

The amount of time post-injury could also contribute to the PR discrepancies. Most of the studies in this review used an inclusion criterion of at least one-year post-trauma. However, five studies did not use this criterion and included patients less than one year after their injury (Sánchez-Navarro et al., 2005; de Sousa et al., 2011; Williams and Wood, 2012; Aboulafia-Brakha et al., 2016; Amorapanth et al., 2016). According to the neuroplasticity principles, the brain recovers and restructures itself after an injury (Nudo, 2013). After a TBI, spontaneous recovery, which refers to the recovery of neurotransmission in spared tissue near and remote from the site of injury (Levin, 2003), occurs within six months after the injury (Nakamura et al., 2009). However, training can also induce plastic changes in the brain occurring months to years after injury (Chen et al., 2010). Conversely, TBI induced irreversible neurodegenerative changes related to widespread brain atrophy. This atrophy progresses over several months and perhaps even years post-injury (Sidaros et al., 2009). Therefore, studies on PR should preferably include patients only one year after their injury to minimize the influence of these processes on PR.

The heterogeneity of patient injuries between samples may also explain PR discrepancies. While focusing on moderate to severe TBI, our review also integrates studies with patients with mild TBI (Aboulafia-Brakha et al., 2016) or ischemic stroke (Sánchez-Navarro et al., 2005), raising the question of the influence of these differences. Only Aboulafia-Brakha et al. (2016) report higher reactivity for TBI group compared to the control. Their inclusion of patients with mild TBI may contribute to this higher reactivity. Since neurocognitive sequelae and the dysfunction of the ANS highly vary regarding the severity of the TBI (Dikmen et al., 2009; Esterov and Greenwald, 2017; Hilz et al., 2017), each study should include only one type of TBI. Second, with a group including stroke patients, Sánchez-Navarro et al. (2005) reported the valence effect of IAPS pictures while this effect was attenuated in the related studies (Soussignan et al., 2005; Saunders et al., 2006; de Sousa et al., 2010; Williams and Wood, 2012), supporting the potential influence of stroke patients' inclusion on this valence effect. Although with brain injuries of the same size and location, patients with TBI and stroke may experience equal neurological, cognitive, and psychological disorders (Castor and El Massioui, 2018), spontaneous recovery would be about three months shorter after a stroke than after a TBI (Chen et al., 2010). Therefore, it seems appropriate to balance samples between TBI and stroke patients if their injuries and deficit profiles are comparable and respect the one-year post-injury delay (see above). To ensure the recruitment of patients with the same profiles, we recommend assessing psychological and neurocognitive deficits and ensuring that the patients present lesions of the same size and location. This inclusion of studies that did not respect post-injury delay and homogeneity of patients group limited general inferences in our review, but it also permitted us to highlight the major role of both methodological issues in future research.

A last factor that could explain PR discrepancies is the divergence between data recording and recording methods across the studies. These divergences were particularly marked in EDA studies. Regarding data recording, we noted differences or lack of information about the sampling rate. The sampling rate refers to the number of samples of the signal taken per second and is measured in hertz (Hz). The data quality and the possibility of smoothing them depend strongly on the selected sampling rate, but several studies do not specify them. For those that

did, most used a sampling rate of 100 Hz, while only Rushby et al. (2016) used 256 Hz. According to the Nyquist theorem, to accurately reproduce the signal the sampling rate must be at least twice as high as the highest frequency in the signal (Landau, 1967). The EDA is considered as a 'slow measure' with a maximal frequency of 35 Hz (Boucsein, 2012); therefore, a sampling of 70 Hz should be enough. However, if the analysis requires the separation of phasic waveforms from tonic signals, which is the case in most of the studies in this review, a sampling no lower than 100–200 Hz is recommended (Figner and Murphy, 2011). In addition, smoothing procedures are sometimes necessary to remove noise from the signal. These procedures, which involve down-sampling, have less impact on the quality of the signal at higher sampling rates. However, the studies in this review did not specify whether they used smoothing methods for EDA data. Given the low sampling rates used in these, these procedures could have an impact on the quality of their data. Therefore, we recommend using sampling rates of at least 100–200 hz. Furthermore, we encourage future studies to specify the values of the sampling rate used and, if applicable, the type of smoothing method used. Discrepancies were also noticeable in the data reduction methods. For example, for the three studies using IAPS pictures, Soussignan et al. (2005) and de Sousa et al. (2010) derived SCR from a pre-stimulus baseline, but its length differed by one second. Sánchez-Navarro et al. (2005) used log transformation [log (SCR-1)] without a pre-stimulus baseline. Regardless of the type of stimulus, this discrepancy in data reduction procedures appears in all EDA studies. Moreover, some authors did not use the baseline to reduce the data or did not specify it (Krpan et al., 2011; Fisher et al., 2015; Aboulafia-Brakha et al., 2016). This lack of methodological specification raises questions as it does not allow for the replicability of studies. Other studies used the baseline before the experiment (de Sousa et al., 2011, 2012; Rushby et al., 2013b; Kelly et al., 2017) or directly before each stimulus (Sánchez-Navarro et al., 2005; Soussignan et al., 2005; de Sousa et al., 2010, 2011; McDonald et al., 2011; Osborne-Crowley et al., 2020). Finally, some authors used log transformation in addition to baseline subtraction (Sánchez-Navarro et al., 2005; de Sousa et al., 2011; McDonald et al., 2011; Kelly et al., 2017). To the best of our knowledge, there is no recognized reference method for physiological data standardization. This is a matter of debate in the EDA literature (Caruelle et al., 2019). The guide issued by the Biopac MP36R & Acknowledge software (Braithwaite et al., 2013) provides some suggestions for EDA data standardization and normalization. First, it is important to distinguish between normalization and standardization methods. The foremost method is intended to correct the data for parametric statistical analysis. If the data are not normally distributed, it is recommended to apply logarithmic or square-root transformations for the SCL and SCR amplitude measurements. As SCR magnitude measurements include data of 0, the log SCR + 1 transformation is recommended for this type of measure. Second, standardization methods are corrections that reduce inter-individual variability and facilitate the comparison of data. There are two common standardization methods. The first is to subtract for SCL or divide for SCR the maximum data from the minimum data taken at rest or during a baseline. But this method is controversial for two reasons: (1) the minimum value depends on the sensitivity of the device and may not correspond to the true value, and (2) the maximum value is inconsistent, even within the same individual (Dawson et al., 2016). To avoid this problem, it is recommended to use a second method of transformation into standard values such as Z-scores, by taking the mean value and standard deviation (Ben-Shakhar, 1985).

To conclude, this review is the first systematic study of PR after moderate-to-severe TBI. This review highlights methodological discrepancies regarding the collection and analysis of physiological data and composition of participants with TBI. For each of these, we propose concrete proposals for improvement in future studies. Furthermore, this systematic analysis made possible to highlight the physiological divergence according to the type of measurement. Based on this, we hypothesized their link with brain injuries after TBI and their impact on the underlying emotional process. We also discuss the role of emotional, sociodemographic on PR. However, studies with multiple simultaneous physiological measures and more homogeneous and controlled TBI samples are needed to test these hypotheses. Finally, the study of PR is the first step in understanding emotional processes and underlying body–brain interactions. The assessment of interoceptive abilities, that is, the perception of the state of the body (Ceunen et al., 2016), is the next step. Indeed, in the emotional process, PR is only effective if the individual is aware of it (Damasio, 2000). Since interoception modulates emotional experience, future studies should also assess this dimension. This will allow for a better and more complete understanding of emotional disorders in this population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AB designed the study, searched the scientific literature, collected data, performed the analyzes, and drafted the manuscript. SI was an independent reviewer who conducted the cross-check. MR revised the manuscript. All authors have contributed to and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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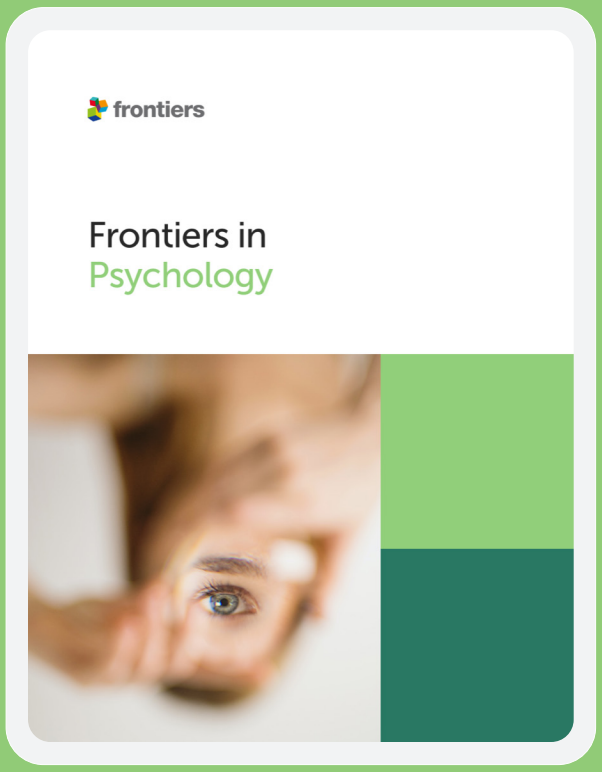

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