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Methods and applications in psychopathology: New methods and trends for the understanding of neuropsychiatric disorders

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Published in
Frontiers in Psychiatry
Frontiers in Psychology

ISSN 1664-8714
ISBN 978-2-8325-3160-0
DOI 10.3389/978-2-8325-3160-0

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Methods and applications in psychopathology: New methods and trends for the understanding of neuropsychiatric disorders

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Citation

Chen, C., Nibbio, G., Kotozaki, Y., eds. (2023). *Methods and applications in psychopathology: New methods and trends for the understanding of neuropsychiatric disorders*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-3160-0

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frontiers | Frontiers in Psychology

TYPE Editorial
PUBLISHED 20 July 2023
DOI 10.3389/fpsyg.2023.1242921

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 20 June 2023
ACCEPTED 11 July 2023
PUBLISHED 20 July 2023

CITATION
Chen C, Nibbio G and Kotozaki Y (2023) Editorial: Methods and applications in psychopathology: new methods and trends for the understanding of neuropsychiatric disorders. *Front. Psychol.* 14:1242921. doi: 10.3389/fpsyg.2023.1242921

Editorial: Methods and applications in psychopathology: new methods and trends for the understanding of neuropsychiatric disorders

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KEYWORDS

psychopathology, depressive disorders, anxiety disorders, psychiatric diseases, computational psychiatry, data-driven approach, probability weighting, latent-class analysis

Editorial on the Research Topic
Methods and applications in psychopathology: new methods and trends for the understanding of neuropsychiatric disorders

Neuropsychiatric disorders are highly prevalent and are causing an enormous disease burden globally. For instance, according to an estimation by the World Health Organization, 4.4 and 3.6% of the global population lived with depressive and anxiety disorders in 2015, respectively (World Health Organization, 2017). The Global Burden of Diseases, Injuries, and Risk Factors Study estimated that in 2019, mental disorders accounted for 4.9% of global disability-adjusted life-years (DALYS), making it one of the top ten leading causes of disease burden globally (GBD 2019 Mental Disorders Collaborators, 2022). One of the most important causes of such a high prevalence, high disability of neuropsychiatric disorders is our lack of precise understanding of the psychopathological and neurobiological mechanisms underlying these disorders, which holds us back from developing effective prevention and treatment strategies.

This Research Topic is a collection of eleven cutting-edge studies that help advance our understanding of the psychopathological and neurobiological mechanisms of neuropsychiatric disorders with novel methods and techniques. Specifically, six studies take a computational psychiatry approach. One study takes a neuroimaging approach, one genetic approach, and one psychometrical approach. Finally, two studies take a meta-analytic approach.

Computational psychiatry represents a novel approach that tries to solve problems in psychiatry by applying mathematical methods (Montague et al., 2012; Chen et al., 2015; Friston, 2023). One theory-driven approach attempts to provide mechanistic insights by specifying and testing psychological and neurobiological processes that are believed to generate the illness or its symptoms. This approach is in line with current conceptualization of mental disorders based on neurobiological processes such as the Research Domain Criteria (RDoC) project (Insel et al., 2010; Barlati et al., 2020) and the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2022). Another data-driven approach attempts to make predictions of diagnosis or treatment with a theory-free perspective by

employing various statistical models and machine learning algorithms. Six articles in this Research Topic employ either a theory- or data-driven approach.

Soda et al. provides mechanistic insights into developmental disorders with a computational model that combines hierarchical Bayesian models and neural network models. In this model, the agent learns the underlying probabilistic structure of the environment with a neural system that acquires a hierarchical Bayesian representation of the underlying structure. In their simulation, the authors manipulated the neural stochasticity in the environment during learning and found that when the neural stochasticity is low (meaning that neural noise is low and that the agent's behavior tends to be deterministic), the agent showed altered hierarchical representation and reduced flexibility, mimicking cognitive changes in developmental disorders. Gauld and Depannemaecker proposes a generic model aimed at capturing the dynamics of psychiatric symptoms. In this model, the symptoms of psychiatric diseases are simulated with internal factors, temporal specificities and symptomatology, with environmental noises. With this model, the authors simulated three different psychiatric disorders. Schizophrenia is characterized by pathology evolving following an outbreak; bipolar disorders is characterized by kindling and bursts in symptoms; persistent complex bereavement disorder is characterized by susceptibility to the external environment (i.e., bereavement).

Hagiwara et al. tries to clarify the common vs. unique cognitive computational mechanisms associated with depression and anxiety, two disorders that often co-occur (Chen, 2022). According to the Cumulative Prospect Theory (Tversky and Kahneman, 1992), people tend to overweight small probabilities and underweight large probabilities (i.e., an inverted S-shaped nonlinear probability weighting curve). Hagiwara et al. found that subjects with more depressive but not anxiety symptoms tend to show a weakened inverted S-shaped probability weighting curve, indicating increased risk aversion at small probabilities and reduced risk aversion at large probabilities. Such an alteration in probability weighting has also been reported in females under high levels of chronic stress (Lei et al., 2021). Interestingly, two studies (Shimizu et al.; Watarai et al., 2023) demonstrate that recalling positive autobiographical memories, such as memories of a happy family vacation, affects probability weighting in a way that is in the opposite direction compared to the influence by depressive symptoms (Hagiwara et al.) and chronic stress in females (Lei et al., 2021). These findings suggest the potential usefulness of such an intervention for the treatment of altered decision-making in psychiatric disorders.

Lei et al. advances our understanding of the comorbidity of depressive and anxiety disorders by investigating the patterns of the co-occurrence of their symptoms. Using latent class analysis, a data-driven approach, the authors identified four symptoms patterns or classes that are characterized by different levels of co-occurrence of depressive and anxiety symptoms. Furthermore, each pattern is associated with distinct psychological risk factors, indicating unique etiologies. Chacko et al. provides insights into the link of stress to PTSD and obesity using natural language processing of over 10,000 peer-reviewed publications. The authors identified 34 metabolic mediators, among which Neuropeptide-Y and cortisol were found to reduce PTSD severity but worsen obesity, while oxytocin reduces both PTSD severity and obesity.

Cognitive task-based neuroimaging such as functional near-infrared spectroscopy is another useful paradigm for the study of neuropsychiatric diseases. In a perspective article, Ren et al. gives a comprehensive introduction to a multi-cognitive task paradigm that includes emotional picture identification task, verbal fluency task, and so on. By alternating between resting state and different tasks, the authors argue, this paradigm helps to probe the function of different brain networks in neuropsychiatric diseases.

Rohlfing et al. employs a genetic approach and investigates the association between catechol-O-methyltransferase (COMT) Val158Met polymorphism and substance use. COMT is an enzyme that degrades catecholamines and the presence of the Met allele in the COMT Val158Met polymorphism is associated with lower COMT activity and thus higher concentrations of extra-synaptic dopamine. The authors found that the presence of the Met allele is associated more cigarettes smoked per day and lower motivation on the monetary incentive delay task. Li et al. takes a meta-analytic approach and evaluates the effect of cognitive bias modification (CBM) on depressive symptoms in adults. CBM is a therapy grounded in the Cognitive Theory of depression which proposes that cognitive bias underlies the development and maintenance of depressive symptoms by changing the availability of negative vs. positive information (Beck and Dozois, 2011). CBM, on the other hand, aims to change these cognitive biases. Based on ten randomized controlled trials, Li et al. reported a significant effect of CBM on depressive symptoms with $g = -0.64$. Moreover, the effect size is higher for CBM targeting interpretation ($g = -1.45$) compared to targeting attention ($g = -0.63$) or imagery ($g = -0.48$). Khan et al. also takes a meta-analytic approach and estimates the prevalence of neuropsychiatric symptoms in patients with systemic lupus erythematosus (SLE) in Pakistan. Based on thirteen studies, the authors estimate that the prevalence is the highest for cognitive dysfunction (32%), followed by headache (10%), seizures (6%), and psychosis (4%). The high prevalence emphasizes the importance of effective management of neuropsychiatric symptoms in addition to clinical treatment of SLE itself. Lastly, Rakshasa-Loots and Laughton employs a psychometric approach and presents the protocol designed to test the reliability and validity of the isiXhosa Translation of the Patient Health Questionnaire (PHQ-9), a widely employed measure of depression severity.

Author contributions

Manuscript drafting: CC. Manuscript revising and approval: All authors. All authors contributed to the article and approved the submitted version.

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.

Publisher's note

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frontiers in Psychiatry

ORIGINAL RESEARCH
published: 08 February 2022
doi: 10.3389/fpsyt.2022.808918

Symptom Patterns of the Occurrence of Depression and Anxiety in a Japanese General Adult Population Sample: A Latent Class Analysis

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Background: Given the high comorbidity and shared risk factors between depression and anxiety, whether they represent theoretically distinct disease entities or are just characteristics of a common negative affect dimension remains debated. Employing a data-driven and person-centered approach, the present study aims to identify meaningful and discrete symptom patterns of the occurrence of depression and anxiety.

Methods: Using data from an adult sample from the Japanese general population (n = 403, including 184 females, age = 42.28 ± 11.87 years), we applied latent class analysis to identify distinct symptom patterns of depression (PHQ-9) and anxiety (STAI Y1). To empirically validate the derived class memberships, we tested the association between the derived classes and personal profiles including childhood experiences, life events, and personality traits.

Results: The best-fitting solution had four distinct symptom patterns or classes. Whereas both Class 1 and 2 had high depression, Class 1 showed high anxiety due to high anxiety-present symptoms (e.g., "I feel nervous") while Class 2 showed moderate anxiety due to few anxiety-absent symptoms (e.g., "I feel calm"). Class 3 manifested mild anxiety symptoms due to lacking responses on anxiety-absent items. Class 4 manifested the least depressive and anxiety-present symptoms as well as the most anxiety-absent symptoms. Importantly, whereas both Class 1 and 2 had higher childhood neglect and reduced reward responsiveness, etc. compared to Class 4 (i.e., the most healthy class), only Class 1 had greater negative affect and reported more negative life events.

Conclusions: To our knowledge, this is the first latent class analysis that examined the symptom patterns of depression and anxiety in Asian subjects. The classes we identified have distinct features that confirm their unique patterns of symptom endorsement. Our findings may provide insights into the etiology of depression, anxiety, and their comorbidity.

Keywords: comorbidity, depression, anxiety, symptom patterns, data-driven, latent class analysis

OPEN ACCESS

Edited by:
Begoña Espejo,
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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: *04 November 2021*
Accepted: *07 January 2022*
Published: *08 February 2022*

Citation:
Lei H, Chen C, Hagiwara K, Kusumi I, Tanabe H, Inoue T and Nakagawa S (2022) Symptom Patterns of the Occurrence of Depression and Anxiety in a Japanese General Adult Population Sample: A Latent Class Analysis. Front. Psychiatry 13:808918. doi: 10.3389/fpsyt.2022.808918

INTRODUCTION

Depressive and anxiety disorders (hereafter, depression, and anxiety) are the most common mental health diseases and causes enormous burden to the society (1). According to the Global Burden of Disease 2016 Study, both depression and anxiety ranked in the top 10 causes of Years Lived with Disability (YLD) in most countries and areas worldwide (2). Importantly, the two disorders often occur together, which causes greater distress (3), poorer treatment outcomes (4), and higher risk of suicide (5). For instance, data from the WHO World Mental Health Surveys indicated that 41.6% of people with 12-month major depressive disorder also had 12-month anxiety disorders (6).

In addition to the high comorbidity, the two disorders also have similar somatic symptoms, such as difficulty in sleeping and fatigue, and neuroendocrine profiles, such as the dysregulation of corticotropin-releasing factor (7). They also share substantial genetic risks (8) and have common psychopathological risk factors such as adverse childhood experience, negative life events, and enhanced sensitivity to punishment (9–12). Therefore, some researchers have argued that depression and anxiety are not exclusively distinct conditions, but are just different manifestations of a common negative affect dimension (13).

However, in spite of the high comorbidity and overlapping symptoms and risk factors, other researchers suggest that depression and anxiety are two separate entities, each with their unique features (14, 15). For instance, according to the Tripartite Model (16, 17), although depression and anxiety share a general distress or negative affect factor (e.g., feelings of upset, insomnia, restlessness, and irritability), depression is specifically associated with the absence of positive affect or anhedonia, while anxiety is specifically associated with physiological hyperarousal or somatic tension.

To resolve the dispute over the relation between depression and anxiety and provide insights into their psychopathology, recently researchers have started to employ latent class analysis (LCA) to identify the patterns of occurrence of depression and anxiety symptoms. Unlike traditional theory-driven and variable-centered approaches, LCA is a data-driven and person-centered technique that classifies individuals into more homogeneous groups (called classes) based on the patterns of symptoms by estimating the probabilities of symptom endorsement (18). This kind of symptom-level analysis may give a more explicit picture of the relationship between depression and anxiety symptoms (17).

By applying LCA to data of three national surveys (Australia, USA, and the Netherlands), Rhebergen et al. (19) identified three unique classes, one characterized by both high depression and anxiety symptoms (probability of symptom endorsement > 0.8), the second moderate depression and anxiety symptoms (> 0.4), and the third moderate depression symptoms only (with the endorsing probability of most anxiety symptoms being smaller than 0.1). In contrast, with another adult sample from the Dutch general population, general practices, and mental health organizations, the authors only identified two classes, one with both high depression and anxiety (probability of symptom endorsement > 0.6), the other high anxiety (>0.7) but moderate depression (>0.2). A class consists of individuals with predominantly high depression symptoms was not found in this Dutch sample. Hettema et al. (20) investigated an American sample of twins and identified four classes, one with almost no symptoms of depression and anxiety (<0.15) and the other three with low, moderate, or high symptoms of both depression and anxiety, respectively. These patterns remained stable at a follow-up survey conducted 1.5 years later. Curran et al. (21) applied LCA to a community-based sample of Irish older adults and identified four classes: one with no or low depression and anxiety (most symptoms < 0.15), the second high anxiety symptoms (most symptoms > 0.6), the third moderate depression (0.1–0.6) and high anxiety symptoms (>0.6), and the fourth both high depression and anxiety symptoms (most symptoms > 0.4). Curran et al. (21) was also the only study that applied LCA separately to males and females, which found that the above symptom patterns did not differ across gender. Taken together, in these previous studies, a subgroup of individuals with both high depression and anxiety has been consistently identified, while a subgroup with predominantly one symptom (depression or anxiety) has not been reliably identified. Although further empirical studies are still needed to clarify the mixed findings, these studies, from a data-driven and person-centered approach, have provided important insights that depression and anxiety tend to occur together in the same individuals.

To our knowledge, no research has explored the symptom patterns of depression and anxiety using LCA in Asian subjects. It has been reported that culture may shape the presentation of depression and anxiety symptoms (22). For instance, Asian individuals with depression and anxiety tend to overemphasize somatic symptoms, such as excessive fatigue and headache (23). They also tend to believe that negative emotions have cognitive and motivational utility and are less likely to engage in hedonic emotion regulation (24). Therefore, in the current study, we set out to investigate the symptom patterns of depression and anxiety in an adult sample from the Japanese general population using LCA. We then employed demographic data, psychological factors, and several established risk factors for depression and anxiety to validate the identified class memberships. Specifically, based on the Tripartite Model described above (16, 17), we used positive and negative affect and subjective wellbeing as psychological factors to validate the identified class memberships. We also used three well-known risk factors of depression and anxiety for the validation purpose, which include adverse childhood experiences, recent life events, and personality (9–12). The current study may provide important, novel insights into the association between depression and anxiety and the psychopathology of these disorders from a Japanese cultural perspective.

MATERIALS AND METHODS

Subjects

The study was part of a larger study conducted between January and August 2014 that aimed to investigate the interaction of early life stress, recent life events, and vulnerability (e.g., personality) in affecting depression, anxiety, and wellbeing in the Japanese

general adult population. All subjects were volunteers and were recruited by flyers posted on the campus of Hokkaido University (a major national university in Hokkaido Prefecture) and word of mouth. Questionnaires were distributed to the volunteers and returned anonymously. It took roughly 90 min to complete all the questionnaires. Of 853 volunteers, 455 participants (53.34%) gave written informed consent and responded to the questionnaires. Fifty-two participants were excluded due to incomplete responses on at least one item of the measures, resulting in a sample size of 403 (184 females, 45.7%; age = 42.28 ± 11.87 years, range 20–81 years). This study was approved by the ethics committees of Hokkaido University Hospital, Tokyo Medical University, and Yamaguchi University Hospital.

Measurements

Depression and Anxiety

The 9-item Patient Health Questionnaire (PHQ-9) (25, 26) was employed to measure depressive symptoms in the past 2 weeks. The nine items represent the nine diagnostic criteria for major depression and were rated on a 4-point scale (0–3) which indicates the frequency of the symptom occurrence. The Cronbach's α of PHQ in the current study was 0.858. Anxiety symptoms were measured using the state anxiety subscale of State-Trait Anxiety Inventory Form Y (STAI-Y1) (27, 28). This subscale consists of 10 anxiety-present items (e.g., "I am tense," "I feel nervous") and 10 anxiety-absent items (e.g., "I feel calm," "I feel satisfied"). Subjects answered how they feel at the particular moment in each statement on a 4-point scale, ranging from 1 (not at all) to 4 (very much so). Anxiety-absent items were reverse scored for calculating the total state anxiety score. The Cronbach's α of total STAI state anxiety, anxiety-present, and anxiety-absent subscales were 0.932, 0.870, and 0.948, respectively.

Demographic and Psychological Characteristics

Demographic information included age, gender, years of education, marital status, number of children, living status, employment, history of smoking, frequency of alcohol drinking (0 = none, 1 = sometimes, 2 = every day), comorbid physical diseases, history and family history of psychiatric diseases.

Furthermore, positive affect, negative affect, and subjective wellbeing were measured using the *Positive and Negative Affect Schedule* (PANAS) (29, 30) and *Subjective Well-being Inventory (SUBI)* (31, 32), respectively.

PANAS has 20 items and measures two broad domains of affect, positive and negative affect. Subjects described their feeling on positive and negative affect using a 6-point Likert scale, ranging from 1 (not at all) to 6 (extremely). Total scores for positive affect and negative affect subscales were separately calculated. The Cronbach's α of total PANAS, positive affect and negative affect subscales were 0.876, 872, and 0.898, respectively.

SUBI has 40 items and measures subjective wellbeing, including general wellbeing-positive affect, social support, and confidence in coping, etc., and subjective ill-being, including upsetability, physical ill-health, and deficiency in social contacts, etc. The wellbeing subscale consists of 19 items rated on a 3-point scale ranging from 1 (not apply to me) to 3 (apply to me). The ill-being subscale consists of 21 items rated on a 3-point scale (1 = always, 2 = sometimes, 3 = never). The total score for wellbeing and ill-being subscales were separately calculated. High scores indicate better states for both wellbeing and ill-being. The Cronbach's α of total SUBI, subjective wellbeing and subjective ill-being subscales were 0.912, 882, and 0.872, respectively.

Risk Factors

Several well-known risk factors of depression and anxiety, including childhood experiences, recent life events, and personality were measured using the Child Abuse and Trauma Scale (CATS) (33, 34), Life Experiences Survey (LES) (10, 35), and Behavioral Inhibition System and Behavioral Activation System Scales (BIS/BAS) (36, 37), respectively.

CATS has 38 items and measure childhood adverse experiences with three subscales: neglect/negative home environment, punishment and sexual abuse. Responses were based on a 5-point rating scale, where 0 indicates never and 4 indicates always. The mean score of the three subscales were used in current study. Cronbach's α of the three subscales was 0.859 (neglect), 0.504 (punishment), 0.824 (sexual abuse), respectively.

LES has 47 items and measures positive and negative life events happened in the past 6-month or 1 year and the impact of those events on a 7-point scale, ranging from−3 (extremely negative) to +3 (extremely positive). The total score of the two subscales were separately calculated.

BIS/BAS has 20 items and measures the sensitivity to cues of threat (i.e., BIS) and reward (i.e., BAS). BAS has 3 subscales: drive, fun-seeking, and reward responsiveness. Participants rated how they agreed with the statement of each item on a 4-point Likert scale, where 1 indicates strongly disagree and 4 indicates strongly agree. The total score for BIS and three subscales of BAS are used in the study. The Cronbach's α of BIS, drive, fun-seeking, and reward responsiveness were 0.785, 0.831, 0.729, and 0.736, respectively.

Statistical Analysis

We conducted LCA in *Mplus* version 8.4 (38) using maximum likelihood estimation. Maximum likelihood is the default estimator in Mplus and has been commonly employed in previous studies. It has high statistical efficiency and has advantages in dealing with large numbers of items given small numbers of subjects (39). Based on the similarity displayed in subjects' response patterns, LCA categorizes them into more homogeneous groups, each with their own symptom endorsement probability. We used all the items of PHQ-9 and STAI-Y1 for the LCA. All items were dichotomized (i.e., absence of a symptom = 0, presence of a symptom = 1) due to a large number of items and a relatively small sample size. Specifically, following Holub et al. (40), the PHQ response option "not at all" was recoded into "absence of a symptom", and options "several days," "more than half the days," and "nearly every day" were recoded into "presence of a symptom". The state anxiety (STAI-Y1) response options "not at all" and "somewhat" were recoded into "absence of a symptom" while "moderately so" and "very much so" were recoded into "presence of a symptom". Instead of LCA, we could have conducted a Latent Profile Analysis (LPA) using the original continuous items. However,

based on simulation studies and expert recommendations, it has been suggested that at least 500 subjects are required for LPA [e.g., (41)] and each identified class should have at least 50–75 subjects [e.g., (42, 43)]. These requirements were not met in our dataset. Furthermore, given the small sample size, the frequency distributions of item responses were excessively skewed due to lack of response on the continuous response options (e.g., on 7 of the 9 items of PHQ, merely 1–14 subjects chose "more than half the days" or "nearly every day"). In cases like this, dichotomization of the responses and the employment of LCA are preferred (44). Nevertheless, we did run the LPA to see if we can reproduce the current LCA results. The LPA results are attached in the **Supplementary Material**. In brief, although with a small sample size in the identified classes, we could largely reproduce the current 4-class solution in LCA. The between-class differences in environmental and personality risk factors are also generally consistently between LPA and LCA.

To avoid convergence on solutions at a local maximum, we ran the LCA with 1,000 random starting values and 250 final stage optimizations. To select the best fitting model, we examined the Akaike information criteria (AIC), Bayesian information criteria (BIC), SSA-BIC (sample size adjusted BIC), entropy, the Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-LRT), and the bootstrap likelihood ratio test (BLRT). Lower AIC, BIC, SSA-BIC indicate better fitting. LMR-LRT and BLRT with significant *p*-values indicate that the current k class model performs better than the previous k-1 class model. Entropy values bigger than 0.8 indicate good class separation. For model comparison, BIC and BLRT were prioritized, together with the interpretability of the derived latent classes (45, 46).

For the description of the winning model, the criteria of probability level per item were: low probability, $\leq$0.15; moderate probability, 0.16-0.59; high probability, $\geq$0.6 (47). After identifying the winning model, Chi-square test and Kruskal-Wallis test (because of the non-normality of the data according to the Kolmogorov–Smirnov test) conducted with IBM SPSS Statistics 26 were used to compare the demographic and psychological characteristics across the latent classes. Then multinomial logistic regression was performed to examine the relationship between risk factors and derived classes. One class was selected as the reference class in the logistic regression if its symptoms were close to healthy individuals. For the multinomial logistic regression, given the small sample size of the derived classes, environmental risk factors (i.e., CATS and LES) and personality were separately employed as independent factors. All non-binary variables were standardized to facilitate comparability. We did not detect any obvious multicollinearity issue (i.e., variance inflation factors all < 5) with the independent variables of the logistic regression.

RESULTS

LCA Analysis

The fitting results and number of subjects in each class are shown in **Table 1**. We chose the 4-class solution as the winning model because it performed better than that 3-class model based on the smaller BIC and significant LMR-LRT and BLRT. The 5-class

TABLE 1 | Fitting statistics for latent class models from 2 to 5 classes.

Number of classes	AIC	BIC	SSA-BIC	df	Entropy	LMR-LRT	BLRT	Number of subjects per class				
								N1	N2	N3	N4	N5
2	14,071.406	14,319.340	14,122.607	62	0.941	$p < 0.000$	$p < 0.000$	220	183			
3	13,585.276	13,957.177	13,662.078	93	0.928	$p < 0.001$	$p < 0.000$	119	129	155		
4	**13,427.402**	**13,923.270**	**13,529.805**	**124**	**0.930**	$\mathbf{p = 0.041}$	$\mathbf{p < 0.000}$	**56**	**78**	**121**	**148**	
5	13,294.317	13,914.153	13,422.322	155	0.930	$p = 0.448$	$p < 0.000$	25	69	77	92	140

AIC, Akaike information criteria; BIC, Bayesian information criteria; SSA-BIC, sample size adjusted BIC; df, degrees of freedom; LMR-LRT, Lo-Mendell-Rubin adjusted likelihood ratio test; BLRT, bootstrap likelihood ratio test. The results of the winning model are shown in bold.

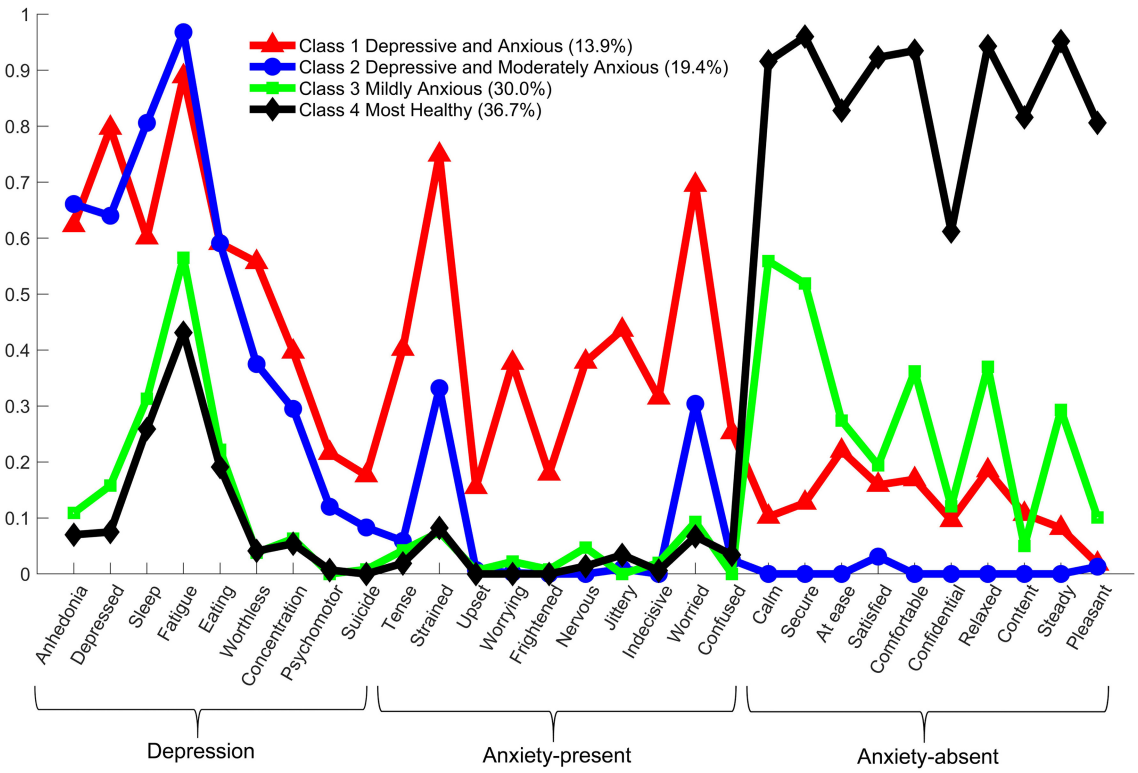

FIGURE 1 | The probability of symptom endorsement by each latent class (i.e., conditional probability).

solution performed no better than the 4-class solution because of the similar BIC values and non-significant *p*-value in LMR-LRT. The 4-class solution also had the highest interpretability and clinical relevance. The average latent class probabilities for the most likely latent class membership in the 4-class model were 0.980, 0.957, 0.933, and 0.970, respectively, indicating a high precision and reliability of the current model selection.

The probabilities of symptom endorsement for each class of the winning model are presented in **Figure 1**. Class 1 (n = 56, 13.9% of subjects) was characterized by moderate to high probabilities of most depression and anxiety-present symptoms (0.15–0.90) and thus labeled "Depressive and Anxious". The second class (n = 78, 19.4%) was characterized by moderate to high probabilities of most depressive symptoms (0.25–1.0), moderate probabilities of two anxiety-present symptoms (i.e., strained and worried, 0.3–0.4), and the lowest probabilities of anxiety-absent symptoms (e.g., calm, secure, < 0.1). This class was thus labeled "Depressive and Moderately Anxious". Class 3 (n = 121, 30.0%) and Class 4 (n = 148, 36.7%) were characterized by moderate probabilities (0.2–0.6) of somatic symptoms (sleep disturbances, feeling tired and trouble in eating), while Class 4 was notably different from Class 3 for its high probabilities of endorsing anxiety-absent symptoms (>0.6). Therefore, Class 3 and 4 were labeled "Mildly Anxious" and "Most Healthy", respectively.

Demographic and Psychological Characteristics

Table 2 displays demographic and psychological characteristics across the four derived classes. There was no significant difference among the four classes in demographic variables, including age, gender distribution, years of education, marital status, number of children, living status, employment, smoking history, frequency of alcohol drinking, the presence of comorbid physical disease, history and family history of psychiatric disease.

As shown in **Table 2**, consistent with the class definitions, Class 1 and 2 had significantly higher PHQ and state anxiety total scores than Class 3 and 4. Importantly, whereas Class 1 and 2 did not differ from each other in terms of PHQ-9 and state anxiety total scores ($p > 0.05$), Class 1 had significantly higher anxiety-present score than Class 2 ($p < 0.05$). Furthermore, Class 1 and 2 also had similar subjective wellbeing and ill-being scores, while Class 1 had more enhanced negative affect than Class 2 ($p < 0.05$). Only Class 2 had significantly lower positive affect than Class 4 ($p < 0.05$), which is consistent with its lowest probabilities of endorsing anxiety-absent symptoms.

Meanwhile, Class 3 and 4 had similar PHQ score, while Class 3 had significantly higher anxiety than Class 4 due to less anxiety-absent ($p < 0.05$) but not more anxiety-present symptoms. Class 3 also had greater negative affect and lower subjective wellbeing than Class 4 (both $p < 0.05$).

TABLE 2 | Demographic and psychological characteristics of the 4 latent classes.

	Class 1 depressive and anxious (n = 56)	Class 2 depressive and moderately anxious (n = 78)	Class 3 mildly anxious (n = 121)	Class 4 most healthy (n = 148)
Demographic				
Age (years)	39.52 (11.319)	42.17 (10.777)	43.00 (11.763)	42.79 (12.651)
Gender: male	53.85%	47.96%	53.24%	52.47%
Education years	15.38 (1.996)	14.54 (2.383)	14.98 (2.280)	14.89 (2.164)
Marital status: unmarried	32.69%	28.57%	18.84%	21.25%
Number of children (0 or ≥1)	60.78%	59.79%	67.63%	70.63%
Living alone	14.00%	16.84%	25.90%	19.62%
Employment: homemakers	7.69%	6.32%	12.41%	14.47%
Smoking history	48.08%	51.02%	47.48%	49.38%
Frequency of alcohol drinking	1.13 (0.634)	1.10 (0.616)	1.15 (0.667)	1.10 (0.636)
Comorbidity of physical diseases	26.92%	24.74%	16.79%	20.00%
History of psychiatric diseases	9.62%	4.08%	2.88%	5.56%
Family history of psychiatric diseases	9.62%	16.49%	12.41%	8.64%
Psychological characteristics				
PHQ-9 total score	7.679 (6.043)[a]	6.051 (3.864)[a]	1.752 (1.823)[b]	1.318 (1.462)[b]
State anxiety total score	54.429 (8.549)[a]	48.026 (3.971)[a]	40.686 (4.227)[b]	30.318 (5.682)[c]
Anxiety-present total score	21.982 (5.594)[a]	15.218 (2.836)[b]	13.140 (2.599)[c]	12.351 (2.539)[c]
Anxiety-absent total score	17.554 (4.914)[a]	17.192 (2.594)[a]	22.455 (2.918)[b]	32.034 (4.293)[c]
PANAS positive affect	30.821 (8.415)	29.333 (6.664)[a]	30.992 (7.155)	33.500 (7.730)[b]
PANAS negative affect	31.661 (7.643)[a]	26.500 (6.920)[b]	23.802 (7.107)[b]	20.493 (7.111)[c]
Subjective wellbeing	36.125 (6.655)[a]	34.962 (5.854)[a,b]	38.264 (5.321)[a,c]	42.777 (5.519)[d]
Subjective ill-being	45.411 (6.347)[a]	49.321 (5.575)[a]	53.554 (4.950)[b]	55.142 (5.049)[b]

Different superscript indicates significant difference at $p < 0.05$, Bonferroni corrected.

Risk Factors

To further validate the identified class memberships, we next used commonly studied environmental and personality risk factors to predict the class memberships with multinomial logistic regression. For this purpose, Class 4 (Most Healthy) was selected as the reference class because it was the closest to healthy individuals.

The results of the multinomial logistic regression with environmental risk factors are shown in **Table 3**. Compared to the reference class, whereas both Class 1 and 2 had higher childhood neglect or a more negative home environment (OR = 1.709 and 1.556, respectively, both $p < 0.01$), only Class 1 reported more negative life events in the past 6-month or 1 year (OR = 1.536, $p < 0.01$).

The results of the multinomial logistic regression with personality risk factors are shown in **Table 4**. Compared to the reference class, all three classes reported significantly higher BIS and lower BAS reward responsiveness, with the change in Class 1 and 2 being greater than that in Class 3 (for BIS, OR = 3.975, 3.480, and 1.416, respectively; for reward responsiveness, OR = 0.389, 0.437, 0.588, respectively). Class 1 and 2 also had higher BAS fun-seeking (OR = 1.714 and 1.797, respectively). Thus,

TABLE 3 | Environmental risk factors predicting class membership: odds ratios and 95% confidence intervals from multinomial logistic regression.

	Class 1 depressive and anxious (n = 56)	Class 2 depressive and moderately anxious (n = 78)	Class 3 mildly anxious (n = 121)
CATS neglect	**1.709 (1.202–2.429)****	**1.556 (1.119–2.162)****	1.177 (0.855–1.620)
CATS punishment	1.195 (0.841–1.697)	0.948 (0.696–1.291)	0.968 (0.737–1.271)
CATS sexual abuse	0.862 (0.636–1.169)	0.930 (0.709–1.219)	0.903 (0.661–1.234)
LES positive life events	0.695 (0.478–1.011)	0.790 (0.588–1.061)	0.848 (0.663–1.084)
LES negative life events	**1.536 (1.142–2.066)****	1.281 (0.953–1.721)	0.971 (0.702–1.342)

*Class 4 served as the reference class. **$p < 0.01$. CATS, Child Abuse and Trauma Scale; LES, Life Experiences Survey. Statistically significant results are shown in bold.*

TABLE 4 | Personality risk factors predicting class membership: odds ratios and 95% confidence intervals from multinomial logistic regression.

	Class 1 depressive and anxious (n = 56)	Class 2 depressive and moderately anxious (n = 78)	Class 3 mildly anxious (n = 121)
BIS	**3.975 (2.585–6.111)*****	**3.480 (2.376–5.098)*****	**1.416 (1.070–1.873)***
BAS Drive	0.852 (0.516–1.408)	0.692 (0.443–1.082)	1.099 (0.771–1.566)
BAS Fun-seeking	**1.714 (1.095–2.684)***	**1.797 (1.193–2.706)****	0.903 (0.636–1.282)
BAS Reward responsiveness	**0.389 (0.232–0.651)*****	**0.437 (0.277–0.691)*****	**0.588 (0.405–0.854)****

*Class 4 served as the reference class. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. BIS, Behavioral Inhibition System; BAS, Behavioral Activation System. Statistically significant results are shown in bold.*

while Class 1 and 2 had higher childhood neglect and BIS and lower reward responsiveness, only Class 1 had more negative life events.

DISCUSSION

In the present study, we investigated the symptom patterns of the occurrence of depression and anxiety by applying LCA in a sample of Japanese general population. We found that a 4-class solution best described our data. Specifically, Class 4 (Most Healthy) manifested the least depressive and anxiety-present symptoms as well as the most anxiety-absent symptoms; Class 3 (Mildly Anxious) manifested mild anxiety symptoms due to lacking responses on anxiety-absent items; Class 1 (Depressive and Anxious) had both high depressive and anxiety symptoms; Class 2 (Depressive and Moderately Anxious) displayed predominantly depression and moderate anxiety symptoms, and the moderate anxiety symptoms were the result of lacking response on anxiety-absent symptoms. Consistent with these unique patterns of symptom occurrence, we found that each class had distinct psychological characteristics and was associated with different risk factors.

To our knowledge, this is the first LCA study that examined the symptom patterns of depression and anxiety in a sample of Japanese general population. In line with findings from Western studies (19–21), we identified one class of subjects with both high depressive and anxious symptoms. However, we did not identify a predominantly high anxiety class (19, 21). That is, high anxiety tends to co-occur with high depression rather than occur alone. In this regard, this finding is somewhat inconsistent with the Tripartite Model which argues that depression and anxiety are different entities (16, 17). Furthermore, whereas Western studies have generally identified one class with almost no symptoms of depression and anxiety (20, 21), here even the healthiest class (Class 4) in our study showed moderate probability of endorsing symptoms in terms of sleep and eating problems and fatigue. This is perhaps explained by the observation that Eastern individuals tend to emphasize somatic symptoms (23). Among subjects with high depressive symptoms (Class 1 and 2), one-third (Class 1) also showed high anxiety symptoms, which is generally consistent with previous reports that among individuals with depression, roughly half suffer from anxiety (6). Notably, we did not identify a depression only class and the explanation of such result, we believe, has its cultural roots. In Asia, the common value of "conformity to norms, emotional self-control, collectivism, family recognition through achievement" [(48), p. 941] is strong and any deviation from the common value is considered inappropriate. As a result, people are afraid of being labeled "weak character" and while reporting depressed mood, they tend to in the meantime emphasize somatic and anxiety symptoms (23).

Another novelty of the current study was that we distinguished anxiety-present ("I feel nervous") and anxiety-absent (e.g., "I feel calm") items for the LCA. Although this distinction is common in anxiety-related inventories including the current STAI, few studies have included this distinction in LCA research of depression and anxiety. Intriguingly, we found

that in two classes with high depression, one was accompanied by high anxiety-present symptoms (Class 1) while the other few anxiety-absent symptoms (Class 2). That is, in terms of anxiety, Class 1 was characterized by high negative symptoms while Class 2 low positive symptoms. This is consistent with their common and unique associations with other psychological characteristic and risk factors (in comparison to the reference class). Specifically, whereas both classes had higher childhood neglect (or a more negative home environment), behavioral inhibition, and fun-seeking, as well as reduced reward responsiveness, only Class 1 had greater negative affect and experienced more negative life events in the past 6 months or 1 year. Furthermore, only Class 2 had lower positive affect than Class 4. Previous studies have identified adverse childhood experiences in particular neglect and negative life events as risk factors of depression and anxiety (9, 10). Here, we confirmed these findings and further showed that they are only partially correct: whereas both Class 1 and 2 were associated with greater childhood neglect (or a more negative home environment), only Class 1 reported more negative life events in the past 6 months or 1 year. Therefore, negative life events are perhaps more sensitive risk factors for negative symptoms of anxiety rather than depression or anxiety due to lack of positive symptoms. Both Class 1 and 2 were associated with enhanced fun-seeking, which may reflect that fact that individuals with high levels of depression or moderate to high levels of anxiety tend to seek out novel, rewarding experiences in order to feel better. The etiological and psychopathological risk factors of this symptom pattern remain to be investigated by future studies.

Classes 1-3 were characterized by higher BIS and lower reward responsiveness on the BAS, with the change in the first two classes being greater. This is consistent with the notion that enhanced sensitivity to punishment and reduced sensitivity to reward are characteristics of depression, anxiety, and negative affect in general (11, 12, 49, 50).

We should also consider several limitations of the study when interpreting our findings. Firstly, we might have lost some information and overestimated the endorsement of symptoms by dichotomizing the responses of the depression and anxiety scales, and future studies with larger sample sizes are required to confirm our findings with continuous variables using LPA. Secondly, our subjects were primarily recruited on campus by flyers and word of mouth in Hokkaido, one of 47 prefectures in Japan. Caution, therefore, should be taken when generalize our findings to the whole Japanese general population. Thirdly, given our sample size, we were unable to apply LCA to males and females separately. It will be interesting for future research to investigate if the symptom patterns we identified exist in both genders. Fourthly, all scales in the current study were self-report measures, childhood experience and recent life events were also self-reported and assessed retrospectively. Our results, therefore, may suffer from recall and expectation bias. Future research should employ objective measures to confirm our findings. Furthermore, the punishment subscale of CATS had a somewhat low internal consistency as indicated by the Cronbach's α (i.e., 0.504). Further research may be needed to confirm the reliability of the scale in Japanese subjects. Nevertheless, the Cronbach's α of the punishment subscale was close to that reported in Japanese subjects in previous studies [(51), in which Cronbach's $\alpha = 0.58$; (52), in which Cronbach's $\alpha = 0.55$] as well as subjects from UK [(53), Cronbach's $\alpha = 0.63$] and Iran [(54), Cronbach's $\alpha = 0.63$]. Our results are also consistent with previous studies in that the Cronbach's α of the punishment subscale was lower than the other two subscales of CATS [i.e., neglect and sexual abuse, (51–54)].

The current study was cross-sectional and future longitudinal studies are required to verify whether our identified symptom patterns are stable over time. Furthermore, to better uncover the underlying mechanism of depression and anxiety, multiple data such as those of neural circuitry, genetic, and molecular may be included in future LCA studies (55, 56). Lastly, the current study used a non-clinical sample, future study should verify our results in clinical patients in order to shed light on the pathophysiology of depression and anxiety.

In conclusion, the current study identified four distinct symptom patterns of the occurrence of depression and anxiety in a sample of Japanese general population. We found two classes with high depression, with one showing concurrent high anxiety. Both classes have distinct features that confirm their unique patterns of symptom endorsement. Our findings may provide insights into the etiology of depression, anxiety, and their comorbidity, and have implications for dissecting the heterogeneity and individualizing the treatment of these disorders.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Hokkaido University Hospital, Tokyo Medical University, and Yamaguchi University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC, HT, TI, and SN: conceptualization and design. IK and TI: investigation. HL, CC, and KH: data analysis. HL and CC: manuscript preparation. All authors revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.808918/full#supplementary-material

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Conflict of Interest: Author IK has received honoraria from Daiichi Sankyo, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Janssen Pharmaceutical, Lundbeck, Meiji Seika Pharma, Mochida Pharmaceutical, MSD, Mylan, Novartis Pharma, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer, Shionogi, Shire, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Tsumura, and Yoshitomiyakuhin, and has received research/grant support from Asahi Kasei Pharma, Astellas, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Mochida Pharmaceutical, Novartis Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, Takeda Pharmaceutical and Tanabe Mitsubishi Pharma. Author TI has received personal fees from Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Janssen Pharmaceutical, MSD, Taisho Toyama Pharmaceutical, Yoshitomiyakuhin, and Daiichi Sankyo; grants from Shionogi, Astellas, Tsumura, and Eisai; and grants and personal fees from Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Mitsubishi Tanabe Pharma, Kyowa Pharmaceutical Industry, Pfizer, Novartis Pharma, and Meiji Seika Pharma; and is a member of the advisory boards of Pfizer, Novartis Pharma, and Mitsubishi Tanabe Pharma. Author SN has received personal fees from EA Pharma, Janssen Pharmaceutical, Kurasie, Kyowa Pharmaceutical Industry, Lundbeck, Meiji Seika Pharma, Mylan, MSD, Takeda Pharmaceutical, and Yoshitomiyakuhin; grants from Astellas, Daiichi Sankyo, Nihon Medi-physics, Novartis Pharma, Tanabe Mitsubishi Pharma, and grants and personal fees from Eisai, Eli Lilly, Dainippon Sumitomo Pharma, Mochida Pharmaceutical, MSD, Otsuka Pharmaceutical, Pfizer, Shionogi and Tsumura.

The remaining 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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frontiers in Psychiatry

REGISTERED REPORT
published: 28 February 2022
doi: 10.3389/fpsyt.2022.840912

isiXhosa Translation of the Patient Health Questionnaire (PHQ-9): A Pilot Study of Psychometric Properties [Stage 1]

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Depression is a debilitating illness, and stigma associated with it often prevents people from seeking support. Easy-to-administer and culturally-specific diagnostic tools can allow for early screening for depression in primary care clinics, especially in resource-limited settings. In this pilot study, we will produce the first open-access isiXhosa-language version of the nine-item Patient Health Questionnaire (PHQ-9), a well-validated measure of depression incidence and severity, using a transcultural translation framework. We will validate this isiXhosa PHQ-9 in a small sample of adolescents living with HIV in Cape Town, South Africa who speak isiXhosa at home. Participants have previously completed the ASEBA Youth Self Report (YSR) form, and responses from the YSR will be used as a gold standard to validate the isiXhosa PHQ-9. If validated through this Registered Report, this isiXhosa PHQ-9 may be an invaluable culturally-specific tool for clinicians serving Xhosa people in identifying clinical or sub-clinical depression.

Keywords: HIV-associated depression, major depressive disorder (MDD), psychometric testing, translation, multicultural tools

OPEN ACCESS

Edited by:
Yuka Kotozaki,
Iwate Medical University, Japan

Reviewed by:
David Eugene Vance,
University of Alabama at Birmingham, United States
Marguerite Schneider,
University of Cape Town, South Africa

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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: *21 December 2021*
Accepted: *21 January 2022*
Published: *28 February 2022*

Citation:
Mudra Rakshasa-Loots A and Laughton B (2022) isiXhosa Translation of the Patient Health Questionnaire (PHQ-9): A Pilot Study of Psychometric Properties [Stage 1]. Front. Psychiatry 13:840912. doi: 10.3389/fpsyt.2022.840912

1. INTRODUCTION

"If I show you where I'm struggling, I feel you have been exposed to my weakness," said Siyanda, a young Xhosa man, in relation to the cultural expectation for Xhosa men to manage mental health issues without seeking support (1, p.56). The constellations of behavioral and somatic issues that comprise major depressive disorder (MDD, or depression) are estimated to affect between 4.4 and 5.0% of people globally (2, 3). Biological and psychosocial factors can predispose individuals to developing MDD (4). Living with a chronic HIV infection, especially, significantly increases the risk of depression (5), with prevalence of depression amongst people living with HIV estimated to be as high as 50% (6, 7). Given the stigma associated with depression across cultures, people with depression may struggle to access mental healthcare resources, as Siyanda suggests. However, early referral and interventions have substantial benefits for the treatment and prevention of depression (8, 9). It is therefore imperative to continue to refine tools for early screening of depression and increase their accessibility in primary care clinics.

The Xhosa people comprise a diverse cultural group who speak variations of isiXhosa. The vast majority of Xhosa people live in the Eastern Cape and Western Cape provinces of South Africa (10). Over the last three centuries, European colonial expansion into the South African heartland occurred at the expense of indigenous populations, including Xhosa people, culminating in systematic disenfranchisement during the apartheid regime (11, 12). Under the apartheid

government, especially, Xhosa people suffered severe marginalization as Afrikaans was the favored language in government and education in place of indigenous languages such as isiXhosa (13). As a result of these institutional barriers, it is difficult for people to access quality healthcare in isiXhosa today (14, 15). In order to reduce this healthcare inequity faced by Xhosa people, it is crucial that clinical resources are made available to them in their home language.

There is no word for "depression" in isiXhosa, but that does not mean that this debilitating illness is not found amongst the Xhosa people. In fact, the prevalence of depression in this group, estimated at 6.9%, is significantly higher than global estimates for depression in the general population (16). Substantial intra-group variability exists, with, for instance, a significantly higher prevalence rate of 31.9% amongst women in Khayelitsha during pregnancy and 12 weeks postpartum (17). Despite this, few isiXhosa-language tools exist for diagnosis of depression. An early study translated the Edinburgh Postnatal Depression Scale (EPDS) into isiXhosa and found satisfactory internal consistency (18), but this scale is limited in its target population. Another study validated an isiXhosa version of the Centre for Epidemiological Studies Depression Scale in a more general population group (16). The ongoing development and validation of the 16-item South African Depression Scale (SADS) in isiXhosa is particularly promising, especially for Xhosa people living with HIV (19, 20). However, the trade-off in developing such a tool is that limited comparisons can be made between scores from the SADS and other established scales until it is validated in other countries and cultures, thereby restricting synthesis of results across global studies.

The nine-item Patient Health Questionnaire (PHQ-9) is a useful measure for depression incidence and severity (21, 22). It has been validated as a diagnostic tool in clinical samples (23) as well as the general population (24), where it shows a high degree of convergent validity with other depression scales such as the Beck Depression Inventory (BDI). Furthermore, the PHQ-9 is easy to administer, especially in resource-limited settings (25), and exhibits similar results whether it is self-administered or carried out by an interviewer (26, 27). It is shown to be useful to screen for depression in both African populations (28) and people living with HIV (29, 30). Numerous validation studies for translations of the PHQ-9 have demonstrated its value as a depression scale in samples across the world (31–33). Given this global body of evidence, the PHQ-9 represents a measure of depression that could facilitate cross-cultural comparisons of depression pathology better than population- or geography-specific scales such as the EPDS or SADS. Despite these many advantages, to the best of our knowledge, an isiXhosa-language version of the PHQ-9 has not yet been validated and made publicly available. [Baron et al. (16) report findings from an isiXhosa version of the PHQ-9, but this version is not available alongside the study except by request to the authors.] Given the utility of the PHQ-9 in rapid screening of depressive symptomatology, a freely-available isiXhosa-language PHQ-9 may be an invaluable mental health triage tool for clinicians serving Xhosa people.

In this pilot study, we aim to produce and validate the first open-access isiXhosa-language version of the PHQ-9 depression scale. This version will be produced using a transcultural translation framework and administered to a cohort of adolescents living with HIV in Cape Town, South Africa. Responses on the PHQ-9 will be compared against those on the ASEBA Youth Self Report (YSR) forms as a gold standard. Our primary hypothesis is that the isiXhosa-language PHQ-9 will exhibit satisfactory reliability, measured as internal consistency using Cronbach's α. We also hypothesize that this translation of the PHQ-9 will show acceptable convergent validity (Pearson's correlation coefficient for PHQ-9 and YSR scores) and diagnostic accuracy (area under Receiver Operating Characteristic curve for PHQ-9 vs. YSR). This pilot study may pave the way for larger-scale validation studies of this isiXhosa-language PHQ-9 and add an easy-to-administer, culturally-specific questionnaire to the local clinician's toolbox.

2. METHODS

2.1. Participants

Participants for this study will be recruited through the Adolescent Cognitive and Brain Imaging Study ("the GOLD study") at Stellenbosch University and Tygerberg Hospital in Cape Town, South Africa. The GOLD study, which draws on the cohort of participants in the landmark CHildren with Early antiRetroviral therapy (CHER) trial, includes adolescents living with HIV who were initiated on antiretroviral therapy (ART) early in life (34). The CHER cohort is active and regularly willing to contribute to sub-studies, with as many as 80 children living with HIV and 80 age-matched HIV- controls participating in recent sub-studies (35).

2.1.1. Inclusion Criteria

Inclusion criteria for participants will be: HIV+ status, currently receiving antiretroviral therapy, with plasma HIV RNA < 40 copies per mL (indicating viral suppression), and speaking isiXhosa at home.

2.1.2. Sample Size Estimation

A priori estimation of sample size in validation studies for psychometric tools is remarkably low (36). We utilized a web-based sample size calculation tool for reliability studies (37), available at this link, with the primary outcome of interest as the Cronbach's α reliability coefficient for the translated PHQ-9. The *a priori* sample size estimation showed that a sample size of $N = 19$ would be necessary to detect a Cronbach's $\alpha = 0.65$ (indicative of a moderate reliability) at 80% power for the nine-item questionnaire. Therefore, we plan to recruit 20 participants for this pilot study.

2.1.3. Ethical Considerations

We will receive written informed assent from participants and written informed consent from participants' parents or legal guardians in their home language for inclusion in the study before participation. The study will be conducted in accordance with the Helsinki Declaration and Good Clinical Practice (GCP)

standards. The protocol for this study will be approved by the Stellenbosch University Human Research Ethics Committee (N21/10/116_Substudy N19/10/135).

2.2. Materials

2.2.1. Patient Health Questionnaire (PHQ-9)

The English-language version of the PHQ-9 was designed with slight adaptations from the original version (21). The adaptations, intended primarily to improve comprehensibility of the scale to adolescents in 2022, were as follows: in item 7, we replaced "reading the newspaper" with "reading," and in the final question, we replaced "if you checked off *any* problems" with "if you chose a number higher than 0." The isiXhosa-language version of the PHQ-9 will be created from this English version using a transcultural translation framework (see Procedure). Both the English-language and isiXhosa-language versions of the PHQ-9 will be freely available in Supplementary Materials.

2.2.2. Youth Self-Report (YSR) Form

The Achenbach System of Empirically Based Assessment (ASEBA) Youth Self-Report (YSR) form (38) measures behavioral issues representing syndromes such as "withdrawn/depressed," "thought problems," and "rule-breaking behavior." The YSR has been validated as a measure of behavioral issues among adolescents (39), including in several studies in sub-Saharan Africa (40). In the current study, we will use data obtained from participants in the GOLD study during previous clinic visits when a validated bilingual (English and isiXhosa) YSR form was administered via an interview by a trained Research Assistant. During these visits, participants were asked (in the language in which they are most comfortable, English or isiXhosa) whether they think they have exhibited any of the behaviors in question over the past 6 months. These responses will be used as a gold-standard to compare with the translated version of the PHQ-9. Participants' most recent YSR scores will be used, and the YSR and PHQ-9 will be administered as closely as possible, and not more than 3 months apart. T scores for the "Withdrawn/Depressed" component within Syndrome Scales and "Affective Problems" component within DSM-Oriented Scales produced using YSR reponses will be used to determine participants' depressive symptoms and classify participants as "clinically depressed," "borderline," or "non-depressed" using ASEBA standards. No new YSR responses will be collected for this study; we will use data from the most recent clinic visit.

2.3. Procedure

2.3.1. Setting

The study site for participant recruitment and data collection will be: Family Centre for Research with Ubuntu (FAMCRU), Ward J8, Tygerberg Hospital, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University. The basic infrastructure necessary for participant recruitment and data collection is already in place at FAMCRU.

2.3.2. Transcultural isiXhosa Translation of the PHQ-9

The process of transcultural translation of psychometric tools involves steps to ensure that translated questionnaires remain accurate, relevant, and culturally acceptable (41, 42). We will adopt this systematic methodology to translate the PHQ-9 into isiXhosa using four steps:

1. Translation from English into isiXhosa by two independent bilingual (English and isiXhosa) speakers;
2. Review of isiXhosa translation by mental health experts and clinical care professionals who speak both languages;
3. Review of translation by a co-production panel involving adults living with HIV and adults with a lifetime history of depression; and
4. Blinded back-translation from isiXhosa into English by two additional independent bilingual translators.

The translated version will be refined after each step to preserve the core meaning and purpose of each item and incorporate culturally-specific idioms describing the affective components measured by the questionnaire where possible. Modifications will be reconciled in consultation with the translators and review panel involved in this process. The final isiXhosa-language version of the PHQ-9 will be available in Supplementary Materials.

2.3.3. Co-production

Knowledge co-production, or participatory research methods, involves incorporating insights from individuals with lived experience of the conditions being studied. We will recruit 3-4 isiXhosa-speaking co-producers as a focus group to review and provide feedback on the isiXhosa translation of the PHQ-9 during the initial stages of this study. Up to two adults living with HIV and two adults who have experienced depression in their lifetime will be recruited through the FAMCRU clinic, Stellenbosch University network, and/or Twitter advertisements. These individuals will be invited to review the isiXhosa PHQ-9 after it has undergone review by a panel of experts and caregivers and suggest edits to improve the accessibility, comprehensibility, and cultural specificity of the translation. Co-producers will be reimbursed for their time.

2.3.4. Participant Recruitment and Informed Consent

Participants will be recruited through the GOLD study at Tygerberg Hospital. Adolescents living with HIV who meet the current study's inclusion criteria will be contacted by FAMCRU research staff to ascertain interest in participation in this study. A trained counselor will discuss the study procedures in person with the potential participant's parent or legal guardian in their preferred language. Informed consent and assent forms will be available in two versions (English and isiXhosa). Parents or legal guardians of the participants will be asked to read and review the consent form. If participants agree to take part in the current study, written informed consent will be received from parents or legal guardians in advance of the study procedures. All participants will also be required to assent to the study procedures. Participants will be reimbursed R350 for their travel costs to visit the clinic for the study in line with Stellenbosch University policies.

2.3.5. Psychometric Testing

Participants will be provided a private space for psychometric testing. A member of the research staff will brief participants on the procedures involved in the study and receive informed assent. The research staff will then confirm that the participants would prefer to respond to questionnaires in isiXhosa and offer them a choice between filling out the questionnaire themselves in writing or having the research staff ask them the questions verbally (for participants who may not be able to write or have a preference for spoken isiXhosa over written isiXhosa). If participants choose to complete the psychometric testing in writing, they will be asked to fill out a short demographic questionnaire and the translated version of the PHQ-9 in writing (paper and pencil). If participants choose to complete the questionnaire verbally, the member of the research staff will read each item on the questionnaire in a neutral manner and write down the response, without judgement or comment. In either case, the research staff member will be available to the participant for any clarifications to ensure participants understand what each question is asking. Once participants have completed the demographic questionnaire and the PHQ-9, the research team member will verify that all nine items of the PHQ-9 have been completed. If the questionnaire is incomplete, the participant's responses will be excluded. If the responses are complete, the research team member will calculate the total score on the PHQ-9 as the sum of the scores from individual items and input responses into a secure electronic data capture programme (Project RedCap), which includes built-in quality control checks. Data will be handled in accordance with the General Data Protection Regulation (GDPR) Act that informs best practice for personal data storage and transfer in Europe.

2.4. Statistical Approach

All statistical analyses will be performed using SPSS Statistics version 25 and R version 4.0.3. To determine the reliability of the isiXhosa PHQ-9, we will calculate Cronbach's α as a measure of internal consistency for the translated version. Inter-item and item-total score correlations will also be calculated. To determine convergent validity for the PHQ-9, Pearson's correlation coefficients will be calculated for the total PHQ-9 scores and T scores for the "Anxious/Depressed" and "Withdrawn/Depressed" syndrome scales on the YSR. To determine the criterion validity of this PHQ-9 version, we will compare participant responses on the isiXhosa PHQ-9 with the YSR forms and calculate diagnostic sensitivity and specificity, predictive values (PPV/NPV), likelihood ratios (PLR/NLR), and Youden's Index. A Receiver Operating Characteristic (ROC) curve will be produced for the isiXhosa PHQ-9 and area under the curve (AUC) will be calculated for the PHQ-9 to determine diagnostic performance in comparison to the YSR. Finally, individual item analyses will be conducted to determine whether mean scores on each item of the PHQ-9 differed between depressed, borderline, and non-depressed participants (as determined by the YSR responses).

DATA AVAILABILITY STATEMENT

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 Stellenbosch University Human Research Ethics Committee (HREC), Study Reference N21/10/116_Sub Study N19/10/135. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AMRL and BL conceptualized the study together. AMRL designed the study and statistical approach, and wrote the initial draft. BL refined experimental design and reviewed the manuscript. Both authors contributed to the article and approved the submitted version.

FUNDING

This study is supported by funding from the Wellcome Trust (Grant No. 218493/Z/19/Z, Translational Neuroscience Ph.D. Programme) and the Harold Hyam Wingate Foundation (Medical Research Travel Grant) awarded to AMRL. Infrastructure for this study was made possible by NIH Grant R01HD099846 supporting the GOLD study.

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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 a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fpsyt.2022.810867

Nonlinear Probability Weighting in Depression and Anxiety: Insights From Healthy Young Adults

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Both depressive and anxiety disorders have been associated with excessive risk avoidant behaviors, which are considered an important contributor to the maintenance and recurrence of these disorders. However, given the high comorbidity between the two disorders, their independent association with risk preference remains unclear. Furthermore, due to the involvement of multiple cognitive computational factors in the decision-making tasks employed so far, the precise underlying mechanisms of risk preference are unknown. In the present study, we set out to investigate the common versus unique cognitive computational mechanisms of risk preference in depression and anxiety using a reward-based decision-making task and computational modeling based on economic theories. Specifically, in model-based analysis, we decomposed risk preference into utility sensitivity (a power function) and probability weighting (the one-parameter Prelec weighting function). Multiple linear regression incorporating depression (BDI-II) and anxiety (STAI state anxiety) simultaneously indicated that only depression was associated with one such risk preference parameter, probability weighting. As the symptoms of depression increased, subjects' tendency to overweight small probabilities and underweight large probabilities decreased. Neither depression nor anxiety was associated with utility sensitivity. These associations remained even after controlling covariates or excluding anxiety-relevant items from the depression scale. To our knowledge, this is the first study to assess risk preference due to a concave utility function and nonlinear probability weighting separately for depression and anxiety using computational modeling. Our results provide a mechanistic account of risk avoidance and may improve our understanding of decision-making deficits in depression and anxiety.

Keywords: decision-making, reward, risk preference, risk aversion, probability weighting, depression, anxiety, computational psychiatry

OPEN ACCESS

Edited by:
Jasmin Vassileva, Virginia Commonwealth University, United States

Reviewed by:
Erdem Pulcu, University of Oxford, United Kingdom
Yoshihiko Kunisato, Senshu University, Japan

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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: *08 November 2021*
Accepted: *17 February 2022*
Published: *24 March 2022*

Citation:
Hagiwara K, Mochizuki Y, Chen C, Lei H, Hirotsu M, Matsubara T and Nakagawa S (2022) Nonlinear Probability Weighting in Depression and Anxiety: Insights From Healthy Young Adults. Front. Psychiatry 13:810867. doi: 10.3389/fpsyt.2022.810867

INTRODUCTION

Depressive and anxiety disorders (hereafter, depression and anxiety) are two most prevalent and disabling mental disorders that greatly limit people's daily activities (1, 2). One frequently reported deficit common to both disorders is impaired decision-making under risk or risk preference. For instance, both depression (3–5) and anxiety (6–10) have been associated with

enhanced risk avoidant behaviors. Risk neutrality is typically considered optimal behavior while excessive risk avoidance may reduce the opportunities of potentially rewarding stimuli and lead to suboptimal outcomes. In fact, these behaviors have been considered an important contributor to the maintenance and recurrence of depression and anxiety, and have been employed a primary treatment target [for reviews, Jacobson *et al.* (11) and Pittig *et al.* (12)].

Despite these fruitful findings, two fundamental questions remain to be addressed. Firstly, given the high comorbidity between depression and anxiety (13), their independent association with risk preference remains unclear. Are they both, or is just one of them, associated with changed risk preference? Secondly, due to different definitions of "risk" in psychology and neuroeconomics and the involvement of multiple cognitive computational factors in decision-making processes, the precise underlying mechanisms of risk preference in depression and anxiety are unknown. Whereas risk commonly refers to the probability of a choice leading to an aversive outcome such as a loss or harm in psychology, it is defined as the variability of possible outcomes of a choice in behavioral economics and neuroeconomics (14).

Notably, previous studies of risk preference in depression and anxiety have generally employed the psychological definition of risk. For instance, two mostly widely employed tasks for the evaluation of risk preference in depression and anxiety are the Iowa Gambling Task (IGT) and the Balloon Analog Risk Task (BART). In the IGT (15), subjects are asked to choose one of four decks of cards to maximize their reward. Unknown to them, two of the four decks are disadvantageous such that although they bring a higher reward, occasionally they are associated with a much higher penalty and frequent choice from these decks will result in long-term loss. The other two decks are advantageous and although they bring lower gains, the occasional penalties are also lower. The proportion of choices taken from the advantageous decks is typically used as an index of task performance and risk-aversion. In the BART (16), subjects are asked to pump a balloon to earn money. Each pump expands the balloon and earns a fixed amount of money. Each pump, however, also increases the chance of the balloon exploding, which causes the loss of all money earned from that balloon (as one trial). The average number of pumps on unexploded balloons is used as an index of risk-taking propensity. Based on these tasks, it has been suggested that patients with depression and anxiety and people with high symptoms of depression and anxiety show reduced risk-taking or increased risk-aversion (3, 5, 7, 8).

However, it has to be noted that these tasks do not allow pure, reliable evaluation of risk preference, because in addition to risk preference (according to the economic definition), both tasks also involve the decision-making process of reinforcement learning (of each card-outcome contingency and balloon exploding probability) and loss aversion (toward penalty and balloon exploding which causes the loss of all reward). These three are different cognitive computational processes and rely on distinct neurobiological mechanisms (14, 17, 18). This may explain why previous studies with the IGT have generated conflicting results, for instance, both impaired and enhanced performance have been reported in individuals with high depression [Must et al. (19), Cella et al. (20) versus Smoski et al. (3)] and high anxiety [Miu et al. (21) versus Mueller et al. (8)]. To clarify whether depression and anxiety are associated with risk preference, one has to use more appropriately designed tasks and computational modeling of the decision-making process that allow the differentiation of relevant cognitive computational processes.

In economics, risk is defined as outcome variance and risk aversion refers to the preference of outcomes with high certainty. For instance, an individual preferring an option with a sure outcome (e.g., $50 guaranteed) over another with an unsure outcome that has equal or greater expected value (e.g., 50% chance of getting $100) is said to be risk-averse, while an individual with the opposite preference is said to be risk-seeking. This risk preference is captured by a utility or utility sensitivity function (e.g., a power function), for which linear utility functions indicate risk-neutrality, concave utility functions indicate risk aversion, and convex functions indicate risk seeking (see **Figure 1**, left panel). To account for mixed risk preference at small versus large probabilities, Prospect theory (22, 23) introduced the probability weighting function and suggested that most people tend to overweight small probabilities (i.e., risk seeking in the case of gain) and underweight large probabilities (i.e., risk aversion in the case of gain). Here, a linear function indicates the subjective probability equals the objective probability indicates risk-neutrality, and a nonlinear function indicates that people have different risk preference at small versus large probabilities (see **Figure 1**, right panel). Therefore, the combination of a utility function and a probability weighting function can more thoroughly capture people's risk preference.

In the present study, we set out to investigate the common versus unique cognitive computational mechanisms of risk preference in depression and anxiety using a reward-based learning-free decision-making task and computational modeling based on the above economic theories. Specifically, we attempted to dissect risk preference into two parameters, utility sensitivity and probability weighting, and investigate their independent association with depression and anxiety using multiple linear regression analysis.

MATERIALS AND METHODS

Participants

This research was part of an ongoing cohort study conducted to predict the mental health of young adults. The study was approved by the Institutional Review Board of Yamaguchi University Hospital and performed according to the latest version of the Declaration of Helsinki. The inclusion criteria were being 20–39 years old. The exclusion criteria were (1) having any self-reported psychiatric disorders, (2) receiving medical examinations due to suspicion of any psychiatric disorders, (3) being suspected of psychiatric disorders and diagnosed as having any psychiatric disorders by a psychiatrist, or (4) being unable to perform the tasks or questionnaires for this study.

Data collected at the baseline of the study during the year 2019 were used for the data analysis here. Specifically, 68 participants

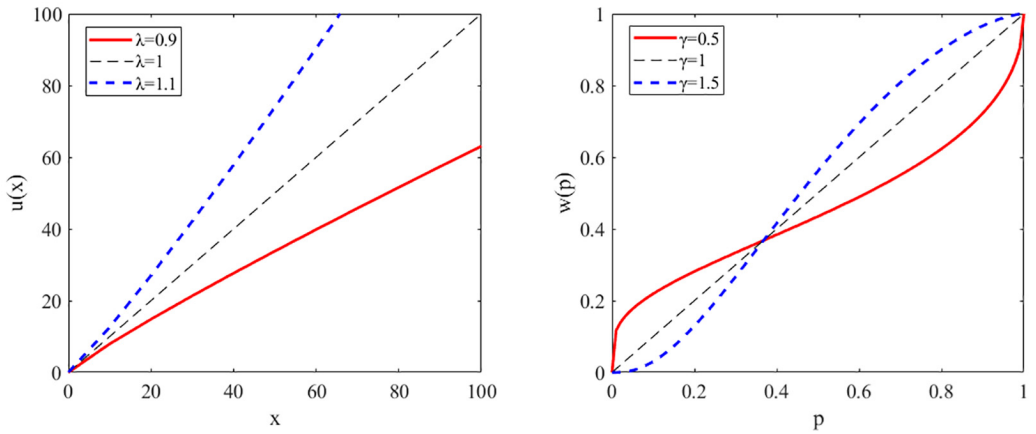

FIGURE 1 | Illustration of the utility and probability weighting function. Left panel: a representative plot of the utility function for risk-averse, risk neutral, and risk-seeking individuals. Utility (u) as a function of reward amount or magnitude (x). Right panel: a representative plot of the probability weighting function showing the decision weight (w) as a function of objective probability (p).

agreed to participate in this study and provided written informed consent. No participant met any of the exclusion criteria. We considered this sample size appropriate for our analysis here, because based on a priori power analysis conducted with G*Power version 3.1.9.7 (24), to detect a significant regression coefficient of moderate effect size [f^2 = 0.15; (25)] with alpha = 0.05, power = 0.8, and two predictors (i.e., depression and anxiety), 43 participants are required.

Demographic Information

Participants first filled out questionnaires about their demographic characteristics, including gender, age, occupation, education level, and socioeconomic status such as whether they had made a student loan as an undergraduate student, their parents' education levels and family income.

Decision-Making Task

We adapted an established task design (26). The task was programmed with MATLAB R2018b (MathWorks) and Psychtoolbox 3.[1] The task had 120 trials and was conducted in three sessions, each separated by a short break. In each trial (**Figure 2**), participants were instructed to choose between two gambling options to maximize their reward. Each option consisted of a reward magnitude (in JPY, the lower number) and the probability of receiving that magnitude of reward (the upper number). For the option pairs of reward magnitude and probability, we used the stimuli generated by Hsu et al. (26) (**Supplementary Table 1**), but replaced the original amount in dollar with that in JPY by multiplying 100 (as an approxiate of the exchange rate). Furthermore, we presented the probabilities as percentages instead of the orignal ratios (e.g, 40/100) used by Hsu et al. (26) to faciliate perception. To ensure that participants were focusing on the task, after a randomly selected trial in every 15 trials, we inserted a test trial (eight in total) which had a correct answer (e.g., 30%, 5,000 versus 50%, 5,000).

[1]http://psychtoolbox.org/

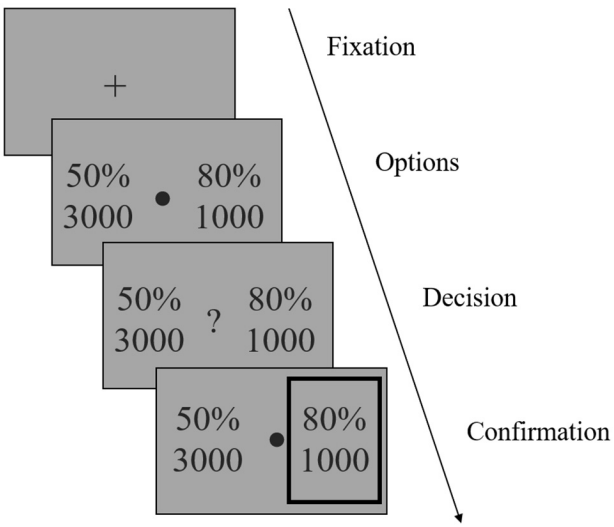

FIGURE 2 | Illustration of the reward-based decision-making task. After a fixation phase, two gambling options were shown (Options phase). Each option consisted of a reward magnitude (in JPY) and the probability of receiving that magnitude of reward. Participants were instructed to choose one option to maximize their reward, by pressing one of two predefined arrow keys once a question mark occurred (Decision phase). The chosen option was then highlighted by a gray frame (Confirmation phase). Note that the gambling options shown in the figure were not actual stimuli used in the study.

After a fixation phase (or inter-trial interval) of 1.5 s, the stimuli were shown on the screen for 3 s (Options phase), after which a question mark occurred and participants indicated their choice by pressing one of two arrow keys within 3 s and as soon as possible once they decided which to choose (Decision phase). The chosen option was then highlighted by a gray frame (Confirmation phase). Participants were informed that failing to respond within the decision phase would be counted as no response and lead to no reward on that trial.

TABLE 1 | Model specification and fitting results.

Model No.	Model description	Equation	Free parameters	AIC
1	Magnitude only	$V(X) = r$	β	165.57
2	Probability only	$V(X) = p$	β	113.82
3	Magnitude and probability	$V(X) = rp$	β	161.38
4	Magnitude with utility function and probability	$V(X) = r^{\lambda}p$	λ, β	105.47
5	Magnitude and probability with probability weighting	$V(X) = re^{-(-\log p)^{\gamma}}$	γ, β	157.85
6	**Magnitude with utility function and probability with probability weighting**	$\boldsymbol{V(X) = r^{\lambda}e^{-(-logp)^{\gamma}}}$	**λ , γ, β**	**96.03**

The winning model is shown in bold.

Each subject received a fixed payment of about 3,000 JPY for participating in the study. We did not implement the performance-adjusted payment because the final aim of our study was to develop useful tools for predicting mental health problems in a public health setting. For such purpose, it is impossible to pay people a certain amount of money based on their task performance in any public health screening tools. Furthermore, previous studies have shown that people's decision-making with hypothetic rewards highly resembles that with real rewards (27).

Depression and Anxiety

The Beck Depression Inventory-II (BDI-II) and the state anxiety subscale of State-Trait Anxiety Inventory (STAI-Y1) were employed to evaluate the symptoms of depression and anxiety, respectively. Since BDI-II also includes two primary symptoms of anxiety, namely agitation and irritability, we also created another variable of depression BDI-pure by excluding these two items.

Data Analysis

IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, Untied States) and MATLAB R2018b (The MathWorks, Inc., Natick, MA, United States) were used for data analysis. All statistical tests were two-sided and $p < 0.05$ was considered significant.

For the computational model-based analysis of the behavioral data, we fitted six models to participants' choice (**Table 1**). Two models used a value function that considered only reward magnitude or probability (i.e., Models 1 and 2). Four models (i.e., Models 3–6) used a value function that considered both magnitude and probability with or without a utility function (i.e., a power function) and/or probability weighting function (i.e., the one-parameter Prelec weighting function).

For the utility function parameter λ, 1 indicates risk-neutrality, <1 indicates risk aversion, and >1 indicates risk seeking. For the probability weighting function parameter γ, 1 indicates rational probability weighting, <1 indicates overweighting of small probabilities and underweighting of large probabilities, and >1 indicates the opposite. Participants were then assumed to choose actions stochastically according to a sigmoidal probability distribution, with an inverse temperature parameter β adjusting the degree of stochasticity in participants' choices. Following Hsu et al. (26), the models were fitted to each participant's behavior using maximum likelihood estimation. The estimation was conducted using the *fmincon* command of MATLAB 2018b. Model selection was based on Akaike information criterion (AIC), which puts a penalty on the increasing number of free parameters. The estimated parameters of the winning model were then used for subsequent data analysis. To investigate the independent association between depression, anxiety, and risk parameters, we conducted multiple linear regression, with the risk parameters as dependent variables and depression and anxiety as independent variables. We also included demographic or socioeconomic factors as covariates for the regression analysis if they were correlated with depression, anxiety, or any of the risk parameters. There were two missing values with the data of father education level, which were replaced with multiple imputation (imputed five times by ordinal logistic regression with other demographic factors as predictors). Father education and mother education were coded as 1 for elementary school level, 2 for junior high school level, 3 for senior high school level, 4 for vocational school level, 5 for undergraduate level, 6 for master's level, and 7 for doctorate level. The data of family income had ten missing values and therefore the variable was excluded from data analysis. The normal P–P plot of regression standardized residual of each regression model was confirmed and presented in **Supplementary Figure 1** (for regression reported in **Table 2**) and **Supplementary Figure 2** (for regression reported in **Table 3**). We did not detect any obvious multicollinearity (i.e., variance inflation factors all <1.7) or homoscedasticity issue with the regression models. Given our small set of predictors and that we were not clear which was the best predictor, we used the standard "Enter" method for the regression models.

Additional Analysis

Given the considerable correlation between BDI and STAI-Y1, we also took two additional approaches to investigating their independent association with the risk parameters. Firstly, we conducted a principle component analysis (PCA, with Varimax rotation) with the individual items of BDI and STAI-Y1 and extracted seven factors that account for 64% of the total variance. The scree plot is shown in **Supplementary Figure 3** and the item structures of the seven factors are shown in **Supplementary Table 1**. As can be seen, Factors 1 and 7 primarily measure anxiety and Factors 3–6 primarily measure depression, while Factor 2 captures both anxiety and depression. For the calculation of the factor score, we employed two methods, one was a commonly used non-refined method, namely simply summing the raw scores of all items loading on the factor, the other was a refined method known as the Anderson-Rubin score (28). The correlation between the score of the extracted factors and

the risk parameters is shown in **Supplementary Table 2**. In brief, a consistent correlation was identified between Factor 3 (which primarily measures depression) and γ across the factor scores. In contrast, the correlation between Factors 5 (which primarily measures depression) and λ was significant for the sum of raw score but not the Anderson-Rubin score. Unfortunately, these correlations became nonsignificant after partialling out mother education.

Secondly, we examined the correlation between individual items of BDI and STAI-Y1 and selected items having the fewest correlations with items from the other scale (**Supplementary Table 3**). For depression, eight items were selected (i.e., symptoms of sadness, suicidal thoughts, loss of interest, worthlessness, changes in sleep, appetite, fatigue, and loss of interest in sex). For anxiety, six items were selected (i.e., feelings of calm, secure, tense, strained, at ease, and confused). Although the selection was rather arbitrary, we considered these symptoms representative of depression and anxiety, respectively. We then ran correlation analysis between the total scores of the selected items (hereafter Depression-selected and Anxiety-selected) and the risk parameters (**Supplementary Table 4**). It was found that Depression-selected but not Anxiety-selected was associated with γ; neither was associated with λ. These results remained even after partialling out mother education. The scatter plot of the associations is shown in **Supplementary Figure 4**.

Furthermore, we used the one-parameter rather than the Prelec-2 parameter weighting function because the former is more straightforward and simplifies the inter-subject analysis, as noted by previous studies (26, 29). Nevertheless, for validation purpose, we ran the estimation with the Prelec-2 parameter weighting function as well as a novel one-parameter weighting function with a log2 base (30). The fitting results are shown in **Supplementary Table 5** and as can be seen, the model with utility function and the Prelec-2 parameter weighting function (model 8) outperformed the main model used here (model 6, AIC = 90.75 versus 96.03), while the model with utility function and the novel one-parameter weighting function with a log2 base (model 10) performed equally well with the main model (model 6, AIC = 95.96 versus 96.03). To validate our results, we therefore reran all the analysis with the parameters estimated from models 8 and 10.

For model 8 with the Prelec-2 parameter weighting function, the results of multiple linear regression using BDI/BDI-pure and STAI-Y1 to predict the risk parameters are shown in **Supplementary Tables 6**, **7**. As can be seen, BDI and BDI-pure but not STAI-Y1 were significantly associated with γ; neither BDI/BDI-pure nor STAI-Y1 was significantly associated with λ. The results of the correlation between the PCA extracted factors and risk parameters are shown in **Supplementary Table 8**. Factor 3 that captures depression was significantly associated with γ but not λ, even after partialling out mother education. Lastly, Depression-selected but not Anxiety-selected was significantly associated with γ but not λ, even after partialling out mother education (**Supplementary Table 4**).

For model 10 with the novel one-parameter weighting function with a log2 base, the results of multiple linear regression using BDI/BDI-pure and STAI-Y1 to predict the risk parameters are shown in **Supplementary Tables 9**, **10**. Here, neither BDI/BDI-pure nor STAI-Y1 was associated with γ or λ. The results of the correlation between the PCA extracted factors and risk parameters showed that only factors measuring depression (i.e., Factors 3, 5, and 6) were significantly associated with γ,

TABLE 2 | Results of the multiple linear regression using BDI.

	Independent variables	Dependent variable: γ			Dependent variable: λ		
		Unstandardized *B* (95% CI)	Standardized beta	*p*	Unstandardized *B* (95% CI)	Standardized beta	*p*
Model 1	BDI	**0.015 (0.002, 0.029)**	**0.389**	**0.027***	−0.007 (−0.019, 0.005)	−0.197	0.268
	STAI-Y1	−0.004 (−0.016, 0.008)	−0.118	0.494	0.009 (−0.001, 0.019)	0.303	0.091
Model 2	BDI	**0.014 (0.000, 0.027)**	**0.346**	**0.043***	−0.006 (−0.018,0.006)	−0.185	0.305
	STAI-Y1	−0.002 (−0.014, 0.009)	−0.071	0.674	0.008 (−0.002,0.019)	0.290	0.111
	Mother education	**0.115 (0.006, 0.224)**	**0.277**	**0.039***	−0.027 (−0.127,0.074)	−0.075	0.594

*$p < 0.05$. *Significant results are shown in bold.*

TABLE 3 | Results of the multiple linear regression using BDI-pure.

	Independent variables	Dependent variable: γ			Dependent variable: λ		
		Unstandardized *B* (95% CI)	Standardized beta	*p*	Unstandardized *B* (95% CI)	Standardized beta	*p*
Model 3	BDI-pure	**0.017 (0.003, 0.032)**	**0.407**	**0.018***	−0.006 (−0.019, 0.006)	−0.175	0.317
	STAI-Y1	−0.004 (−0.015, 0.007)	−0.120	0.474	0.008 (−0.002, 0.018)	0.285	0.105
Model 4	BDI-pure	**0.016 (0.002, 0.030)**	**0.363**	**0.030***	−0.006 (−0.019, 0.007)	−0.163	0.358
	STAI-Y1	−0.002 (−0.014, 0.009)	−0.074	0.652	0.008 (−0.002, 0.018)	0.273	0.127
	Mother education	**0.113 (0.005, 0.222)**	**0.273**	**0.040***	−0.027 (−0.128, 0.074)	−0.076	0.590

*$p < 0.05$. *Significant results are shown in bold.*

most of which remained after partialling out mother education (**Supplementary Table 11**). None of the factors were associated with λ. Lastly, again, Depression-selected but not Anxiety-selected was significantly associated with γ but not λ, even after partialling out mother education (**Supplementary Table 4**).

In summary, across three different methods of analyzing the symptoms of depression and anxiety [i.e., (a) incorporating them simultaneously in multiple linear regression to predict the risk parameters, (b) examining the correlation between the underlying latent factors of depression and anxiety extracted using PCA and the risk parameters, and (c) selecting items with the fewest correlations with items from the other scale to create Depression-selected and Anxiety-selected and then examining the correlation between these new variables and the risk parameters] and three different probability weighting functions for computational modeling (i.e., Prelec-1 parameter, Prelec-2 parameter, and one-parameter function with a log2 base), the most consistent pattern of result observed was the association between depression and γ. Namely, as the symptoms of depression increased, subjects' tendency to overweight small probabilities and underweight large probabilities decreased.

RESULTS

Among 68 participants that conducted the decision-making task, 11 failed to respond on over five trials and/or made over two incorrect choices on the eight test trials, two almost always chose the option with the higher probability which did not permit reliable model fitting, two had fitted parameters over three standard deviation (SD) above the mean of all participants which was also far greater than previously reported [e.g., Hsu et al. (26)]. These subjects were therefore excluded and the data of the remaining 53 participants were used for further analysis. Importantly, the excluded participants did not differ from the remaining participants in terms of BDI, BDI-pure, or STAI-Y1 (all $p > 0.4$). Among the remaining participants, 21 were males and 32 females, the mean age was 22.48 (SD 2.92) years. The mean scores of BDI, BDI-pure, and STAI-Y1 were 7.98 (SD 7.67), 7.57 (SD 7.02), and 37.45 (SD 8.89), respectively.

For the computational model-based analysis, as shown in **Table 1**, model 6 that had a utility parameter λ and probability weighting parameter γ was the winning model since it had the smallest AIC.

To investigate the independent association between depression, anxiety, λ, and γ, we conducted multiple linear regression for λ and γ, respectively, with BDI and STAI-Y1 as independent variables. As shown in **Table 2** (Model 1), BDI but not STAI-Y1 was significantly associated with γ ($B = 0.015$, 95% CI = [0.002, 0.029], $p < 0.05$). Neither BDI nor STAI-Y1 was significantly associated with λ. The partial regression plot of BDI/STAI-Y1 and the parameters are shown in **Figure 3**. Among demographic factors, only mother education level was associated with γ, we therefore incorporated this variable as a covariate in the regression analysis. As reported in **Table 2** (Model 2), even after controlling the influence of mother education, the association between BDI and γ remained significant ($B = 0.014$, 95% CI = [0.000, 0.027], $p < 0.05$). Notably, mother education was also significantly associated with γ ($B = 0.115$, 95% CI = [0.006, 0.224], $p < 0.05$), although its standardized regression coefficient was smaller than that of BDI (i.e., 0.277 versus 0.346).

Given that BDI has two items that are also considered the primary symptoms of anxiety, namely agitation and irritability, we therefore created another variable of depression, BDI-pure, by excluding these two items. We repeated the above multiple linear regression. As shown in **Table 3**, only BDI-pure was associated with γ ($B = 0.017$, 95% CI = [0.003, 0.032], $p < 0.05$), this remained even after controlling mother education ($B = 0.016$, 95% CI = [0.002, 0.030], $p < 0.05$).

To provide a visual illustration of the change in γ (i.e., probability weighting) given the change in BDI, we plotted the simple scatterplot of the association between BDI and γ in **Figure 4** (left panel). We also categorized participants based on their score of BDI, such that those within the lower quartile were categorized as having low depression ($n = 17$) and those within the upper quartile were categorized as having high depression ($n = 16$). The plot of the probability weighting function for each group mean is shown in **Figure 4** (right panel). As can be seen, the probability weighting of the low depression group is similar to previously reported in Japanese healthy young adults (29), in which participants tend to overweight small probabilities while underweight large probabilities. In contrast, this tendency is decreased in the high depression group.

DISCUSSION

To our knowledge, this is the first study to assess risk preference due to a concave utility function and nonlinear probability weighting separately for depression and anxiety using computational modeling. We showed that depression, but not anxiety, is associated with the nonlinear probability weighting parameter. That is, as the symptoms of depression increases, the typical overweighting of small probabilities and underweighting of large probabilities shown in people with low depression become attenuated. The probability weighting of the low depression group is also similar to previously reported in Japanese healthy young adults (29), both consistent with the Prospect Theory (22, 23). In contrast, neither depression nor anxiety was associated with utility sensitivity.

Depression and anxiety often co-occur with each other, as a result, comorbid major depressive disorder and an anxiety disorder (13, 31) and anxious-depression [or major depressive disorder with subthreshold anxiety symptoms; (32)] are highly prevalent. This co-occurrence is associated with greater distress, higher risk of suicide, poorer treatment outcomes, and higher rate of recurrence (33–36). One psychopathological mechanism proposed to account such co-occurrence is risk-avoidant behaviors, which has been reported to be common to both depression and anxiety (see section "Introduction"). Nevertheless, the independent association between depression, anxiety, and risk preference has been seldom investigated (37). In the only study that investigated depression, anxiety, and

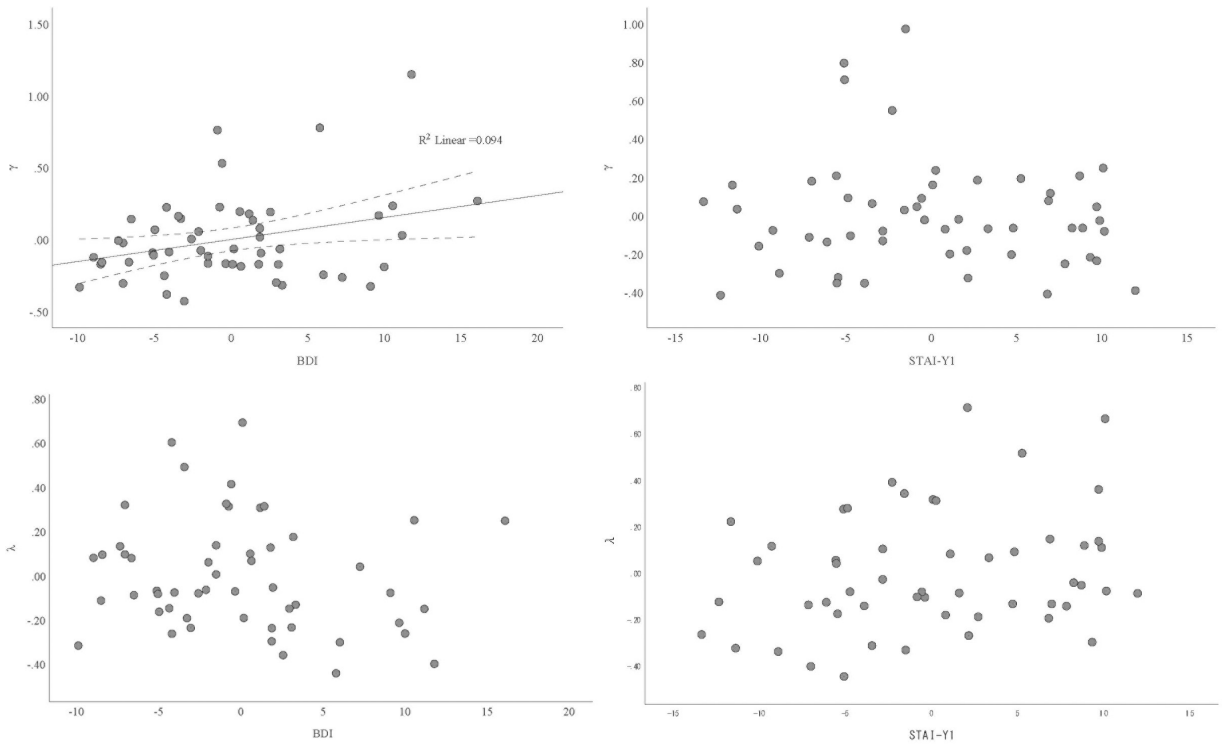

FIGURE 3 | Partial regression plot of the association between depression/anxiety and γ/λ.

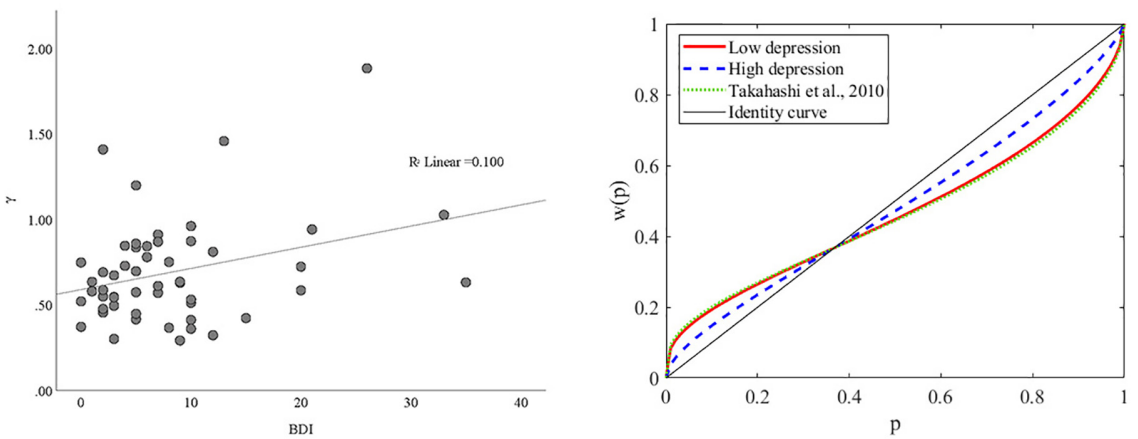

FIGURE 4 | The association between BDI and γ. **(Left panel)** Scatterplot of the association between BDI and γ. **(Right panel)** Probability weighting function plots for subjects with high and low depression. The mean of γ for the low and high depression groups were 0.5964 and 0.7772, respectively. The mean of γ for a similar group of Japanese young adults was 0.57 in Takahashi et al. (29).

utility sensitivity-based risk preference, Charpentier et al. (10) showed that patients with generalized anxiety disorder (GAD) had higher risk aversion (as indicated by a smaller λ) compared to healthy controls. Meanwhile, anxiety was positively associated with risk aversion when controlling depression, the opposite (i.e., the association between depression and risk aversion while controlling anxiety), however, was nonsignificant. The precise reason of such inconsistency between our and Charpentier et al.'s (10) results is unclear, future research is required to investigate if the difference in subject characteristics (healthy volunteers versus patients), task design (whether combine gain-only gambles with gain-loss mixed gambles), computational modeling (whether incorporate utility sensitivity and probability weighting simultaneously) may potentially explain the gap.

So far, in the field of computational model-based analysis of decision-making, reduced reward sensitivity and reinforcement

learning rate have been considered major decision-making deficits in depression (38, 39). However, as suggested by previous studies with IGT and BART, enhanced risk aversion is likely to be another critical deficit. Here, by removing the learning component and teasing apart utility sensitivity and probability weighting, we showed that depression is associated with underweighting of small probabilities (compared to those with low symptoms of depression), or in other words, enhanced risk aversion at small probabilities. It remains for future studies to test if the assumption of reduced reward sensitivity and reinforcement learning is true or just a confounding effect of probability weighting.

Our findings are consistent with previous reports of mood influence on judgment (40–42). For instance, when in a sad mood, people tend to underestimate the probabilities of positive events, whereas in a happy mood, they tend to overestimate such probabilities (41). Several theoretical explanations have been proposed, for instance, people's feelings are projected to the judgment (42) or their feelings are used as information for the judgment (43). From the perspective of the psychopathology of depression, the underweighting of small probabilities is a result of the depressogenic schemata or distorted cognition (44). One common depressogenic schemata is the 0-or-100 thinking (or black and white thinking, all-or-nothing mindset), that is, depressed patients tend to consider things in a dichotomous or polarized manner. With such a schemata, given two options one with high and the other low probability of getting a reward, people with high levels of depression will underestimate the low probability while overestimate the high probability when making the choice.

It is unclear why we did not observe an association between anxiety and both parameters of γ and λ. One previous study that employed the economic definition of risk has reported enhanced risk-aversion in patients with GAD and panic disorder (9). However, they did not remove the confounding effect of depressive symptoms and their sample size was relatively small (i.e., $n = 10$ for GAD and panic disorder each). Future research is required to confirm our findings and clarify the association between anxiety and risk preference.

Our study also has limitations. Firstly, we limited the age of our participants to 20–39 years to remove the confounding of age and improve statistical power, which, however, also limits the generalization of our conclusion to older adults and adolescents. Secondly, to simplify the task, we focused on decision based on only reward without considering loss. The Cumulative Prospect Theory argues that valuation differs between situations of reward and loss (23) and it is possible that our results may not apply to decisions involving loss. Thirdly, our subjects were healthy volunteers and therefore the symptoms of depression and anxiety here we evaluated were primarily in the normal range. Future studies are required to confirm if the association we observed also exist in clinical patients.

Despite these limitations, our study represents an important, first step toward the precise understanding of the cognitive computational mechanisms of decision-making in depression and anxiety. Such endeavors may help to elucidate the psychopathological basis of these disorders and facilitate the identification of their underlying neurobiological impairments.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Yamaguchi University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC and SN: conceptualization and design. KH, CC, HL, and MH: investigation. KH, YM, and CC: data analysis and manuscript preparation. TM: resources. All authors contributed to manuscript revision.

FUNDING

This study was supported by grants from SENSHIN Medical Research Foundation, Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number 19K17063), and Kanae Foundation for the Promotion of Medical Science to CC.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.810867/full#supplementary-material

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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 a potential conflict of interest.

frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 26 July 2022
DOI 10.3389/fpsyg.2022.941019

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychology

RECEIVED 11 May 2022
ACCEPTED 27 June 2022
PUBLISHED 26 July 2022

CITATION
Chacko TP, Toole JT, Richman S, Spink GL Jr, Reinhard MJ, Brewster RC, Costanzo ME and Broderick G (2022) Mapping the network biology of metabolic response to stress in posttraumatic stress disorder and obesity.
Front. Psychol. 13:941019.
doi: 10.3389/fpsyg.2022.941019

Mapping the network biology of metabolic response to stress in posttraumatic stress disorder and obesity

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The co-occurrence of stress-induced posttraumatic stress disorder (PTSD) and obesity is common, particularly among military personnel but the link between these conditions is unclear. Individuals with comorbid PTSD and obesity manifest other physical and psychological problems, which significantly diminish their quality of life. Current understanding of the pathways connecting stress to PTSD and obesity is focused largely on behavioral mediators alone with little consideration of the biological regulatory mechanisms that underlie their co-occurrence. In this work, we leverage prior knowledge to systematically highlight such bio-behavioral mechanisms and inform on the design of confirmatory pilot studies. We use natural language processing (NLP) to extract documented regulatory interactions involved in the metabolic response to stress and its impact on obesity and PTSD from over 8 million peer-reviewed papers. The resulting network describes the propagation of stress to PTSD and obesity through 34 metabolic mediators using 302 documented regulatory interactions supported by over 10,000 citations. Stress jointly affected both conditions through 21 distinct pathways involving only two intermediate metabolic mediators out of a total of 76 available paths through this network. Moreover, oxytocin (OXT), Neuropeptide-Y (NPY), and cortisol supported an almost direct propagation of stress to PTSD and obesity with different net effects. Although stress upregulated both NPY and cortisol, the downstream effects of both markers are reported to relieve PTSD severity but exacerbate obesity. The stress-mediated release of oxytocin, however, was found to concurrently downregulate the severity of both conditions. These findings highlight how a network-informed approach that leverages prior knowledge might be used effectively in identifying key mediators like OXT though experimental verification of signal transmission dynamics through each path will be needed to determine the actual likelihood and extent of each marker's participation.

KEYWORDS

psychoneuroimmunology, metabolism, posttraumatic stress disorder, obesity, computational model, regulatory logic, homeostasis

Introduction

The biological and behavioral link between posttraumatic stress disorder (PTSD) and obesity has gathered some empirical traction, particularly because of the elevated co-occurrence of the two conditions (Mitchell et al., 2021). Indeed, veterans with PTSD consistently present with elevated body mass index (Buta et al., 2018) with 83% qualifying as overweight (BMI = 25–29), or obese (BMI $\geq$ 30) (Hall et al., 2020). This frequency of occurrence does not appear to differ significantly between sexes. A large study conducted recently by the Veterans Health Administration (VHA; Breland et al., 2020, N = 4,867,049), found that 44.2% of female veterans had a mean BMI of 29.9 (SD = 6.5) and 41.7% of male veterans had a mean BMI of 29.7 (SD = 5.7), again pointing to an elevated rate of obesity in this population. Importantly, a nationally representative investigation of PTSD and obesity among veterans (N = 3,157) found that 5.8% of veterans had co-occurring PTSD and obesity, while 32.7% of them reported obesity and 16.4% reported PTSD (Stefanovics et al., 2020). Moreover, these same authors found that veterans with co-occurring PTSD and obesity also suffered from a higher occurrence of other psychiatric disorders such as anxiety and depressive disorders, suicidal ideation, nicotine dependence as well as a myriad of physical health problems including migraine headaches, diabetes, hypertension, and insomnia.

Current explanations for the convergence of PTSD and obesity often implicate various types of eating disorders [e.g., night eating syndrome (Dorflinger and Masheb, 2018), binge eating (Hoerster et al., 2015), bulimia nervosa (Mitchell et al., 2012), anorexia nervosa (Castellini et al., 2018; Longo et al., 2019), and emotional eating (Dorflinger and Masheb, 2018)], emerging as maladaptive coping strategies, which mediate and maintain the relationship between PTSD and obesity. Consistent with this view, PTSD is widely considered a behavioral risk factor for Metabolic Syndrome (MetS), including diabetes, dyslipidemia, hypertension, and obesity (Bartoli et al., 2013). Indeed, our understanding of the underlying biological regulatory mechanisms that jointly drive PTSD and obesity is still in its nascent stages, particularly as it applies the persistence and co-occurrence of these conditions. In a reductionist approach, investigations of the physiological response mechanisms underlying PTSD have typically focused narrowly on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Dunlop and Wong, 2019). In contrast, a broader physiology has been implicated in obesity, one involving interplay between thyroid regulation, immune function as well as sex hormone regulation (Lainez and Coss, 2019) in maintaining energy homeostasis (Schwartz et al., 2017). Only in recent years have potentially important directions been proposed that focus on the convergence of stress responsive mechanisms active in both conditions (Xiao et al., 2020; Oroian et al., 2021). For instance, Michopoulos et al. (2016) reported on the co-occurrence of PTSD and metabolic disorders such as obesity and diabetes, suggesting that PTSD involves endocrine responses, which might lead to metabolic dysregulation as a function of trauma exposure. More specifically, the latter points to mechanistic interactions linking HPA axis function with that of the hypothalamic-pituitary-thyroid (HPT) axis. Phenotypically distinct yet also co-occurring, PTSD and obesity seem to engage both illness-specific well as overlapping stress-response mechanisms which might be recruited preferentially depending on the individual as well as on the history and context of events to drive the onset of a single or dual pathology.

In this article we leverage the known physiology of HPA, HPT and immune regulation to extract elements of these mechanisms from the peer-reviewed literature using large-scale automated text-mining. Documented interactions linking stress-responsive endocrine and immune mediators are then used to assemble a cohesive mechanistically informed network. We then analyze the uninterrupted paths in the network that facilitate the propagation of stress response through a cascade of metabolic regulatory mediators to affect either pathology independently or both pathologies jointly. By formally representing the close integration of these regulatory axis and the extent of their cross-talk in dictating behavioral responses, such network-informed methods have the potential to be highly effective in identifying key mediators of dysregulation in complex stress-mediated co-morbidities and by doing so offer a new and important perspective on their treatment.

Materials and methods

Network creation

In this work we establish an evidence-based regulatory network linking stress, PTSD, and obesity, by extracting endocrine and immune mediators with documented involvement in these conditions as well as their functional interactions from the Elsevier Biology Knowledge Graph database (Elsevier, Amsterdam) (Kamdar et al., 2020) using the Pathway Studio* suite of software tools (Nikitin et al., 2003). Updated on a weekly basis, this database currently recognizes in excess of 1.4 M biological entities (molecules, cell types, diseases, clinical measures, etc.) connected through over 13.5 M relationships (co-expression, regulatory, binding interactions, etc.) extracted by automated text mining from over 5 M full-text peer-reviewed publications and over 32 M PubMed abstracts describing *in vitro* as well as *in vivo* animal and human studies (including results from over 300,000 clinical trials). The query of this database conducted in the context of this work supported an initial 302 regulatory interactions (edges) previously extracted from 10,673 full text of peer-reviewed journal publications

using the MedScan natural language processing (NLP) engine (Novichkova et al., 2003; Daraselia et al., 2004).

Network reliability

Subsequent to model creation, we attempt to control for false positive interactions by testing each of the latter using network analytical concepts proposed by Guimerà and Sales-Pardo (2009) and based on the conservation of connectivity patterns that are broadly conserved in biological and social networks such as modularity or the presence of densely connected subnetworks. By comparing the properties of a given network to those that might be expected in biological networks of comparable size and complexity, the authors compute a reliability R_{ij} for each network interaction, or the estimated probability that the link "truly" exists given our observation of the whole underlying network. We extend this notion further by the adjusting the probability of an interaction being spurious based on the extent of documentation or number of citations C_{ij} supporting this interaction. Accordingly, an interaction linking node i to node j that presents with a high reliability R_{ij} base on its role in supporting a biologically plausible network structure and that is well documented in addition would correspond to a low spurious score S_{ij} (Eq. 1).

$$S_{\mathrm{ij}} = \frac{(1 - R_{\mathrm{ij}})}{C_{\mathrm{ij}}} \quad (1)$$

The spurious score S_{ij} was computed for each of the initial 302 regulatory interactions producing values ranging from 0 to roughly 68% that were in turn used to prune the network. We observe that these values decrease almost linearly for the 50 or so highest values. As shown in **Figure 1**, a linear regression was fit to the decrease in spurious score in this region (observations 10 through 30) producing an adjusted R^2 value of 0.98 with an average absolute residual error of 0.007. Using a standard one-sample t test to identify significant deviations from this linear regression we found that these occurred consistently with $p < 0.01$ for spurious scores below 30% indicating an inflection point and significant stabilization in spurious score. Accordingly, associations with spurious scores above this threshold were considered unreliable and removed from the final network (see **Supplementary Table 1**).

Analysis of network structure and traversing paths

As a means of assessing the degree of biological fidelity capture by this literature-informed network we computed various fundamental network topological features and properties (Barabási and Oltvai, 2004; Huber et al., 2007; Mason and Verwoerd, 2007). These include measures describing the general structure of the overall network such as the as its size and complexity such as network diameter and the network connection density. The network diameter represents the breadth of the network and is computed as the shortest distance between two most remote nodes. Likewise, we computed the characteristic path length, or the mean minimal distance between any two nodes, as a measure of the efficiency of information propagation through the network. As an indicator of network complexity, we computed the network connection density, or the total number of edges in the current network represented as a fraction of all the possible edges in a fully connected network with the same number of nodes. This measure is known to vary significantly across levels of biology and physiological compartments (Frankenstein et al., 2006). Finally, as connection patterns in biological networks tend to favor the emergence of highly subnetworks, or clusters, we also compute the network clustering coefficient (Guimerà and Sales-Pardo, 2009; Di Camillo et al., 2012) using the software package Cytoscape (Shannon et al., 2003).

At the level of individual nodes, we computed different centrality measures to describe their relative role within the network. First, we estimated the closeness centrality to describe how well-connected a given node is to the remainder of the network overall. This is computed as the average length of the shortest path between a given node and all other nodes in the network. To describe how a node might act as a key broker of information or gatekeeper between adjacent highly connected sub-networks, we computed the betweenness centrality. The measure is proportional to the frequency with which a node is positioned along the shortest paths between two other nodes. This same concept is extended to a more detailed analysis of minimal path length where we computed all paths of minimal length containing one or two intermediate nodes separating stress from obesity and stress from PTSD. These network analyses were conducted using the Python package NetworkX (Hagberg et al., 2008).

Results

General characteristics of the network

The original network produced by the NLP text-mining consisted of 33 nodes and 302 regulatory interactions. Analysis of the estimated reliability if these interactions indicated that roughly 1 in 8 of these (∼34 edges) did not contribute toward improving alignment of the overall network topology with what might be expected of a typical biological network containing the same number of nodes. These were removed to yield a truncated network consisting of the same 33 nodes connected through 268 regulatory interactions supported by a total of 10,637 reference citations (**Figure 2** and **Supplementary Table 1A**). The functional class assigned to these source-target relationships

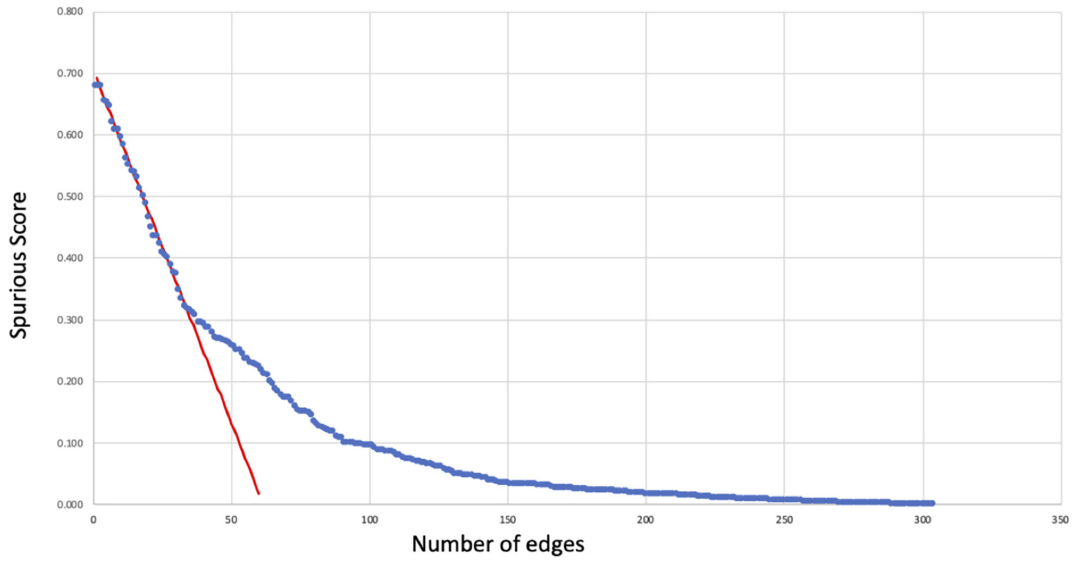

FIGURE 1
Reliability of regulatory interactions. Spurious scores S_{ij} (Eq. 1) computed for each of the initial 302 regulatory relationships (blue dots) as an estimate of the likelihood that these interactions might be false positives. These scores decrease linearly (red regression line) to S_{ij}~30% below which the rate of change slows considerably. As a result, regulatory relationships with $Sij \geq 30\%$ were removed as having a high likelihood of being spurious or false positive occurrences.

by MedScan (Novichkova et al., 2003; Daraselia et al., 2004) included direct regulation (23 edges), regulation (44 edges), molecular synthesis (19 edges), molecular transport (122 edges), and co-expression (60 edges). Relationships where the mode of action was not assigned were excluded leaving 179 relationships where the source upregulates the downstream target (positive polarity) and 89 where it downregulates the latter (negative polarity). On average, each of the 33 nodes interacted through these functional relationships with approximately 8 upstream and 8 downstream neighbors on average (**Supplementary Table 1B**) leading to an overall network connection density of roughly 25%. Perhaps not surprisingly, insulin (INS) and glucose appear as highly influential nodes with insulin having the highest number of upstream regulators (indegree 24) and glucose affecting the largest number of downstream targets (outdegree 20). High closeness centralities for both nodes (0.67 for insulin and 0.76 for glucose) indicated that these connections were distributed in a way that support a broad network-wide involvement. Insulin also emerged as the dominant mediator of information flow across the various network neighborhoods with a betweenness centrality of 1.88, or roughly 50% more than its closest rivals triglyceride energy stores (betweenness 1.16), TSH (betweenness 1.06), and ADIPOQ (betweenness 1.01).

While a dominant role of mediators closely related to the regulation of glucose makes intuitive sense and would support the plausibility of this metabolic response network it is also important to examine overall network structure and patterns of information flow (**Supplementary Table 2**). With respect to the overall breadth of the network, the shortest path linking the 2 most remotes nodes consisted of 4 cascading relationships (network diameter of 4) with on average any pair of nodes being separated by at least two edges or at least one intermediate mediator node (1.87 characteristic path length). On average nodes in the immediate neighborhood of any given node in this network would connect would connect with each other with a connection density exceeding 40% of all possible neighborhood interactions (0.41 clustering coefficient). A cursory examination of similar statistics reported in the literature describing biological networks existing at different levels of granularity suggest that the metabolic response network presented here shares many structural similarities with organ-level networks as opposed to intra-cellular or social networks (Albert and Barabási, 2002; **Supplementary Table 2**). Indeed, a map connecting 55 functional regions of whole cerebral cortex in cat (Hilgetag et al., 2000) share a strikingly similarity with the network presented here in terms of overall connection density, average number neighboring nodes and characteristic path length separating nodes. Likewise, a theoretical network based on the functional connectivity in cat and macaque monkey cortex (Young, 1993; Sporns and Kötter, 2004) and enriched in functional motifs delivers a virtually identical clustering coefficient of approximately 0.4. These similarities with functional connectivity in mammalian brain contrast sharply with the much lower clustering that appears characteristic of neuronal networks in *C. elegans* (0.28) (Watts and Strogatz, 1998) and the much higher clustering in social interaction networks (e.g., film actors) (Watts and Strogatz, 1998) and language (Yook et al., 2001).

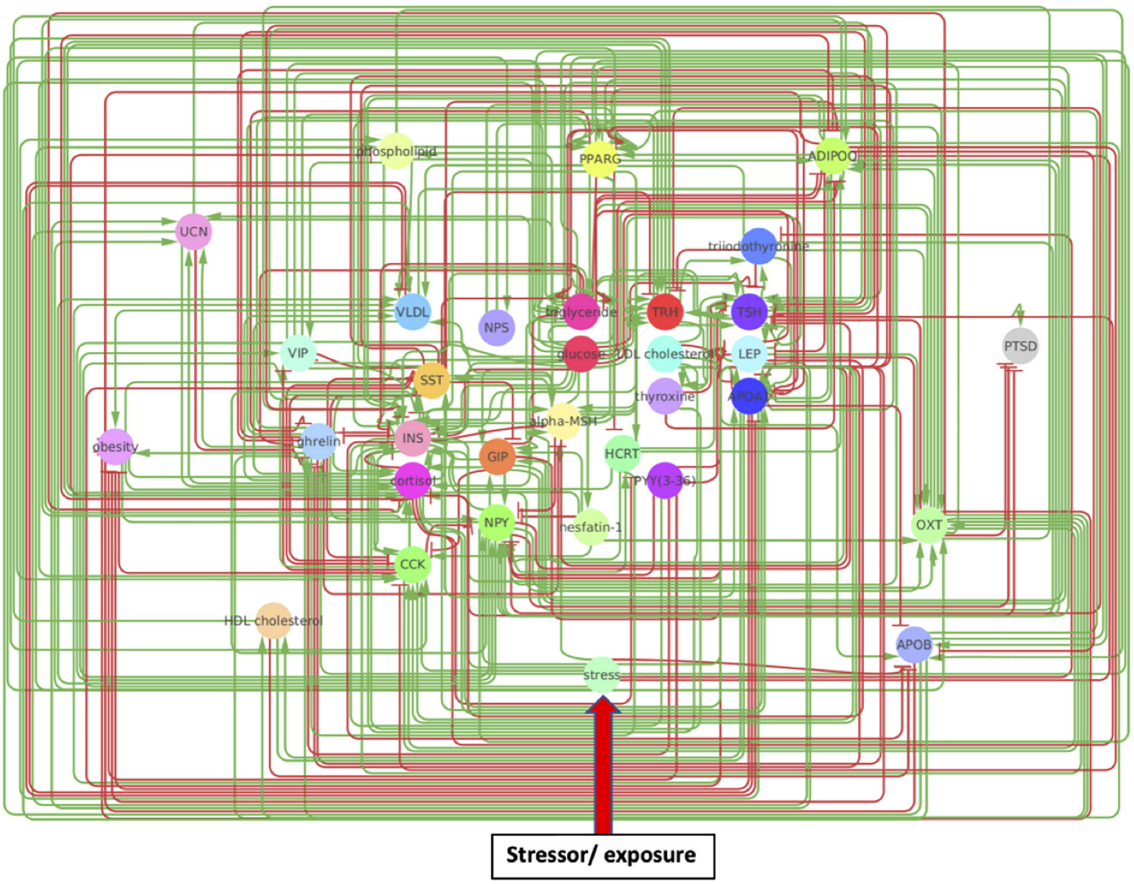

FIGURE 2
A metabolic network model. Created through Pathway Studios, this model involves directional effects between metabolic markers implicated in PTSD and obesity. Arrows indicate directional regulatory edges between mechanisms, such that a green arrow indicates the source node upregulates the target node while a red arrow indicates the source node downregulates the target node.

Similarly, while intracellular metabolic pathways exhibit a network diameter of similar magnitude, individual nodes are only half as connected with neighbors on average (Jeong et al., 2000). Though not an exhaustive comparison, the dominant role of core glucose regulators as well as the overall topological organization of the propose text-mined response network would suggest that it is to a large extent compatible with known functional networks existing at a similar level of biology.

Shared and unique mediators of posttraumatic stress disorder and obesity

In order to identify metabolic mediators that play a key role in exacerbating PTSD and obesity, we conducted an analysis of the shortest possible paths facilitating the transmission of stress response onto these two pathologies. We found 11 such direct paths where stress affected these pathologies directly by regulating only one of eight possible intermediate network nodes. These consisted of adiponectin (ADIPOQ), apolipoprotein B (APOB), the gastrointestinal hormone cholecystokinin (CCK), cortisol, ghrelin, leptin (LEP), neuropeptide Y (NPY), and oxytocin (OXT). While five of these exercised a direct and unique effect on obesity only, both pathologies were jointly affected by the remaining three, namely cortisol, NPY, and OXT (**Figure 3** and **Supplementary Table 3**). Unfortunately, cortisol and NPY while mediating reduced severity in PTSD are predicted to concurrently exacerbate obesity. Indeed, only increased levels of OXT expressed in response to stress were predicted to jointly reduce severity of symptoms in both PTSD and obesity. Interestingly this effect continues to apply to stress response involving a cascade of two intermediate mediators (**Supplementary Table 4A**). We found a total of 76 such two-step regulatory cascades. Of these 21 jointly propagated the effects of stress onto both pathologies concurrently. Of these only seven concurrently alleviated the severity of PTSD and obesity. All involved transmission of stress response through OXT via one of the following upstream regulators: CCK, cortisol, ghrelin, LEP, fear

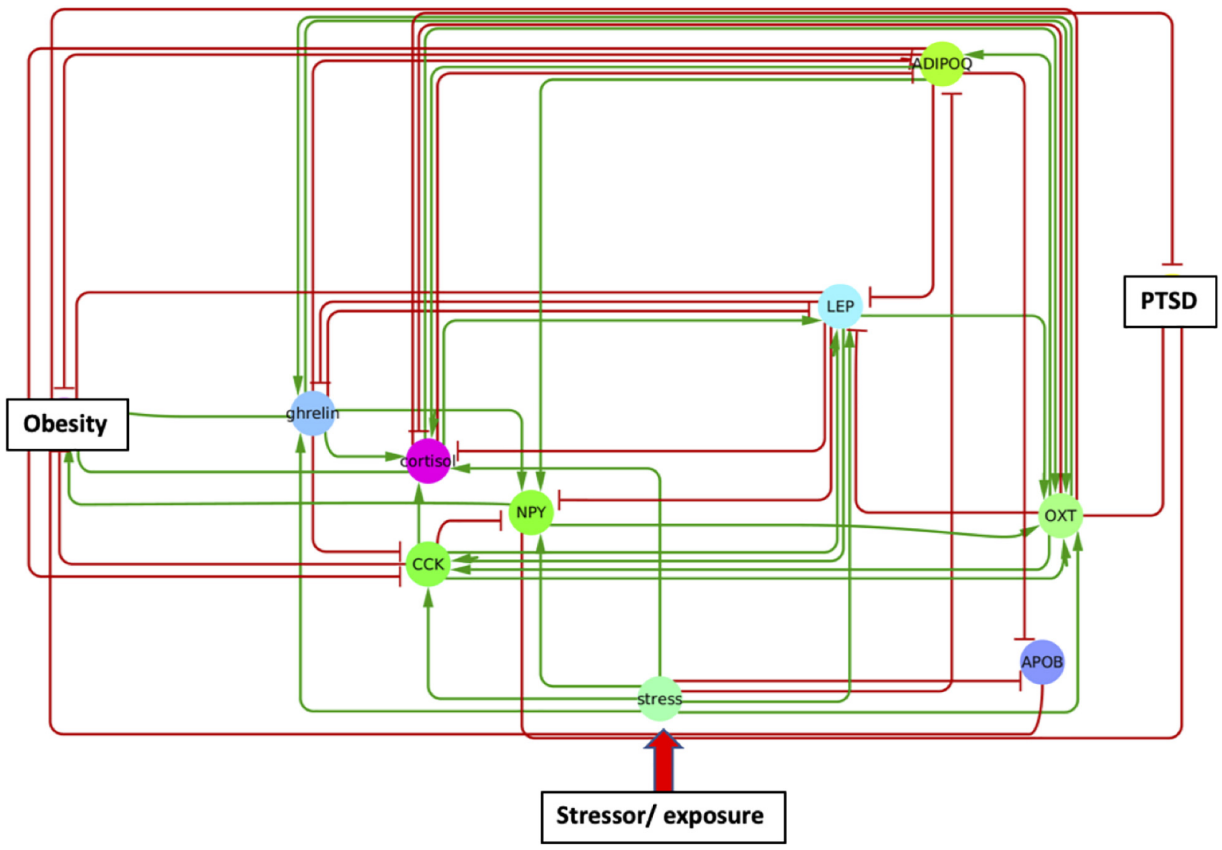

FIGURE 3
A single metabolic mediator subnetwork. Subnetwork of shortest paths linking stress to PTSD and obesity through only one intermediate metabolic mediator. Shared paths leading to both PTSD and obesity involved the convergent actions of cortisol, oxytocin (OXT), and neuropeptide Y (NPY).

mediator Neuropeptide S (NPS), NPY or through vasoactive intestinal polypeptide (VIP). This being said, transmission of stress through regulation of OXT simultaneously exacerbated both pathologies when also mediated through thyroid hormone triiodothyronine or T3. All other shortest stress response paths promoted divergent effects, alleviating one pathology while exacerbating the other. In addition to these stress response cascades jointly affecting both pathologies, we identified 45 paths involving two sequential mediators that uniquely affected obesity (**Supplementary Table 4B**), 25 of which promoted a stress-induced reduction in obesity. Likewise, we identified 11 cascades through which stress uniquely affected PTSD and not obesity (**Supplementary Table 4C**). Interestingly, thyroid-stimulating hormone or TSH is common to all these metabolic pathways. Four such pathways attenuated the effects of stress and reduced PTSD severity. These involved upstream regulation of TSH by either cortisol, ghrelin, NPY or OXT. The frequency with which all of the individual network elements mentioned above are recruited into these stress response pathways is summarized in **Figure 4**.

Discussion

Posttraumatic stress disorder and obesity are two major prevalent public health concerns in the United States across both military veterans and the general public (Farr et al., 2014). Given the pervasiveness of these two conditions and the inadequate understanding of their underlying mechanisms and pathways, the current study explored how stress affects PTSD and obesity through varied metabolic mediators. We find multiple regulatory cascades involving as few as one or two mediators that support the mechanistic engagement of distinct metabolic response processes to stress that jointly affect PTSD severity and obesity. Whereas many of these paths drove the severity of PTSD and obesity in opposing directions, stress-mediated release of oxytocin was found to concurrently downregulate the severity of both conditions. These results suggest that established graph theoretical concepts might be applied to existing peer-reviewed knowledge to discover the basic physiological mechanisms recruited in support of this co-morbidity.

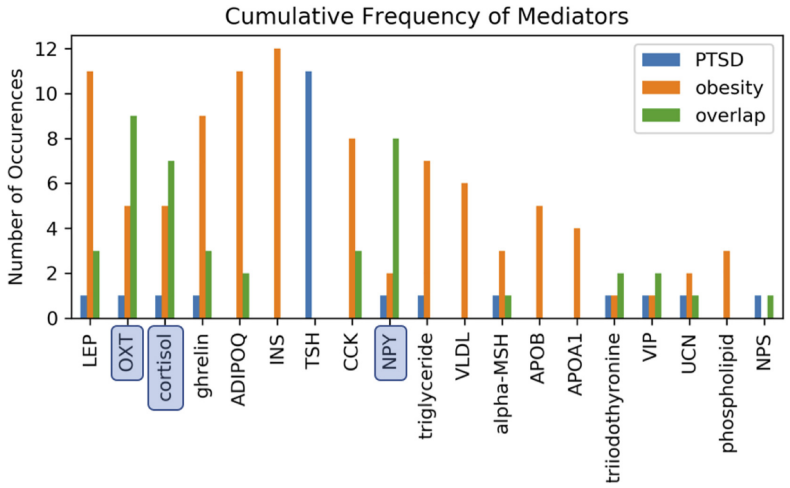

FIGURE 4
Involvement of cascading regulators. Mediation of one or both health conditions involving two-intermediate metabolic regulators reported as the number of available path occurences. Paths annotated as overlapping involve the same two intermediate mediators to simultaneously link stress to both PTSD and obesity. Oxytocin (OXT), neuropeptide Y (NPY), and cortisol were most frequently involved in jointly mediating PTSD and obesity.

First and perhaps foremost, it is interesting to observe that the current body of published knowledge contained sufficient information of individual elemental interactions to derive a regulatory network linking an environmental trigger such as stress with health outcomes, both physiological and behavioral, through known metabolic circuitry. Not only was this text-mined network cohesive, allowing for continuous directed paths to each pathology, but it displayed topological features and information flow patterns that were consistent with those broadly conserved across biological networks (Guimerà and Sales-Pardo, 2009; Di Camillo et al., 2012). Moreover, the architecture of this network was especially consistent with real-world functional networks reported in mammalian brains (Albert and Barabási, 2002), a level of physiology particularly relevant to this work. Of note, almost one third of the cascades theoretically available to support the propagation of stress response across this model network jointly affected both pathologies, a proportion reminiscent of the ratio of PTSD and obesity comorbidity reported by Stefanovics et al. (2020). NPY, cortisol, and OXT played a key role in directly propagated stress response to PTSD and obesity as well as in cascades recruiting other metabolic mediators. Interestingly, with the exception of the thyroid hormone T3, all cascades involving OXT were predicted to concurrently alleviate the effects of stress on PTSD severity and obesity. In contrast, NPY and cortisol were predicted to exert divergent effects on these health outcomes. Low levels of NPY are found to contribute to chronic PTSD (Rasmusson et al., 2000; Sah et al., 2009; Sah and Geracioti, 2013; Tural and Iosifescu, 2020) and the efficacy of NPY administered intranasally toward relieving PTSD symptoms is supported in empirical studies (Sayed et al., 2018) earning it the name "resiliency hormone" (Sah et al., 2009). Unfortunately, there is an even larger body of evidence indicating that NPY, a potent orexigenic (appetite-inducing) peptide (Beck, 2006; Assan et al., 2021), when released in response to stress stimulates adipogenesis, inducing an increase in adiposity and exacerbating obesity as well as triggering a cascade of other metabolic alterations (Masodkar et al., 2016; Ailanen et al., 2017). The involvement of cortisol highlights the metabolic sequalae to stress. Once again, the network model presented here predicts that this HPA regulated glucocorticoid will drive divergent outcomes in these pathologies, with stress-induced cortisol exacerbating obesity, while reducing PTSD severity. Expressed at lower basal levels resulting from a maladaptation of the HPA axis to increased GR sensitivity, the role of cortisol in PTSD has justifiably been broadly studied (Dunlop and Wong, 2019), though much less so in obesity (Oroian et al., 2021). Nonetheless, the exogenous role of stress impacting obesity through elevated cortisol reactivity and maladaptive coping behaviors (e.g., comfort eating) has gained much empirical traction (Herhaus et al., 2020). Indeed, heightened consumptive behaviors as a function of HPA axis reactivity was found when CRH was endogenously administered to healthy non-obese adults (George et al., 2010).

The joint mediation by the oxytocinergic system across PTSD and obesity is further described in focused work by Thienel et al. (2016) as well as that of Witteveen et al. (2020). Broadly considered a "natural medicine" attenuating the effects of stress, and promoting resilience and healing (**Carter et al., 2020**), OXT has been found to impart both preventive and curative effects in PTSD (van Zuiden et al., 2017; Donadon et al., 2018). Importantly, a hybrid intervention with OXT and

psychotherapy has been shown to have a potent effect on PTSD severity (Flanagan et al., 2018), though these effects reportedly vary across the sexes (Frijling et al., 2015). Likewise, OXT, being anorectic, functions as a "nutrient status sensor" (McCormack et al., 2020, p. 122), and is found to reduce obesity across humans, rodents, and non-human primates (Niu et al., 2021), through its effect on consumptive behaviors by simultaneously regulating cognitive control as well as food reward processing (Spetter et al., 2018). Importantly, increased OXT signaling and secretion are known to regulate both energy intake and energy expenditure which result in weight loss by its effect on fat mass loss (as opposed to lean mass loss) (McCormack et al., 2020). In addition, there is evidence that OXT is involved in reversing insulin resistance and glucose intolerance, thus reducing obesity (Zhang et al., 2013). Collectively, these results suggest that OXT, an essential regulator of the gut-brain axis (Olszewski et al., 2017) also exercising key roles in various other neurobehavioral pathways and homeostatic systems (McCormack et al., 2020), might be a biomarker and even a potential target of intervention worthy of further study in the management of both PTSD and obesity.

Though not an exhaustive validation of the over 260 regulatory interactions captured in this network, interpretations of the literature made by the MedScan natural language processing engine would appear consistent with those of the human reader, at least in this focused verification those metabolic mediators identified as playing a key role in the comorbidity of obesity and PTSD. This technology continues to evolve and though results are highly dependent on the validation set and metrics, it is not unreasonable to expect a disambiguation accuracy exceeding 85% (Yepes and Berlanga, 2015) in the interpretation of medical texts. This is consistent with the experience of our group where we found accuracy of interpretation exceeding 90% in an endocrine regulatory network counting over 200 interactions validated by consensus with a second NLP engine and a human domain expert reader (Morris et al., 2019). It is also important to remember that in this work every citation was attributed an equal credibility in its support of a given interaction, irrespective of the possible differences in publication date or source publication. The development of useful quality metrics continues to be an active field for our group (Jackson, 2021) and others. Although they are useful in highlighting those regulatory cascades through which stress propagate, it is important to remember that these paths were identified based on connectivity alone. Though theoretically available, the relative kinetics of signal transmission through each path will determine the actual likelihood and extent of its participation. Nonetheless we propose that the current analysis offers an efficient framework for collecting, reconciling, and operationalizing existing community knowledge toward informing on key markers in the design of studies that can precede even pilot level investigation. Moreover, the resulting networks offer a mechanistically informed description of biology relevant to an illness of interest without being illness-specific. Hence, representing accrued knowledge in this way creates a lasting and widely applicable model of what we know that transcends a specific study data set while also ensuring the consistency of the latter with peer-reviewed observations of the broader research community.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

TPC was primarily responsible for literature review, model creation, results analysis, and manuscript writing. SR was primarily responsible for network analysis and generation and interpretation of results. JT was primarily responsible for supervision of manuscript writing, expertise on computational modeling techniques, and clinical applications. GLS, MJR, RCB, and MEC contributed to the design of the study as well as the interpretation of results, assessment of clinical validity, and writing of the manuscript. GB was responsible for oversight and funding of project, definition and supervision of the research, manuscript writing, and expertise on computation modeling techniques. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Rochester Regional Health in conjunction with Elsevier BV (Amsterdam) under a collaborative research sponsorship (GB) and United States Department of Veterans Affairs through an Interagency Personnel Agreement (IPA) (GB and TPC) award. Elsevier BV was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.941019/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 06 September 2022
DOI 10.3389/fpsyt.2022.930466

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

RECEIVED 28 April 2022
ACCEPTED 07 July 2022
PUBLISHED 06 September 2022

CITATION
Shimizu N, Mochizuki Y, Chen C, Hagiwara K, Matsumoto K, Oda Y, Hirotsu M, Okabe E, Matsubara T and Nakagawa S (2022) The effect of positive autobiographical memory retrieval on decision-making under risk: A computational model-based analysis. *Front. Psychiatry* 13:930466. doi: 10.3389/fpsyt.2022.930466

The effect of positive autobiographical memory retrieval on decision-making under risk: A computational model-based analysis

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Psychiatric disorders such as depressive and anxiety disorders are associated with altered decision-making under risk. Recent advances in neuroeconomics and computational psychiatry have further discomposed risk-based decision-making into distinct cognitive computational constructs and showed that there may be disorder-specific alterations in these constructs. As a result, it has been suggested these cognitive computational constructs may serve as useful behavioral biomarkers for these disorders. However, to date, little is known about what psychological or behavioral interventions can help to reverse and manage the altered cognitive computational constructs underlying risk-based decision-making. In the present study, we set out to investigate whether recalling positive autobiographical memories may affect risk-based decision-making in healthy volunteers using a description-based task. Specifically, based on theories of behavioral economics, we dissected risk preference into two cognitive computational constructs, utility sensitivity and probability weighting. We found that compared to recalling neutral memories, retrieving positive autobiographical memories increased utility sensitivity (Cohen's d = 0.447), indicating reduced risk aversion. Meanwhile, we also tested the influence of memory retrieval on probability weighting, the effect, however, was unreliable and requires further in-depth investigation. Of clinical relevance, the change in risk aversion after recalling positive memories was in the opposite direction compared to those reported in psychiatric disorders. These results argue for the potential therapeutic effect of positive autobiographical memory retrieval for the amendment of altered risk-based decision-making in psychiatric disorders.

KEYWORDS

positive autobiographical memory, decision-making, risk preference, probability weighting, computational neuroscience

Introduction

Psychiatric disorders such as depressive and anxiety disorders are associated with deficits in cognition and decision-making (1–4). For instance, both depressive and anxiety disorders have been characterized by excessive risk aversion or avoidant behaviors (5, 6). In behavioral economics, risk is defined as the variability of outcome and people's attitude toward risk is called risk preference. Preferring outcomes with high certainty (e.g., $50 guaranteed over 50% chance of getting $100) is said to be risk-averse, while the opposite is called risk-seeking and having no preference is known as risk-neutral. Among these three preferences, risk-neutrality is considered rational and characterizing an economic man. Importantly, excessive risk aversion has been considered a key contributor to the maintenance and recurrence of depressive and anxiety disorders (3, 7, 8).

To provide a mechanistic account of decision-making, recent advances in neuroeconomics and computational psychiatry have further discomposed risk-based decision-making into multiple, distinct cognitive computational constructs (9, 10). For instance, two commonly studied constructs of risk preference are utility sensitivity and probability weighting. In standard expectation-based theories in economics, risk preference is captured by a utility or utility sensitivity function (e.g., a power function). Here, a linear utility function indicates risk-neutrality, a concave utility function indicates risk aversion, and a convex function indicates risk-seeking. Most individuals are considered to have a concave utility function (i.e., being risk-averse) because of the law of diminishing marginal utility (11). Nevertheless, people tend to have different risk preferences at small vs. large probabilities. To account for this phenomenon, Prospect theory (12, 13) introduced probability weighting function. Thus, most individuals tend to overweight small probabilities (i.e., risk seeking) and underweight large probabilities (i.e., risk aversion), as indicated by an inverse-S-shaped, non-linear probability weighting function.

Using this computational model-based framework, it has been reported that generalized anxiety disorder is associated with a more concave utility function [indicating risk aversion, (14)]. In contrast, obsessive-compulsive and hoarding disorders (15) and depression (16) are associated with an altered probability weighting function, in which patients with obsessive-compulsive and hoarding disorders and individuals with more depressive symptoms tend to underweight small probabilities and overweight large probabilities compared to healthy subjects. These disorder-specific changes argue for the usefulness of the cognitive computational constructs underlying risk-based decision-making as behavioral biomarkers of these disorders.

Despite these fruitful progresses made by recent research, little is known about what psychological, behavioral, or dietary interventions can help to reverse and manage the altered cognitive computational constructs underlying risk-based decision-making in psychiatric patients. In the present study, therefore, to provide insights into the development of effective interventions that may help to treat decision-making impairments in clinical patients, we conducted a randomized controlled crossover experiment with healthy volunteers to investigate if recalling positive autobiographical memories may affect risk-based decision-making and its cognitive computational constructs. Here, to evaluate risk-based decision-making, we used a description-based task in which subjects were given explicit information on reward magnitude and probability. The reason we focused on positive autobiographical memory retrieval was that it activates the midbrain dopaminergic reward system, including the striatum and the medial prefrontal cortex (17–19). The latter has been suggested to be the neural substrate of risk preference and probability weighting (20–22).

Materials and methods

Participants

The study was approved by the Institutional Review Board of Yamaguchi University Hospital and preregistered on the University hospital Medical Information Network Clinical Trial Registry (UMIN-CTR, register ID: UMIN000044704). Thirty-four healthy subjects were recruited *via* posters placed on campus and through word-of-mouth. This sample size was similar to previous studies (18) and considered appropriate according to a priori power analysis (to detect a moderate effect size of $d = 0.50$ using a within-subject design, with a power of 0.8, alpha $= 0.05$, two-sided, 34 subjects were required). One subject dropped out because of being sick on the scheduled experimental day, leaving thirty-three subjects for the final analysis (18 males, 15 females, age: 21.18 $\pm$ 0.98 years, all were undergraduate students).

The study was carried out according to the Declaration of Helsinki. All subjects provided written informed consent. To remove the influence of age, we limited subjects to those in their twenties. The exclusion criteria were reporting any current memory or mental disorders (or currently seeking medical examinations due to suspicion of these disorders), being unable to retrieve 20 or more items of positive and neutral memories, respectively, in the autobiographical memory recall test (see below), and being judged to be unsuitable as a subject due to other issues. No subject was excluded because of meeting any of these exclusion criteria.

Procedure and design

The study was conducted on two separate days (Figure 1A). On day 1, subjects provided written informed consent after receiving a detailed description of the study and filled out demographic information. They were explained that the objective of the study was to investigate the effect of positive autobiographical memory retrieval on decision-making. They then conducted an autobiographical memory recall test, in which, given 87 common life event cues (e.g., getting an acceptance letter), subjects selected memories in which they had been personally involved. The 87 common life event cues were created based on previous studies (18, 23) and our pilot testing. For each selected memory, subjects were asked to recall only positive or neutral events and then give a brief description and indicate the location and date of the event. For the brief description, they were asked to be specific so that they could easily recall the event later upon reading the description. Furthermore, they also rated the valence (neutral or positive) and emotional intensity (1–4: 1 = not intense, 4 = very intense) of the memory as well as how they felt when recalling the memory (1–4: 1 = neutral, 4 = very good). In preparation for the day 2 intervention session, twenty of each subject's memories with a positive valence and the highest combined emotional intensity and feeling ratings (the sum of the two) were selected as positive memories. Similarly, twenty of each subject's memories with a neutral valence and the lowest combined emotional intensity and feeling ratings were selected as neutral memories.

Subjects returned for the main experimental session on another day (i.e., day 2) within a week. Before the day 2 laboratory visit, subjects were instructed to get enough sleep on the previous night and refrain from engaging in intensive physical activities, smoking, and drinking coffee and energy drinks for at least 2 h before coming to the laboratory visit. They were also asked to reschedule the experiment if they were sick or did not feel well on the experimental day. Upon arriving, subjects first answered questions to confirm whether they adhered to the above instructions and then filled out the Positive and Negative Affect Schedule [PANAS, (24)] indicating their baseline mood. PANAS measures mood at the moment in terms of positive affect and negative affect using 10 words that describe feelings. Each word was rated on a scale of 1 ("not at all") to 6 ("extremely"). Based on PANAS, no subject at the time had extremely high positive or negative mood (positive affect: range 11–41; negative affect: range 10–32).

We used a within-subjects randomized controlled crossover design for the main study (Figure 1A). Subjects were randomly assigned to receive the experimental and control interventions in a counterbalanced order and immediately after each intervention, they conducted a decision-making task. The above 20 positive memories were used for the experimental intervention, and the 20 neutral memories was used for the control intervention. Given that the decision-making task (120 trials, see below) we employed here took about 15 min and typically required one short break amid, we split the intervention and decision-making task into two sessions. Thus, in session 1, subjects first recalled 10 memories, after which they conducted 60 trials of the decision-making task. After a short break of about 1 min, in session 2, subjects recalled the remaining 10 memories and then conducted the remaining 60 trials of the decision-making task. For data analysis, nevertheless, we combined the data of the two sessions.

For each memory, subjects were shown the initial cue together with their written responses in the day 1 autobiographical memory recall test (see Supplementary Figure S1 for an example) for 14 s. During this period, they were asked to recall and elaborate on the memory for 14 s silently. Following previous studies (17–19), for each memory, subjects indicated the valence and emotional intensity of the memory and reported how they felt when recalling the specific memory (4 s each).

During the memory retrieval (for both experimental and control interventions), subjects' heart rate (HR) and heart rate variability (HRV) were monitored using an Apple Watch Series 4 (Apple Inc.), the accuracy of which has been validated (25, 26). Immediately after memory retrieval in each section, subjects indicated their present mood in terms of pleasure, relaxation, and vigor using a visual analog scale (27). For data analysis of HR, HRV, and mood, the average of the two sessions was used. After the first phase of the intervention and decision-making task, subjects rested for 5 min as a washout period.

Decision-making task

We adapted the decision-making task used by Hsu et al. (20). In this task (Figure 1B), given two gambling options each consisting of a reward magnitude (in Japanese yen) and reward probability (in percentage indicated by a black bar), subjects were asked to choose the one that maximized the reward they receive. We used the exact stimuli of reward magnitude and probability generated by 17 but multiplied the magnitude by 100 to reflect the exchange rate (from dollars to Japanese yen).

After an inter-trial interval or fixation phase of 1.5 s, the options were presented for 3 s. After a question mark occurred in the center, subjects had to indicate their choice by pressing one of two predefined keys within 3 s. The chosen option was then highlighted by a gray frame. Subjects were told that failing to respond within 3 s would be treated as no response and they could get no reward on that trial.

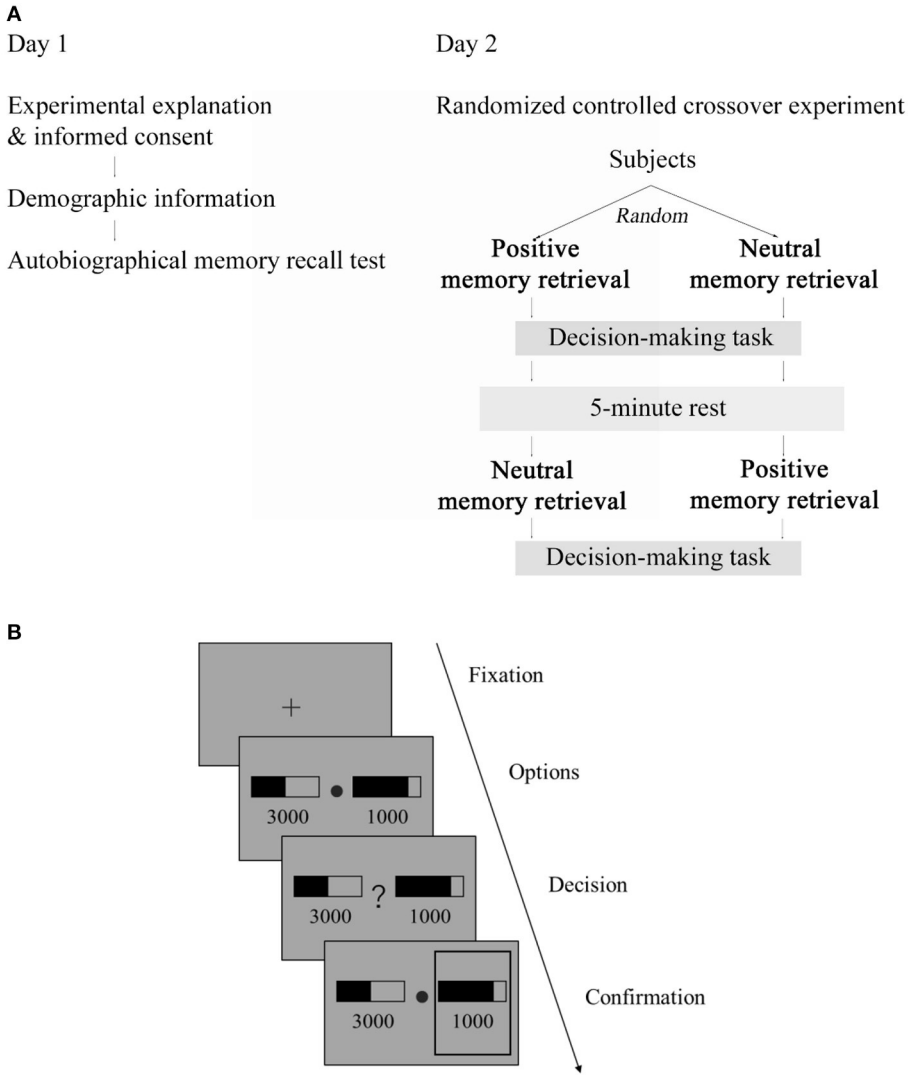

FIGURE 1
Schematic illustration of the procedure and decision-making task. **(A)** Procedure, the study was conducted on two separate days: on day 1, subjects performed an autobiographical memory recall test; on day 2, they were assigned to receive memory retrieval intervention in a randmozed controlled crossover experiment. **(B)** Illustration of the decision-making task. After a fixation phase, two gambling options, each consisting of a reward magnitude (in JPY) and the probability of receiving that magnitude of reward (indicated by a black bar), were shown. A question mark then occurred in the center and subjects were asked to choose one option that maximized their reward. The chosen option was highlighted by a gray frame.

Computational modeling of the decision-making behavioral data

As shown in Table 1, we fitted four models to simulate subjects' choice behaviors. One was based on the standard value function in which magnitude was multiplied by probability. The other three further introduced a non-linear utility function (i.e., a power function) and/or a non-linear probability weighting function [the one-parameter Prelec weighting function, (28)]. λ and γ are the parameters of utility sensitivity and probability weighting, respectively. Subjects were modeled to choose between two options according to their value difference based on the softmax rule whose stochasticity was controlled by an inverse temperature parameter β.

To fit the models to subjects' choices, we used a Bayesian hierarchical expectation-maximization method (6, 29). In brief, given a current estimate of group-level prior distribution for each model parameter, we randomly sampled 100,000 sets of parameters and used the resulting likelihoods as importance weights to update the current prior distributions. This procedure

TABLE 1 Model specification and fitting results.

Model No.	Model description	Equation	Free parameters	Bayesian hierarchical expectation-maximization		Maximum likelihood	
				iBIC Neutral	iBIC Positive	AIC Neutral	AIC Positive
1	Linear utility and linear probability weighting	$V(X) = rp$	β	5,206.8	5,180.9	157.07	156.22
2	Non-linear utility and linear probability weighting	$V(X) = r^{\lambda}p$	λ,β	5,025.5	5,038.5	108.85	120.06
3	Linear utility and non-linear probability weighting	$V(X) = re^{-(-\log p)^{\gamma}}$	γ,β	3,672.9	4,086.6	151.43	150.32
4	Non-linear utility and non-linear probability weighting	$V(X) = r^{\lambda}e^{-(-\log p)^{\gamma}}$	λ,γ,β	3,527.8	3,907.8	102.63	112.30

Smaller iBICs and smaller AICs indicate better model fits. Neutral, neutral autobiographical memory retrieval. Positive, positive autobiographical memory retrieval. r indicates reward and p indicates probability.

was repeated iteratively until the estimate of model evidence stopped increasing. We then estimated the parameters for each subject as a weighted mean of the final 100,000 parametrizations. The prior distributions for β, λ, and γ were modeled as gamma distributions and were initialized to support wide ranges of possible values.

We compared different models using the integrated Bayesian Information Criterion (iBIC), which penalizes the sum of model evidence for each subject by the number of parameters and the number of choices made (30). Smaller iBIC values indicate more parsimonious model fits. As can be seen from Table 1, the fourth model incorporating both non-linear utility and non-linear probability weighting had the smallest iBIC and was the winning model. Parameters estimated from this model, therefore, were used for subsequent analysis.

In addition to the Bayesian hierarchical expectation-maximization method with population-level priors, we also tested a commonly used individual-level fitting method without population-level priors, the maximum likelihood method, which was executed with the Matlab command "fmincon". For model selection, the Akaike Information Criterion (AIC) was employed. Smaller AICs indicate more parsimonious model fits. Similar to iBIC, the fourth model incorporating both non-linear utility and non-linear probability weighting was the winning model.

Statistical analysis

MATLAB2018b and IBM SPSS Statistics 26.0 were used for statistical analysis. The normality of the data was checked using the Shapiro–Wilk test. Paired *t*-tests or Wilcoxon signed-rank tests were used to compare differences between interventions. G*Power Version 3.1.9.7 (31) was used to estimate effect sizes (Cohen's *d*). A significance level of $p < 0.05$ was used.

Results

Memory and feeling ratings, mood, HR, and HRV

During neutral memory retrieval, subjects on average endorsed 93.14% of the memories to be neutral during neutral memory retrieval and endorsed 98.14% of the memories to be positive during positive memory retrieval (Figure 2A). Meanwhile, compared to neutral memory retrieval, subjects rated memories during positive memory retrieval as being more intense (paired *t*-test, $t = -12.755$, $p = 4 \times 10^{-14}$, $d = 2.22$) and feeling better (paired *t*-test, $t = -21.301$, $p = 2 \times 10^{-20}$, $d = 3.71$).

Furthermore, as shown in Figure 2B, compared to neutral memory retrieval, subjects reported feeling more pleasant (paired *t*-test, $t = -6.696$, $p = 1 \times 10^{-7}$, $d = 1.17$) and vigorous (paired *t*-test, $t = -4.101$, $p = 3 \times 10^{-4}$, $d = 0.714$) after positive memory retrieval. There was no difference in feelings of relaxation (Wilcoxon signed-rank test, $Z = -0.009$, $p = 0.993$, $d = -0.115$), HR (paired *t*-test, $t = -0.795$, $p = 0.433$, $d = 0.141$), or HRV (paired *t*-test, $t = 1.359$, $p = 0.184$, $d = -0.240$).

Consistent with previous studies (17, 18), these results suggest that the protocol of memory retrieval is reliable.

Decision-making parameters: Bayesian hierarchical expectation-maximization method

We first fit the computational models to subjects' choices with a Bayesian hierarchical expectation-maximization method. As plotted in Figure 3A, between-intervention comparison showed that compared to after neutral memory retrieval, subjects had greater λ (Wilcoxon signed-rank test, $Z = -2.457$,

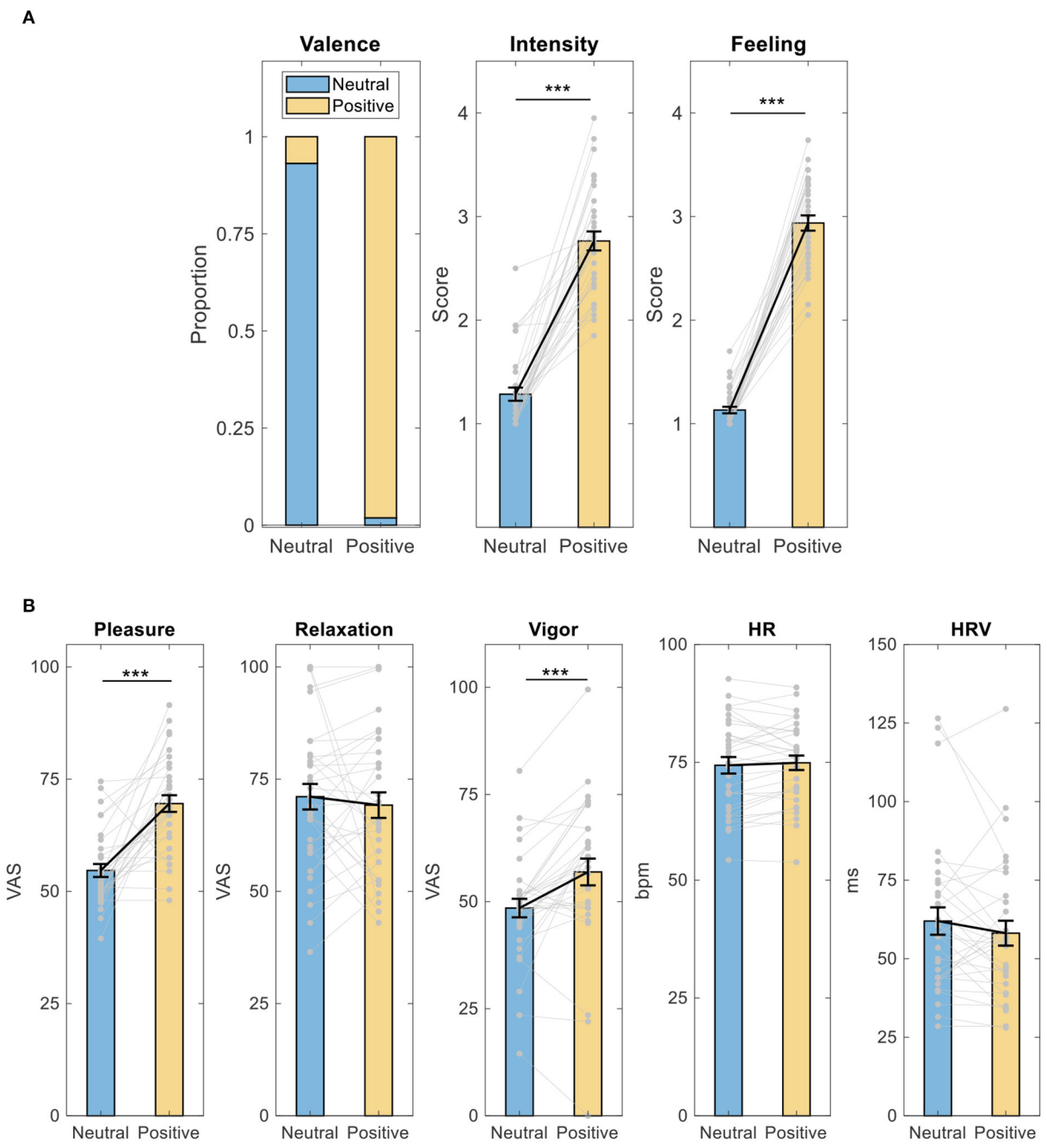

FIGURE 2
Intervention effect on memory and feeling ratings, mood, HR, and HRV. **(A)** Memory and feeling ratings; **(B)** mood, HR, and HRV. ***$p < 0.001$, paired t-test. HR, heart rate. HRV, heart rate variability; VAS, visual analog scale; bpm, beat per minutes; ms, milliseconds. Data shown as mean ± SE.

$p = 0.014$, $d = 0.354$) and smaller γ (Wilcoxon signed-rank test, $Z = -2.046$, $p = 0.041$, $d = 0.427$) after positive memory retrieval. Greater λ indicates that subjects became less risk-averse after positive memory retrieval (Figure 3B, left panel). Since after positive autobiographical memory retrieval, subjects had a λ closer to 1 (Wilcoxon signed-rank test, $Z = -1.278$, $p = 0.023$, $d = 0.354$ based on the absolute value of the difference of λ from 1), this also indicates subjects became more risk-neutral or rational in utility sensitivity after positive memory retrieval.

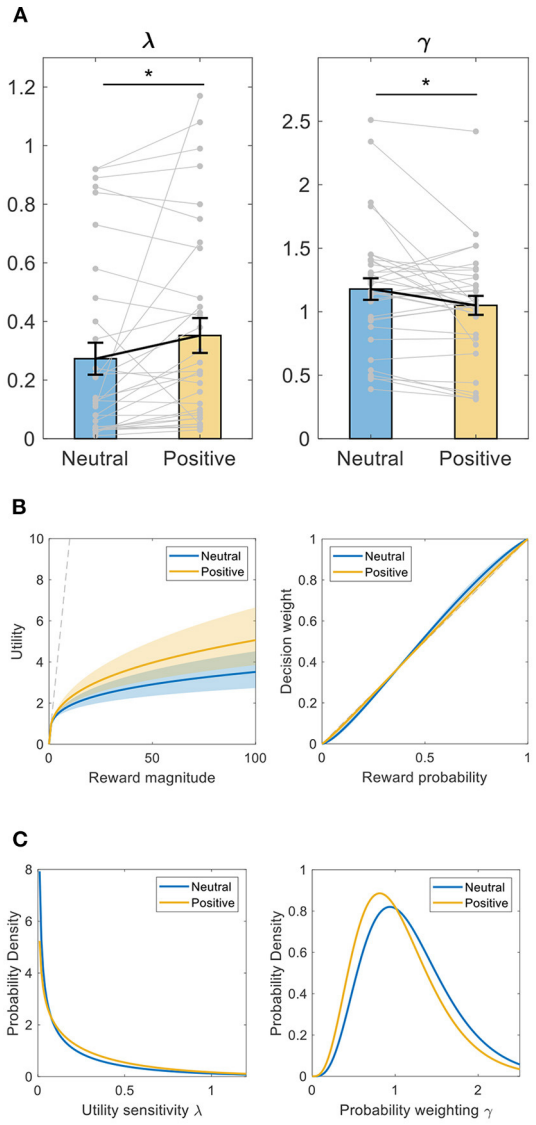

FIGURE 3
Intervention effect on decision-making parameters using Bayesian hierarchical expectation-maximization method. **(A)** utility sensitivity λ and probability weighting γ. *$p < 0.05$, Wilcoxon signed-rank test. Data shown as mean ± SE. **(B)** illustration of the utility and probability weighting function changes after positive memory retrieval, plot with the mean ± SE of each parameter. Left panel, utility (u) as a function of reward magnitude (x). Right panel: decision weight (w) as a function of objective probability (*p*). The dashed line represents linear utility or probability weighting. **(C)** the estimated population prior distributions for utility sensitivity λ and probability weighting γ.

Smaller γ indicates that subjects became either purely less S-shaped in probability weighting or more linear, objective in probability weighting (Figure 3B, right panel). The latter, however, was not supported by the data because subjects had a similar absolute value of the difference of γ from 1 (since $\gamma = 1$ indicates objective probability weighting) after positive vs. neutral memory retrieval (Wilcoxon signed-rank test, $Z = -1.063$, $p = 0.288$, $d = 0.314$). Therefore, compared to neutral memory retrieval, subjects became less S-shaped in probability weighting after positive memory retrieval. That is, they became more risk-seeking at small probabilities and more risk-averse at large probabilities.

We also plotted the estimated population prior distributions for λ and γ, respectively, in Figure 3C. Consistent with the above individual data, compared to after neutral memory retrieval, the prior distribution of λ shifted toward the right side or bigger values while that of γ shifted toward the left side or smaller values after positive memory retrieval.

Decision-making parameters: Maximum likelihood

We also fit the computational models to subjects' choices with a maximum likelihood method. As plotted in Figure 4A, compared to after neutral memory recall, subjects had greater λ (Wilcoxon signed-rank test, $Z = -2.315$, $p = 0.021$, $d = 0.346$) after positive memory recall. Greater λ indicates that subjects became less risk-averse after positive memory recall (Figure 4B, left panel). Since after positive memory recall, subjects had a λ closer to 1, this also indicates subjects became more risk-neutral or rational in utility sensitivity after positive memory recall. In contrast, there was no difference in probability weighting parameter γ after positive vs. neutral memory recall (Wilcoxon signed-rank test, $Z = -0.884$, $p = 0.376$, $d = 0.080$).

Discussion

To our best knowledge, this is the first study that investigates the influence of positive autobiographical memory retrieval on decision-making under risk. This is also one of the few studies that investigate whether psychological, behavioral, or dietary interventions affect decision-making under risk [e.g., refer to (32) for a study of an internet-based cognitive behavioral therapy and self-report risk-taking behaviors in patients with generalized anxiety disorder, and (33) for a study of probiotics and decision-making with the Iowa Gambling Task in patients with Fibromyalgia]. Here, using both a Bayesian hierarchical expectation-maximization method with population-level priors and a maximum likelihood method without population-level priors, we identified a consistent effect of positive memory retrieval on utility sensitivity (λ), suggesting that subjects became more risk-neutral or rational in utility sensitivity after positive memory retrieval. Importantly, the change here is in the opposite direction compared to those reported in depressive disorders (34), seasonal affective disorder (35), and generalized anxiety disorder (14). These results suggest that positive

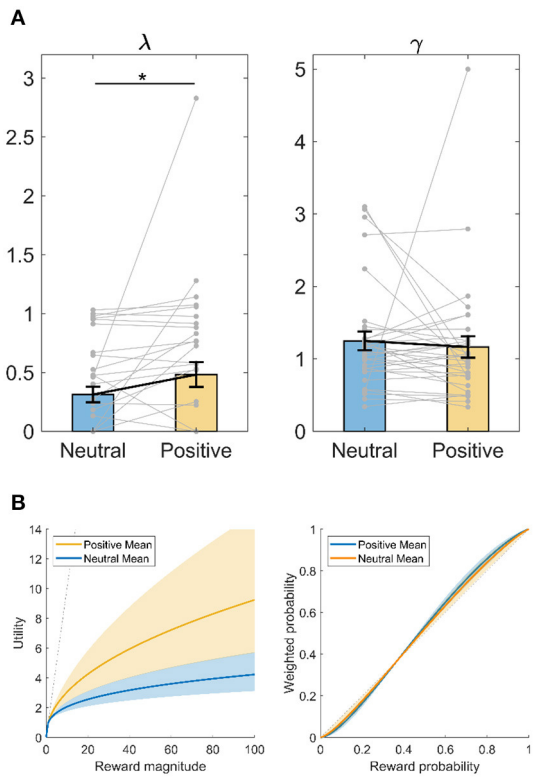

FIGURE 4
Intervention effect on decision-making parameters using maximum likelihood method. **(A)** Utility sensitivity λ and probability weighting γ. *$p < 0.05$, Wilcoxon signed-rank test. Data shown as mean ± SE. **(B)** Illustration of the utility and probability weighting function changes after positive memory retrieval, plot with the mean ± SE of each parameter. Left panel, utility (u) as a function of reward magnitude (x). Right panel: decision weight (w) as a function of objective probability (*p*). The dashed line represents linear utility or probability weighting.

autobiographical memory retrieval may have therapeutic effects for patients with these mental disorders. These results may have important clinical implications because these and similar decision-making deficits are resistant to clinical treatment and remain even when patients are in remission (36, 37).

In contrast, the effect of positive memory retrieval on probability weighting (γ) was present in the Bayesian hierarchical expectation-maximization fitting but absent in the maximum likelihood fitting. It raises the possibility that the influence of positive memory retrieval on probability weighting may be unreliable and requires further in-depth investigation. Altered probability weighting, specifically, S-shaped probability weighting with the tendency to underweight small probabilities and overweight large probabilities has been reported in patients with obsessive-compulsive and hoarding disorders (15) and people with high levels of depression (16). It will be interesting for future studies to confirm if positive memory retrieval helps alleviate such S-shaped probability weighting and has potential therapeutic effect.

As one subfield in positive psychology, positive emotions have been attracting much research interest (38, 39). For instance, positive emotions have been shown to broaden attention, increase cognitive flexibility, and enhance resilience (38, 39). As an essential strategy to increase positive emotions, positive autobiographical memory retrieval activates the brain reward system especially the striatum and the mPFC (17–19), buffers the hypothalamic-pituitary-adrenal axis response to acute stressors (19), and reduces delay discounting or impulsive choices (18). Adding to these findings, the present study suggests that positive autobiographical memory retrieval reduces risk-aversion. As mentioned in the introduction, one potential underlying neural mechanism of such effects might be the enhanced activation of the mPFC. The mPFC has been linked to risk processing and greater activation of the ventral mPFC is associated with higher risk-seeking (22). It remains for future neuroimaging studies to test if the mPFC mediate the effects of positive autobiographical memory retrieval reported here. Based on our findings and evidence reviewed above, habitual positive autobiographical memory retrieval may be employed as an important clinical interventional strategy for patients with depressive and anxiety disorders. People generally take photos of positive, important moments in everyday life, many further share those photos with others *via* social networking services. Those photos can be used as cues for positive memory retrieval to enhance stress coping and modify altered decision-making tendencies.

Our findings are consistent with previous reports that positive mood is associated with optimism about future events and risk-taking behaviors [for a review, (40)]. For instance, when in a happy mood, people tend to think positive events are more likely and negative events less likely (41). They are also more willing to pay for lotteries (42). One recent study has tried to elucidate the underlying cognitive and neural computational mechanism of this phenomenon and showed that task feedback-induced positive mood increases the weighting of potential gains while decreases the weighting of potential losses (43). The ventral mPFC and the anterior insula were found to mediate these effects, respectively. By focusing on reward alone and removing the influence of loss, the current study further showed that positive autobiographical memory retrieval reduces risk aversion, providing new cognitive computational explanations for the above phenomenon. In contrast to incident mood and task feedback used in previous studies, recalling positive autobiographical memories used in the present study has the potential to be employed as a therapeutic tool for managing altered decision-making under risk in patients with mental disorders.

Our study has several limitations. Firstly, to increase statistical power and remove the influence of age, we limited

our subjects to those in their twenties. This, however, also refrains us from generalizing our findings to other age groups. Secondly, we tested only the immediate effect of positive autobiographical memory retrieval. How long the effect lasts is another important question to be answered by future studies. Thirdly, we investigated decision-making after positive autobiographical memory retrieval and used decision-making after neutral autobiographic memory retrieval as the control condition. That is, we did not conduct the same task at baseline before memory retrieval, which did not allow us to explicit show how each memory retrieval affects decision-making. The reason was that we used a crossover design and subjects had already performed the decision-making task twice, one after positive and the other after negative memory retrieval; including the decision-making task at baseline would be too demanding and effort-consuming for subjects. Fourthly, we focused on decision-making with reward only, and therefore our results may not be generalizable to decision-making with loss. Fifthly, to evaluate risk-based decision-making, we used a description-based task in which subjects were given explicit information on reward magnitude and probability. There is, however, another paradigm known as experience-based decision-making in which decision variables are not explicitly known and subjects had to learn those information based on trial-and-error experience. Recent studies suggest that people make inconsistent choices in description vs. experience based tasks, a phenomenon known as the "description-experience gap" (44, 45). It will be interesting for future studies to test if positive autobiographical memory retrieval affects decision-making in experience-based tasks. Sixthly, the effects we observed were only small to medium in size (i.e., $d = 0.377$ and 0.447). Since pictures are generally easier to recall than words (46), greater effects may be achieved by employing photographs of people's happy moments for memory retrieval. Seventhly, since it is fairly easy for subjects to notice the purpose of the study, we did not blind subjects about the purpose of the study and this might have caused some expectation bias. Nevertheless, we speculate that such bias is unlikely to be a concern here because it is generally hard for subjects to think of the influence of memory retrieval on decision-making, especially considering the fact that all of them were medical undergraduates and were not trained in relevant fields such as economics or cognitive psychology. Future studies are required to address these limitations and confirm and improve the findings reported in the present study.

Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Yamaguchi University Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CC and SN: conceptualization. NS, YM, CC, KH, KM, and YO: methodology. TM: resources. NS, YM, and CC: formal analysis. NS, CC, KM, MH, and EO: investigation. NS and CC: writing—original draft preparation. All authors: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by grants from the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number 19K17063) and SENSHIN Medical Research Foundation to CC.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.930466/full#supplementary-material

SUPPLEMENTARY FIGURE S1
A typical screen shown to a subject during the memory retrieval intervention. The upper line is the initial cue ("getting an acceptance letter"). The lower line is the scanned image of the subject's response record in day 1 autobiographical memory recall test.

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frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 14 October 2022
DOI 10.3389/fpsyt.2022.992657

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

RECEIVED 12 July 2022
ACCEPTED 14 September 2022
PUBLISHED 14 October 2022

CITATION
Rohlfing N, Bonnet U, Tendolkar I, Hinney A and Scherbaum N (2022) Subjective reward processing and catechol-*O*- methyltransferase Val158Met polymorphism as potential research domain criteria in addiction: A pilot study.
Front. Psychiatry 13:992657.
doi: 10.3389/fpsyt.2022.992657

Subjective reward processing and catechol-*O*-methyltransferase Val158Met polymorphism as potential research domain criteria in addiction: A pilot study

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The Research Domain Criteria (RDoC) approach seeks to understand mental functioning in continuous valid dimensions ranging from functional to pathological. Reward processing is a transdiagnostic functioning domain of the RDoC. Due to prototypical abnormalities, addictions are especially applicable for the investigation of reward processing. Subjective reward processing is challenging to determine and differs between genotypes of the catechol-*O*-methyltransferase gene (COMT) Val158Met polymorphism for incomparable daily life experiences. Thus, we implemented the monetary incentive delay (MID) task with comparable reward cues and visual analog scales (VAS) to assess subjective reward processing in male abstinent cannabis-dependent individuals ($N = 13$) and a control group of nicotine smokers ($N = 13$). COMT Val158Met genotypes were nominally associated with differences in cigarettes smoked per day and motivation in the MID Task ($p = 0.028$; $p = 0.017$). For feedback gain, activation of the right insula was increased in controls, and activation correlated with gain expectancy and satisfaction about gain. Subjective value is not detached from reward parameters, but is modulated from expectancy and reward by the insula. The underlying neural mechanisms are a fundamental target point for treatments, interventions, and cognitive behavioral therapy.

KEYWORDS

subjective reward processing, COMT Val158Met polymorphism, research domain criteria, insula, gain expectancy

Introduction

The US National Institute of Mental Health has developed the Research Domain Criteria (RDoC) approach to explore the underlying biological causes of mental disorders (1). For this purpose, a research framework has been established to link and integrate current clinical syndromes with basic biological and behavioral components. The goal seeks to understand mental functioning in continuous valid dimensions ranging from functional to pathological. The RDoC framework consists of five predefined domains of functioning. The negative and the positive valence systems cover loss and reward constructs, such as loss, reward anticipation, reward prediction error, habit, and reward valuation including delay (2). Constructs are analyzed in a multi-dimensional approach comprising genes, circuits, observed behaviors, and self-reports (3).

Motivation is the energizing of behavior in pursuit of a goal, and obtaining goals or basic needs appropriately is rewarding (4). Thus, reward processes and motivation are closely linked. For example, reward contingency is used in current cognitive/behavioral treatments for schizophrenia and addiction to modify behavioral deficits or excess in motivation (5). Reward-related symptoms appear in the diagnostic criteria for multiple disorders and are thus transdiagnostic in nature (6). Reward processing abnormalities are a key component in the development and manifestation of a wide range of psychopathologies, including addictions (5). For instance, cannabis use is associated with amotivational syndrome (6). The effect of cannabis use on neural reward processing has been investigated intensively with the well-established reward paradigm of the monetary incentive delay (MID) task (7). The results display alterations in reward-related neural functioning (8, 9). For example, cannabis users showed hypoactivity in the left insula cortex in response to loss and loss avoidance outcomes (8). Cannabis and nicotine are often used at the same time and altered reward functioning could also be verified for nicotine use (10, 11). According to previous findings, nicotine use does not affect amotivational syndrome (6). The co-use of cannabis and nicotine and mutual reinforcement is a critical matter of prevention and public health (10).

Physical reward parameters or reward cue properties, such as magnitude, cannot precisely define subjective reward value (12). Value is an internal component of reward and is represented in subjective preferences, such as individual needs or emotional valence (5, 13). Representations are generated by brain mechanisms mediated by dopamine neurons in the substantia nigra and VTA, and phasic dopamine responses increase with the expected reward value (13). Nevertheless, the assessment of unobservable subjective value is a central challenge in reward research (5). One way to resolving this issue is to ask people how rewarding they find something and to compare choices between objectively equal rewards (5, 13).

Within the RDoC approach, genetic variants are among the units of analysis (3). The Val158Met polymorphism of the gene for catechol-*O*-methyltransferase (COMT) leads to valine to methionine exchange at position 158 of the protein (14). Homozygotes for the 158Met allele exhibit 35–50% lower brain COMT activity than homozygotes for 158Val with higher extrasynaptic dopamine levels, while heterozygotes show an intermediate enzyme function (15). Wichers et al. investigated the effect of the Val158Met polymorphism on the ability to experience reward in daily life (16). Homozygotes for 158Met generated almost similar amounts of subjective wellbeing from a "bit pleasant" daily life experience as 158Val homozygotes did from a "very pleasant" experience. The ability to experience reward increased with the number of "Met" alleles. Despite the genetic differences in subjective reward processing, the daily life experiences in the study of Wichers et al. were neither comparable reward cues nor objectively equal rewards. Reward experience was operationalized as the effect of event appraisal on positive affect and associations between COMT genotype, event appraisal, and positive affect were examined with regression analysis. In addition, reward sensitivity was also measured with self-reports, as well as behavioral tasks (17). Increased reward sensitivity was predictive of substance use, substance use disorders, greater cravings, and positive affective responses in alcohol cue reactivity paradigms. In this context, genetic modulation of reward sensitivity *via* dopamine transmission may be of special interest to understand individual differences (17, 18).

The aim of the present pilot study is to investigate reward processing for the first time dimensionally in the context of the RDoC approach, rather than focusing on mental disorder categories only (3). Reward processing is a transdiagnostic functioning domain of the RDoC. Due to prototypical abnormalities, addictions are especially applicable for the investigation of reward processing and the focus is on the potential effects of nicotine and cannabis on amotivational syndrome and dimensions of subject reward processing, such as motivation. Subjective reward processing differs between Val158Met genotypes for incomparable daily life experiences and was assessed with delay after the experiences. In the present study, this issue was methodically resolved with visual analog scales (VAS) or self-reports, comparable reward cues, and a constant reinforcement rate. We hypothesized that homozygotes for 158Met would be more satisfied with the achieved gain in the MID Task than individuals with the other genotypes.

Materials and methods

Participants

Thirteen inpatients with cannabis dependency and 13 volunteers without cannabis abuse participated in the study. The sample size was set to a minimum of 24 participants to anticipate results for the main study (19, 20). All participants

were male subjects, right-handed smokers of European ancestry. The participants had been instructed to discontinue cigarette smoking for at least 2 h before the study and were interviewed and assessed by a clinical psychologist. The diagnosis of the cannabis-dependent inpatients was confirmed with the International Diagnostic Checklists for DSM-IV and axis I or II disorders other than nicotine dependence were excluded for all participants (21, 22). A urine drug test was conducted to control for the use of cannabis and other drugs (23). Any history of the abuse of other drugs, psychiatric, neurological or chronic diseases, head trauma, loss of consciousness, impaired vision, and the use of medication for volunteers were exclusion criteria. Nicotine dependence was assessed with the Fagerström Test (FTNA) and the participants were matched on nicotine dependence, age, verbal intelligence, and years of education (24). The groups did not differ in any dimension of the controlled variables ($P \geq 0.064$).

Cannabis consumption was assessed with self-report questionnaires and the European Addiction Severity Index questionnaire (EuropASI) (25). Only cannabis-dependent inpatients with at least 4 days of abstinence and without withdrawal symptoms were included. The mean age of initial use was 16 years (SD = 2), the mean cannabis use was 8 years (SD = 6), and 12 grams per week (SD = 5). The mean abstinence was 24 days (SD = 24).

Genotyping

DNA was extracted from the EDTA anticoagulated blood samples of all participants. A fragment containing the COMT Val158Met polymorphism (dbSNP: rs4680) was amplified with polymerase chain reaction (PCR). Sanger sequencing of this fragment was conducted commercially (26). Analyses of the sequences were performed by eye aided by the software Lasergene (27). **Table 1** summarizes the genotypes of both study groups. Hardy Weinberg equilibrium was fulfilled for all study groups.

TABLE 1 *COMT* genotypes of individuals who smoke ($N = 13$) and are cannabis dependent ($N = 13$).

COMT genotype	Nicotine N (percent)	Cannabis N (percent)	Σ
Val/Val	7 (54)	4 (31)	11
Val/Met	4 (31)	5 (38)	9
Met/Met	2 (15)	4 (31)	6
Σ	13 (100)	13 (100)	26

Reward reaction task and subjective reward processing

The reward reaction task was based on the monetary incentive delay (MID) task (7). Participants had to react to monetary reward cues with the push of a button (**Figure 1** and **Supplementary material**).

The amount of gain and loss varied between 1, 2, and 3 Euros corresponding to the number of 1 Euro coins on the picture. The participants started with a credit of 5 Euros. They completed one practice run and two test runs. In the test runs, the target presentation was adapted to the individual reaction rates and an average hit rate of 50% was predefined. The participants were informed that they would be paid the higher outcome of one of the two test runs. Subjective reward processing was assessed with visual analog scales (VAS) correspondingly to the study of Wrase et al. (28). Before the reward reaction task, the participants were asked to rate their motivation and gain expectancy. After the task, they rated their effort for a gain of 3 Euros compared with 2 Euros and 1 Euro, their fear of a loss of 3 Euros compared with 2 Euros and 1 Euro, and their satisfaction with the achieved gain. Finally, the participants completed the items of the personality trait Reward Dependence of the Temperament and Character Inventory (TCI) (29).

fMRI data acquisition

fMRI data acquisition was performed on a 3 T magnetic resonance scanner (Magnetom VISION Siemens®) with a circularly polarized standard head coil (CP-Headcoil). For anatomical reference, a 3 D Magnetization Prepared Rapid Gradient Echo (MPRAGE) data set was acquired with the following parameters: TR = 9.7 ms, TE = 4 ms, flip angle 12°, matrix = 256 × 256, and voxel size 1 mm × 1 mm × 1mm. For functional scans, a gradient-echo echo-planar imaging (GE-EPI) sequence was conducted with the parameters TR = 1.9 s, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, and voxel size = 3.8 mm × 3.8 mm × 3.3 mm. FMRI volume acquisition was time-locked to the offset of the cues.

fMRI data analysis

fMRI data were analyzed for BOLD responses to reward anticipation and feedback. Data analysis was conducted with SPM8 (30). Voxel time series were interpolated to adjust non-simultaneous slice acquisition within each volume. Motion artifacts were corrected. Head movements were below 3 mm in translation and 3° in rotation from one volume acquisition to the next. The anatomical images were coregistered with the mean functional images. For normalization, the coregistered image was first spatially normalized to the standard template provided by the Montreal Neurological Institute (MNI-Template), and the obtained normalization parameters were then applied to all functional images. Voxel time series were smoothed with a Gaussian kernel (FWHM = 8 mm).

In the first-level analysis, a statistical model with all conditions was computed for each participant according to

FIGURE 1
Cues for gain (green), neutral (black), loss (red) 250 ms, delay (cross) 2.25–2.75 s target (white square), and feedback with outcome 1650 ms.

TABLE 2 Activated brain regions through reward anticipation and feedback in individuals who smoke ($N = 13$) and are cannabis dependent ($N = 13$).

Contrast	Study group ($N = 13$)	Brain region	x	y	z	t	*P*
Anticipation gain vs. loss	Nicotine	R insula	39	−7	7	4.32	0.001
	Cannabis	R anterior cingulate cortex (ACC)	9	29	28	3.45	0.005
Anticipation loss vs. gain	Nicotine	L inferior frontal gyrus (IFG)	−54	17	31	4.50	0.001
	Cannabis	R primary somatosensory cortex	33	−40	58	3.76	0.001
Feedback gain	Nicotine	L postcentral gyrus	−60	−22	49	6.21	0.001
	Cannabis	R middle temporal gyrus (MTG)	57	−28	−2	7.15	0.001
		R superior temporal gyrus (STG)	60	−34	16	5.69	0.001
		R inferior frontal gyrus (IFG)	48	20	16	4.88	0.001
Feedback loss	Nicotine	R middle frontal gyrus (MFG)	24	56	−8	6.75	0.001
		R inferior frontal gyrus (IFG)	51	32	1	5.79	0.001
		R insula	27	23	−11	4.63	0.001
	Cannabis	R middle temporal gyrus (MTG)	60	−49	10	5.43	0.001
		R inferior frontal gyrus (IFG)	60	8	10	5.18	0.001
		R cingulum	12	−34	46	4.36	0.001

the general linear model approach (31, 32). Gain and loss were contrasted with the neutral conditions, e.g., "anticipation of gain" vs. "no anticipation." Contrasts were calculated as t-statistic for each voxel.

In the second-level analysis, contrasts within the reward anticipation and feedback conditions were calculated for each group with a one-sample t-test at a significance level of $P < 0.005$ and a cluster threshold of $k > 5$. One-sample t-tests were FDR-corrected (33). Contrasts between cannabis-dependent inpatients and the control group were calculated for each condition with a two-sample t-test at a significance level of $P < 0.005$ and a cluster threshold of $k > 9$. The activated brain areas were determined on the basis of the coordinates of Hägele et al. (34). Regions of interest (ROIs; radius 5 mm) were sphere shaped and centered upon the peak voxel within each area of interest. The ROIs beta-values for each condition were extracted and converted into percent signal change using the Marseille Region of Interest Toolbox (35) software package (36).

Behavioral data analysis

With t-tests and multivariate analyses of variance, subjective reward processing, Reward dependence, and reaction times were analyzed for group differences between cannabis-dependent inpatients and the control group. Subsequently, these variables were analyzed for Pearson's correlations with activated brain region and the number of met alleles. Bonferroni corrections were conducted to control the family-wise error rate. With Kruskal–Wallis H tests, group differences for nicotine use and subjective reward processing were analyzed between genotypes. Behavioral data analysis was calculated with the software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Results with a p-value below 0.05 were considered statistically significant.

Results

Reward anticipation and feedback

Table 2 gives an overview of the brain regions revealing the main effects of reward anticipation and feedback. During feedback, no loss, activation of the right inferior frontal gyrus was increased in individuals who smoke ($x = 51$; $y = 32$; $z = 1$). Table 3 contains the brain regions with activation differences between the groups. Individuals who smoke showed an increased activation of the right insula for the anticipation of gain vs. loss ($x = 60$; $y = 5$; $z = 4$), and for feedback gain ($x = 21$; $y = 23$; $z = -8$; Figure 2).

TABLE 3 Contrasts with differently activated brain regions ($P \leq 0.001$).

Contrast	Group comparison	Brain region	x	y	Z	t
Anticipation gain vs. loss	Nicotine > Cannabis	R insula	60	5	4	3.96
Anticipation loss vs. gain	Nicotine > Cannabis	L inferior frontal gyrus (IFG)	−48	50	1	3.96
Feedback gain	Nicotine > Cannabis	R insula	21	23	−8	3.46
Feedback loss	Nicotine > Cannabis	R inferior frontal gyrus (IFG)	63	11	16	4.37
		L inferior frontal gyrus (IFG)	−48	14	13	4.02
		L putamen	−30	5	4	3.91
		R insula	30	23	1	3.65

Subjective reward processing and catechol-*O*-methyltransferase genotype

Individuals who smoke and cannabis-dependent inpatients did not differ significantly in subjective reward processing or reward dependence (all $P > 0.28$; **Supplementary material**).

A Kruskal–Wallis H test showed nominal differences in cigarettes per day $\chi 2(2) = 7.118$, $p = 0.028$ and motivation $\chi 2(2) = 8.192$, $p = 0.017$ between COMT genotypes with a mean rank of 11.00 for Val/Val, 11.72 for Val/Met, and 20.75 for Met/Met and 11.86 for Val/Val, 19.06 for Val/Met, and 8.17 for Met/Met. There were statistically significant correlations for the anticipation of gain vs. loss in cannabis dependents, for feedback loss in smokers, and for feedback gain in individuals who smoke and cannabis-dependent inpatients (**Supplementary material**). For feedback gain, activation of the insula correlated negatively with gain expectance and positively with satisfaction with the achieved gain in individuals who smoke and cannabis-dependent inpatients ($p < 0.004$; $p < 0.014$).

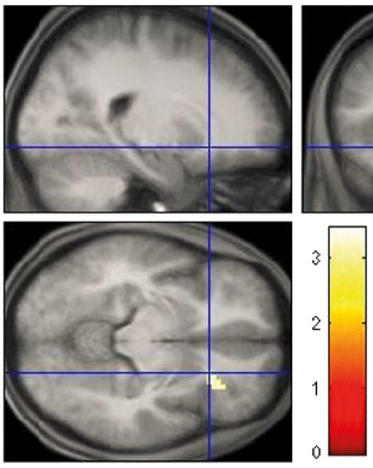

FIGURE 2
Increased right insula activation for feedback gain in smoking vs. cannabis-dependent individuals.

Discussion

In the present pilot study, we investigated subject reward processing and the COMT Val158Met polymorphism in abstinent cannabis-dependent inpatients and individuals who smoke with the well-established reward paradigm of the MID Task and found the commonly activated brain regions for this task (**Table 4**; 37). The aim was to take reward processing into account dimensionally across different forms of addiction, rather than only focusing on overarching mental disorder categories. The study focused on the application of the RDoC as well as the feasibility to assess subject reward processing.

Subjective reward processing did not differ between nicotine and cannabis in any dimension. Nonetheless, the results suggest that the most likely dimensions for differences in a larger sample are effort gain and satisfaction about gain. Because of the small sample size and other methodical limitations, the claim was not to draw a statistical inference for genetic neuroimaging and the sample size was set to a minimum of 24 participants. The sample size should not have been set in terms of cannabis and nicotine use, but the COMT genotype. In the total sample, homozygotes for 158Met were not more satisfied with the achieved gain than carriers of the other genotypes, which is probably due to the sample size. However, genotypes nominally differ for cigarettes per day and motivation with the highest number of cigarettes and the lowest motivation rank for homozygotes of 158Met. Tentatively, one might assume that homozygotes for 158Met may have less negative subjective effects of nicotine and thus smoke more (38). Reduced

TABLE 4 The main findings for the MID Task, the COMT Val158Met polymorphism, and its implications.

- **For feedback gain:** Activation of the right insula was increased in controls and activation correlated with gain expectancy and satisfaction about gain.
- Subjective value is not detached from reward parameters, but is modulated from expectancy and reward by the insula
- **COMT Val158Met:** Genotypes were nominally associated with differences in cigarettes smoked per day and motivation in the MID Task.
- Homozygotes for 158Met may have less negative subjective effects of nicotine and thus smoke more.

motivation in homozygotes of 158Met has previously been found in men of a Swedish sample (39). For individuals who smoke, cigarettes per day and motivation correlated negatively. The profile of nicotine changes from stimulant to sedative with increasing dosage (40). The present correlation can thus be attributed to the "Nesbitt's paradox" (38). Cannabis also affects motivation (41). Therefore, cigarettes and motivation were putatively not associated with cannabis dependence. In individuals who smoke, cigarette use correlated negatively and motivation positively with the activation of the right inferior frontal gyrus during feedback no loss. The right inferior frontal gyrus has been assigned to self-control, reward prediction errors, and sensation seeking and high sensation seekers are less sensitive to punishment (42–45). Higher cigarette use may hence imply lower self-control and response inhibition. Moreover, the present results suggest that motivation may be high precisely when predictions do not occur regardless of negative consequences.

For anticipation gain vs. loss, individuals who smoke had increased activation of the right insula compared with cannabis dependents. Acute THC increases perfusion in the insula with stronger increases for Val/Met heterozygotes (46). In anticipating rewards, insula activation is associated with motivational salience and sensitivity to reward magnitude (47, 48). Acute nicotine sensitizes and chronic smoking enhances the right insular response to gain and loss anticipation (11, 49). In contrast, activation of the left insular is reduced through acute cannabidiol and correlates with the salience of reward anticipation (48). The different contrast of anticipation gain vs. loss in the present study rather than gain vs. neutral cues in previous studies could be due to the diminished success probability of 50% (37). The current results suggest an overall desensitizing effect of the co-use of nicotine and cannabis on the insula and a decrease in salience for reward anticipation.

For feedback gain, individuals who smoke had increased activation of the right insula compared with cannabis-dependent inpatients. For reward feedback, the insula is involved in affective responding (37). The right anterior insula mediates interoceptive awareness (50). It integrates affective value with bodily states for reward-related adaptive behavior (51, 52). In the total sample, the activation of the right insula during feedback gain correlated negatively with gain expectancy and positively with satisfaction about the achieved gain. This finding indicates that the right insula interconnects gain expectancy with the evaluation of the reward-related performance and outcome independent of the substance. Additionally, the gain of the second test run correlated negatively with gain expectancy and positively with satisfaction. Higher gain expectancy at the beginning reduces reinforcement and thus motivation over the course of the MID Task, which impairs task monitoring and performance. Moderate or lower expectations have the opposite effect and therefore increase satisfaction with the outcome. The insula and interoceptive awareness are also crucial for drug cravings (53–55). The insula elicits conscious interoceptive urges, such as drug craving in response to rewarding and drug stimuli, respectively. For cannabis-dependent inpatients, gain expectancy correlated negatively with satisfaction and abstinence. Satisfaction correlated positively with consumption. These associations suggest a sensitizing effect of cannabis on subjective reward processing with an increase in gain expectancy and satisfaction. The dose-dependent increase in satisfaction is putatively due to the acute psychoactive effect of cannabis (56). Acute subjective changes in relaxation and perception caused by cannabis are also related to its effect on the insula (46). Positive subjective drug expectancies impair decision-making of addicted patients (57). The impairment consists of an overreliance on habits at the expense of goal-directed behavior and may be particularly symptomatic for early abstinence. As subjects had no experience with the MID Task (7), rationally, they should have quoted a middle gain expectancy. The negative correlation between abstinence and gain expectancy confirms drug-associated habitual biases during early abstinence. Moreover, insular functioning is highly dependent upon dopamine transmission and aberrant activation indicates impaired cue processing (58). Higher-than-predicted rewards generate positive prediction errors and elicit brief dopamine activations, whereas lower-than-predicted rewards generate negative prediction errors and induce decreases in activity (12). Accurately predicted rewards do not change the activity. For cannabis-dependent inpatients, gain expectancy correlated negatively with the activation of the right anterior cingulate cortex during the anticipation of gain vs. loss. The anterior cingulate cortex is involved in error monitoring and is affected by nicotine and cannabis (59, 60). For error monitoring, the expectation about an action is compared with the outcome and a deviation elicits the correction of behavioral responses (61). Any expectancy such as the current gain expectancies distract *per se* from task performance. Higher gain expectancies may additionally shift and bias attention toward cues for monetary gain under the neglect of losses. In consideration of the diminished success probability of 50%, however, it is just as important to avoid losses, as it is to gain money. Increased activity of the anterior cingulate cortex may suggest that cannabis-dependent inpatients with lower gain expectancy differentiated more effectively between gain and loss cues and thus, equally focused on and endeavored to avoid losses.

At first glance, the assessment of subjective reward processing seems exceptionally challenging. Subjective reward values such as preferences, needs, or emotional valence are unobservable, highly individual, and thus indefinable by physical reward parameters (12). In the present study, this issue was methodically resolved with visual analog scales (VAS) or self-reports, comparable reward cues, and a constant

reinforcement rate. The variable gain instead of a predefined gain for all subjects was a limitation of the study. Nevertheless, the results suggest that subjective value is not completely detached from reward parameters, but a quotient between value and parameter: previous gain expectancies namely modulate the subsequent reward evaluation. Abnormalities in reward processing are prototypical for addictions and comprise a sensitizing effect of cannabis on subjective reward processing with an increase in gain expectancy and satisfaction according to the present results. Higher gain expectancies, whether cannabis-induced or not, reduce reinforcement, motivation, and satisfaction of the outcome and the insula might function as an inverse balance between expectation and satisfaction. The COMT Val158Met polymorphism might influence motivation. Any expectation distracts from task performance by affecting error monitoring and response correction of reward-related behavior negatively. Addiction research suggests that expectations or biases might be traced back to the overreliance on habits at the expense of goal-directed behavior. The same bias and overreliance on habits were reported for non-clinical obsessive-compulsive symptoms (62). Obtaining goals or basic needs in an appropriate manner is rewarding, and the pursuit of a goal defines motivation (4). Therefore, cognitive biases and the underlying neural mechanisms of error monitoring, response correction, and goal attainment might be the most fundamental target points of mental functioning and treatment.

In the RDoC framework, subjective reward processing can be assigned to the domain of the negative and positive valence systems. The COMT Val158Met polymorphism, the reward system including the insula, performance in the MID Task, and self-reports were utilized as units of analysis. Subjective value is not detached from reward parameters but is a modulated from expectancy and reward by the insula. The insula is crucial for the interconnection of expectance and evaluation and aberrant activation might imply incongruence. Cognitive biases and the underlying neural mechanisms are thus the most fundamental target point for treatments, interventions, and cognitive behavioral therapy in further research. Examples of initial approaches are Cognitive Bias Modification and Emotional Bias Modification (63–65). These approaches are likely to be intensively extended and to be future of RDoC diagnostics and predominantly neural psychotherapy.

Data availability statement

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

Ethics statement

This study was reviewed and approved by Ethics Committee at the University of Duisburg-Essen. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NR and NS designed the study. NR was involved in the data acquisition and wrote the manuscript. AH was involved in genotyping. UB, IT, AH, and NS revised the manuscript. All authors read and approved the manuscript.

Funding

This study was funded by the LVR-Hospital Essen, Hospital of the University of Duisburg-Essen, Essen, Germany.

Acknowledgments

We acknowledge support from the Open Access Publication Fund of the University of Duisburg-Essen.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.992657/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Perspective
PUBLISHED 25 October 2022
DOI 10.3389/fpsyt.2022.985076

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

RECEIVED 03 July 2022
ACCEPTED 04 October 2022
PUBLISHED 25 October 2022

CITATION
Ren Y, Cui G, Zhang X, Feng K, Yu C and Liu P (2022) The promising fNIRS: Uncovering the function of prefrontal working memory networks based on multi-cognitive tasks.
Front. Psychiatry 13:985076.
doi: 10.3389/fpsyt.2022.985076

The promising fNIRS: Uncovering the function of prefrontal working memory networks based on multi-cognitive tasks

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The diversity of cognitive task paradigms using functional near-infrared spectroscopy (fNIRS) and the lack of theoretical explanations for these functional imaging atlases have greatly hindered the application of fNIRS in psychiatry. The fNIRS brain imaging based on multiple cognitive tasks could generally reflect the working patterns and neurovascular coupling changes in the prefrontal working memory network. By alternating the stimulation patterns of resting and task states, six typical symptom-related functional brain imaging waveforms related to psychiatric disorders are identified and three joint networks of the prefrontal working memory, namely, the attentional working memory primary coordination network, the perceptual content working memory secondary network, and the emotional-behavioral working memory executive network, are initially represented. This is the first attempt to characterize the cognitive, emotional, and behavioral regulation of the prefrontal working memory network using fNIRS, which may promote the application of fNIRS in clinical settings.

KEYWORDS

fNIRS, prefrontal cortex, working memory network, neurovascular coupling, psychiatric disorders

fNIRS in psychiatry

The improvement of diagnosis and treatment of psychiatric disorders relies on accessible neuroimaging tools that can identify associated frontal lobe dysfunction. Functional near-infrared spectroscopy (fNIRS) is an emerging functional neuroimaging method, non-invasively using the absorption and scattering relationships between multiple wavelengths of near-infrared light and chromophores in brain tissue [see (1) for more technical details]. It detects the brain activity near the brain surface by monitoring the relative concentration changes in oxy-hemoglobin [oxy-Hb] and deoxy-hemoglobin [deoxy-Hb] in the microvasculature of brain tissue during cognitive activity in real-time (2, 3).

During neural activities, consumed oxygen is compensated by increased blood supply, leading to an increased [oxy-Hb] and decreased [deoxy-Hb], a process understood as part of the neurovascular coupling mechanism (4, 5). Neurovascular coupling is the basis for functional brain imaging (6, 7). As early as 1890, Roy and Sherrington proposed the theory of neurovascular coupling that is "an increase in cerebral blood flow is induced during neural activity for a better energy supply"; thus, the change in local oxygenated hemoglobin will cause a series of other reactions. Changes in [oxy-Hb] and [deoxy-Hb] are often associated with neuronal activity in specific regions related to distinct human functions (8); thus, it is capable of real-time acquisition of cerebral oxygen signals as well as dynamic monitoring of physiological and pathological processes in the cerebral cortex.

Although NIRS can only observe the functional activity of about 2 cm of cerebral cortex under the probe, compared with PET, single-photon emission computed tomography (SPECT), fMRI, and other neurological effect technologies, it is relatively mobile, concise, and easy to meet measurement conditions, allowing subjects to be tested in a more natural and comfortable environment. As a result, more realistic data are obtained and could be used by psychiatrists. In recent years, several studies have shown that patients with psychiatric disorders have impaired function in the prefrontal cortex [e.g., (9, 10)]. The fluctuation differences of the [oxy-Hb] and [deoxy-Hb] among different regions of the prefrontal cortex can characterize different types of mental disorders (11–17). To some degree, the functions of the prefrontal cortex could reflect the working patterns of working memory networks (18). However, the representation mechanism of the prefrontal working memory network reflected by fNIRS imaging is still not clear.

The fNIRS, in conjunction with the verbal fluency task, holds promise for understanding, detecting, and differentiating psychiatric disorders, and has the potential for developing accessible neuroimaging biomarkers for different psychiatric disorders (19). The multi-site study (13) is the first large-scale, case-control study that demonstrates the utility of NIRS to differentiate the diagnosis of major psychiatric disorders in natural clinical settings using verbal fluency tasks.

However, in China, it is generally found in clinical psychiatry that the current diagnostic criteria developed in Japan for unipolar depression and bipolar depression are of low diagnostic compliance in clinical application. Due to the low diagnostic compliance, the application of fNIRS in psychiatry is constrained. The low diagnostic compliance may be related to factors as follows: (1) there is only a single diagnostic reference imaging of bipolar and unipolar depression. It does not take into account the dynamic feature of the disease and the states of patients. With the remission of the disease, changes in brain functioning have an impact on the corresponding cerebral blood flow diagram. Some studies show that patients with depression show non-dominant hemisphere activation in thinking during depressive states and with their recovery from depression, a preference is returned to the dominant hemisphere in thinking (20). Besides, the change in a particular brain region or waveform is unstable and variable due to the patient's state. Schecklmann et al. (21) suggest that the analysis of brain waveforms in groups or strings is more valuable and reproducible. (2) Different cognitive tasks and modalities should be incorporated as the stimulation covers a wider and various brain regions. In fact, cognitive resources required for various tasks are different, which might lead to confusion with slight changes in task requirements. (3) Only the change in [oxy-Hb] is considered, but not [deoxy-Hb]. Culver et al. (22) reported that the sum of [oxy-Hb] and [deoxy-Hb] concentration is more advantageous in the near-infrared cerebral blood flow topographic images, and is more suitable for large samples and long-term stimulation mode. (4) Language typological differences between Chinese and Japanese may cause differences in the same language task such as verbal fluency task, let alone among different cognitive tasks with varied difficulties. Therefore, it is crucial to find a suitable clinical task in China that can reflect the dynamic changes in patients' status based on energy coupling mechanisms.

Multi-cognitive tasks paradigm

Multi-cognitive tasks include four cognitive tasks, namely the emotional picture identification task, (category) verbal fluency task, finger-tapping task, and setting-based sentence fluency task. The alternation of adaptive tasks and primary tasks as well as the alternation of resting and task states ensures the various representations of the prefrontal cortex in its cognitive regulation and cognitive dysfunction. A detailed introduction of tasks involved in the multi-cognitive tasks' paradigm is shown in Table 1. The involved tasks exhibit theoretical significance. Most fNIRS studies on speech production have employed the verbal fluency task in patients with psychiatric disorders (21, 23), whereas setting-based sentence fluency task is adapted from visual picture naming [see (24, 25)], which has been scarcely studied in fNIRS. As for the adaptive tasks, the emotional identification task is essential in studies of emotions [see (26) for a review on emotion perception]. Finger-tapping tasks are one of the most common paradigms used to study the human motor system in functional neuroimaging studies [see (27) for a review]. Our multi-cognitive tasks paradigm combined these tasks in adaption to induce greater activation of prefrontal working memory networks as well as emotion regulation, taking the alternation of task properties and of resting and task states into consideration for the concern about patients.

During the multi-cognitive tasks, the relative concentration fluctuations of [oxy-Hb] and [deoxy-Hb] are recorded to reflect

TABLE 1 Detailed introduction of the multi-cognitive tasks.

Multi-cognitive tasks	Task property	Task requirement	Task timing
1. Emotional picture identification	Adaptive task	Identify whether pictures are positive/negative/neutral	15 pictures presented 4 s with a 2-s button response respectively (total: 1.5 mins)
2. (Category) Verbal fluency task [e.g., (15–17)]	Main language task	Categorize the hyponymy of a given category	Four category neutral words with 30-second-response and 30-second-rest respectively (total: 4 mins)
3. Finger tapping task	Adaptive task	Imitate the finger movement shown on the computer screen	Each hand imitates the given movements for 30 s with a 30-second-interval (total: 2 mins)
4. Setting-based sentence fluency task	Main language task	Produce sentences based on the given negative pictures	4 negative pictures with 30-second-production and 30-second-rest respectively (total: 4 mins)

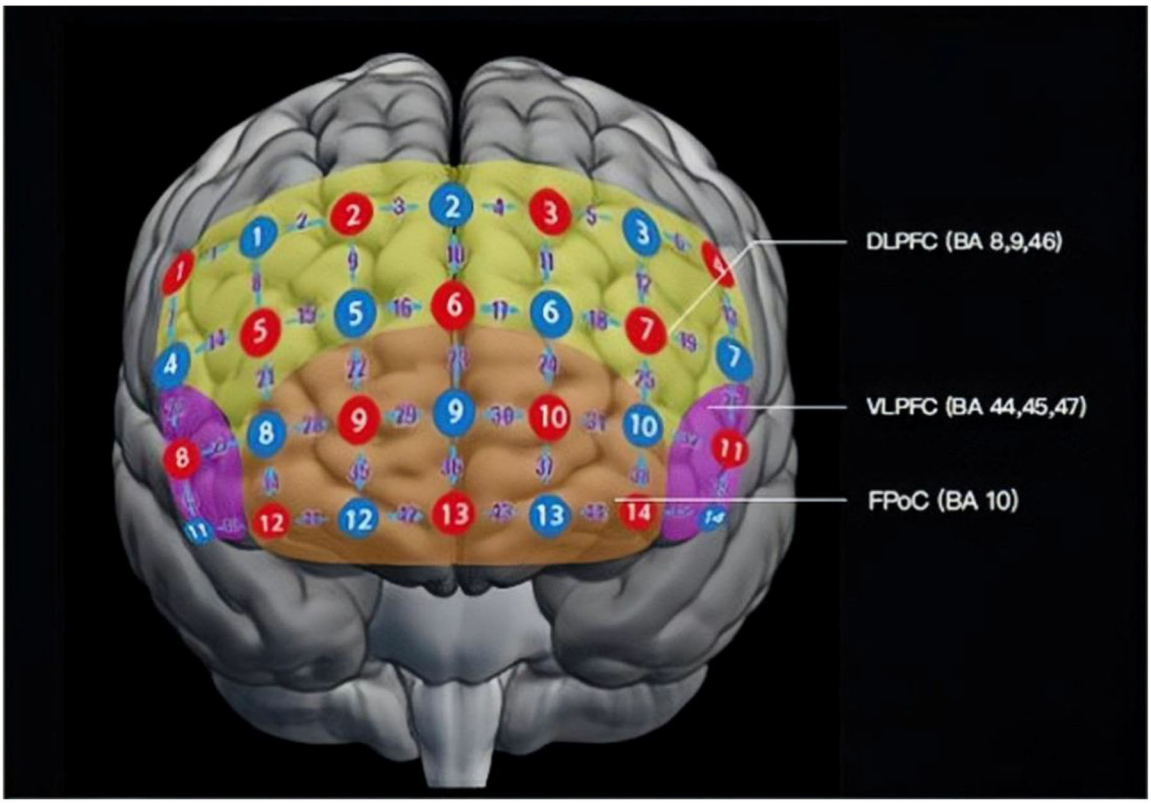

FIGURE 1
Layout of probes of the fNIRS probe in a frontal view. There are 14 emission probes (red) and 14 detector probes (blue) placed on the forehead of the patients at a distance of 3.0 cm, forming 45 channels (purple numbers). Detecting areas mainly cover DLPFC (BA 9, 46; yellow), VLPFC (BA 44, 45, 47; pink), and FPoC (BA 10, 11, 47; orange). BA, Brodmann's area; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; FPoC, frontal pole cortex.

different mental disorders from a 45-channel fNIRS system (Foire-3000, Shimadzu Corporation, Japan) (see Figure 1).

The symptoms (states) are identified and analyzed in the way of full-channel waveform, phase changes, and waveform composition ratios, and six typical waveforms (see Figure 2) with clinical significance are summarized to correlate with the typical symptom among various mental disorders (17). It has helped in the diagnosis of bipolar disorder and unipolar depression (15), major depressive disorder and generalized anxiety disorder (16), schizophrenia (28), and other mental disorders.

Functions of the prefrontal working memory network

The aim is to analyze functional abnormalities in the prefrontal cortex with fNIRS using various paradigms in

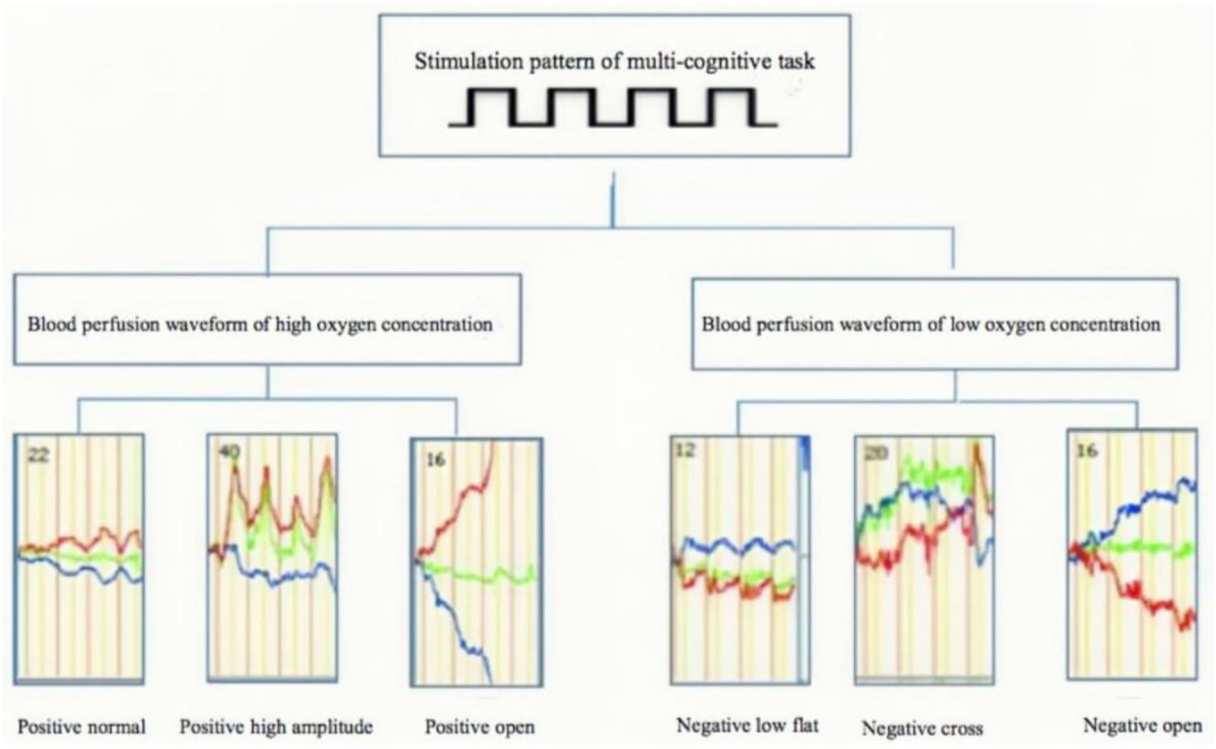

FIGURE 2
Hyperbolic waveform of multi-channel [oxy-Hb] and [deoxy-Hb] blood perfusion.

psychiatry, with (letter) verbal fluency task as the primary task in the clinical diagnostic setting [e.g., (29)] and other supplementary tasks such as emotional facial recognition task [e.g., (30)], working memory tasks [e.g., (31)], and emotional words task [e.g., (32)]. However, the lack of theoretical explanations for these functional imaging atlases has greatly hindered the application of fNIRS in psychiatry. The theoretical linkage between the fNIRS data showing neurovascular coupling and the patterns of the working memory network is unclear.

One of the primary functions of the prefrontal lobe is executive function. In empirical and theoretical papers, primary factors underlying executive functions are: (a) inhibition and switching (33–35), (b) working memory (34, 36–40), and (c) sustained and selective attention (37, 39–41). Originating from Baddeley and Hitch (42), there are several models of working memory [e.g., (43, 44)]. One common feature shared is the limited capacity resource of working memory that some theorists relate to attention [e.g., (44, 45)]. It is clear that the prefrontal function is closely related to attention, working memory, and executive function. Based on the memory model of information processing (46), which is the information flow of stimulus to memory (see Figure 3), the potential problems of working memory network are presented among patients of psychiatric disorders with fNIRS. Based on the practical diagnosis using multi-cognitive tasks and theoretical studies on the prefrontal cortex, we propose that the brain imaging of the prefrontal cortex in alternating stimulus modes of resting and task modes reflects the joint working mode of the three memory networks: the attentional working memory primary coordination network, the perceptual content working memory secondary network, and the emotional-behavioral working memory executive network.

Attentional working memory primary coordination network

In the neural network, the attentional working memory network is regarded as the main coordination network due to its importance. Attention is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought with the essence of focalization and concentration of consciousness. It implies withdrawal from some things in order to deal effectively with others [(47), pp. 403–404)]. Broadbent's (48) attention filter theory states that stimuli that are given notice and attention could enter working memory for further information processing. In the information processing model, attention serves as a filter.

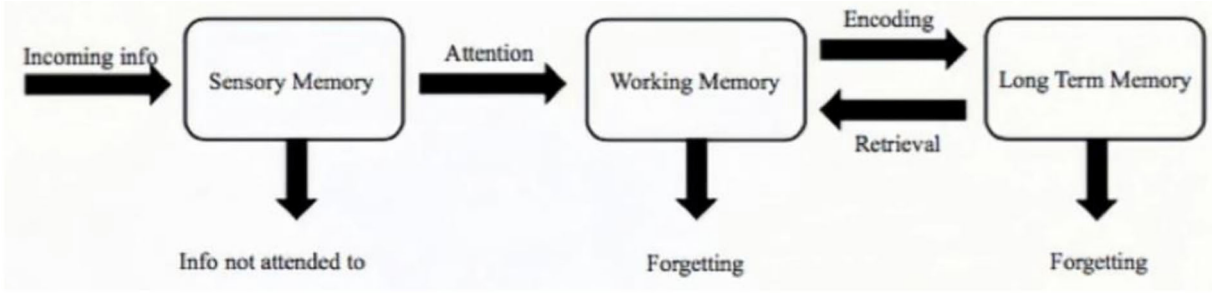

FIGURE 3
Information processing model.

An important function of prefrontal DLPFC (18) is to guide thinking and attention in a top-down pattern. Prefrontal cortex deficits can lead to attention disorders, including attentional impairment, distraction, and supervisory attention disorder, difficulty in shifting attentional focus, selective attention disorder, and decreased arousal. According to the pool-of-resources theory, we regard attention more as a resource pool, which can be flexibly allocated in competing tasks. In patients with DLPFC impairment, the distribution of attention is unorganized and uncontrollable.

Attention plays an important role in multi-cognitive tasks. Through the four tasks in the multi-cognitive tasks, attention is distributed and adjusted according to the timing and task requirements, reflecting its status in the working memory network. Patients need to pay attention to the multi-cognitive tasks which take 11.5 mins in total. The varied requirements and cognitive contents lead to the adapted allocation and consumption of attentional resources. Attention should be allocated flexibly to the four different cognitive tasks. For example, in the emotional picture identification task, patients need to focus on the picture, and judge its emotional valency according to the emotional effect of the visual stimulation presented. While in the main (category) verbal fluency task, patients need to retrieve words that belong to the same category, which requires the involvement of language processing. The distribution of attention should be automatic and adjusted flexibly according to the scene in healthy controls with little cognitive consumption, thus showing a relatively flat waveform. However, the recorded waveforms by fNIRS in multiple cognitive tasks are messy and of great fluctuation in patients with attention deficits. It is shown that attention engagement and its flexible allocation are required to ensure smooth performance on multiple cognitive tasks. Besides, the attentional working memory primary coordination network influences the subsequent perceptual content working memory secondary network and the emotional-behavioral working memory executive network.

Perceptual content working memory secondary network

The central executive function of the prefrontal cortex is closely related to working memory. Working memory is the ability to keep in mind an event that has just occurred, or bring to mind information from long-term storage, and use this representational knowledge to regulate behavior, thought, and emotion. During information processing, only the stimulus given attention could enter the working memory for further processing. We believe that with allocated attention, the perceptual content working memory secondary network is the working memory network responsible for cognition assessment and thinking regulation. It can be evaluated and analyzed through two main tasks in multiple cognitive tasks, namely (category) verbal fluency task and the setting-based sentence fluency task.

Take the most common working memory model as an example, Baddeley and Hitch's (42) model divided working memory into the central executive and the slave system. The central executive is the overall controller to coordinating among different tasks. The slave system includes a phonological loop and visuospatial sketchpad. The phonological loop holds the speech-based information for rehearsal. Visuospatial sketchpad holds visual-spatial information not only for its initial processing but also when it is later retrieved from long-term memory. The final element of the model, the episodic buffer (49), is responsible for the integration of information from different components of both working memory and long-term memory.

The difference between auditory and visual stimulus processing in the model demonstrates that modality plays its function, as shown in the division of phonological loop and visual-spatial sketchpad. In multi-cognitive tasks, task instructions are all presented with both visual and auditory modalities. Pictures are presented in both the emotional picture identification task and the setting-based sentence fluency task to activate the visuospatial sketchpad. The setting-based sentence fluency task requires a description of the picture and triggered

feelings, which requires the integration of working memory and long-term memory information, thus activating episodic buffer. Whereas in the (category) verbal fluency task, vocabularies are presented on the computer screen along with its auditory speech sounds, activating mostly the language-related factor, the phonological loop. The multiple cognitive tasks cover multiple modalities, auditory and visual, verbal and pictorial, activating working memory to a larger extent.

Besides, the differences of perceptual contents in multiple cognitive tasks lead to various working memory demands, i.e., the cognitive resources varying among different tasks. The emotional picture task involves mostly instantaneous memory, in which judgments about the emotion valency pictures are momentarily presented. The finger-tapping task is more likely to reflect somatization control with finer regulation. (Category) Verbal fluency tasks and setting-based sentence fluency tasks both involve language processing, which requires the involvement of both working memory and long-term memory. In (category) verbal fluency task, patients need to activate and retain the presented word such as "vegetable" in mind, that is, short-term memory needed to maintain current task requirements, and then extract the required words through word association network to seek the subcategory of the word "vegetable," which activates the semantic memory in the long-term memory. In the setting-based sentence fluency task, pictures enter the short-term memory and activate the visuospatial sketchpad of working memory. The integration of the relevant information shown in the picture to show the relevant information and the emotions aroused by the long-term schemas is needed. Especially, the cognitive resource demand for sentence production in setting-based sentence fluency tasks is much higher than that of word retrieval in (category) verbal fluency tasks. Following Levelt (50), we may distinguish four stages of production: conceptualizing, formulating, articulating, and self-monitoring. We conceptualize what we wish to communicate, formulate this thought into a linguistic plan, execute the plan through the muscles in the speech system, and monitor our speech. The setting-based sentence fluency task at the sentence production level is more difficult than the (category) verbal fluency task at the vocabulary retrieval level. To some degree, the difficult differences in perceptual content among tasks of picture judgment, movement imitation, and language processing enlarge the scope of cognitive resource consumption, which helps to improve the discrimination validity.

Emotional-behavioral working memory executive network

Another important function of the prefrontal cortex is the control and regulation of emotions (51). According to Arnsten (18), patients with psychiatric disorders become uncontrolled, reacting in a reflexive and rapid manner, mainly due to the decreased prefrontal function leading to the dominance of emotions taken over by amygdala. Patients pay attention to the most salient stimulus and lack the ability to control their attention. Therefore, we believe that the executive functioning of the brain under different perceptual content tasks is regulated by emotion.

It is widely accepted that the valence of a word (neutral, positive, or negative) influences lexical processing. The model of motivated attention and affective states (52) proposes that emotional stimuli, regardless of polarity, capture attention to a greater extent than neutral stimuli due to the survival-related salience which both positive (e.g., food) and negative (e.g., threat) stimuli convey. In order to minimize the emotional effects of words in (category) verbal fluency task, neutral category words are chosen in the (category) verbal fluency task, functioning as a benchmark of emotions. Thus, the neutral characteristic of (category) verbal fluency task could reflect the homeostasis of subjects' emotions. Both the emotional picture identification task and the setting-based sentence fluency task use pictures with emotional valence as a stimulus to examine patients' responses to and processing of emotional information. The emotional picture identification task is the decision of overall feeling toward pictures with positive, negative, and neutral valency. Whereas the setting-based sentence fluency task involves only pictures with negative valency, along with higher order thinking. Compared with the emotional picture identification task, the setting-based sentence fluency task has a higher cognitive load as language production is required (see section Emotional-behavioral working memory executive network), through which the influence of cognitive burden on emotion regulation and processing is reflected. By comparing the two tasks, how participants cope with more difficult tasks and how their perception of emotions under pressure could be manifested. Emotional instability and more depression-anxiety waveforms are seen in setting-based sentence fluency tasks with emotion arousal compared to emotional picture identification tasks as well as (category) verbal fluency tasks.

Discussion and future directions

Working memory networks, as a central element in cognition, are of great significance. Language is a verbal behavior of human intelligence, in which its underlying cognitive and psychological mechanisms are inseparable from working memory. It is pointed out that research should be based on cognition and psychology, seeking its behavioral manifestations outward and its neural basis inward (53). Based on clinical diagnosis and the summarized six classical waveforms, we further delineate the traditional classical cognitive and psychological mechanism—working memory. The

investigation of patients' attention, their performance on various perceptual contents, and emotional behavior executive functions from a cognitive perspective will facilitate the study of relevant neural mechanisms, which is of great significance for the development of cognitive science and phenotypic markers in medicine. The characteristics of the working memory network are indirectly represented through fNIRS by detecting the relative concentration changes in [oxy-Hb] and [deoxy-Hb], which contribute to a further neurological understanding of the working mode and characteristics of the prefrontal working memory network.

It is found that prefrontal functional connections during cognitive tasks are related to the neurovascular coupling mechanism and the effective utilization pattern of energy (oxygen) during cerebral nerve activity (54–56). The coordinated operation of the working memory network is based on the efficient use of energy by neurotransmitters and neurovascular coupling mechanisms, in which six typical waveforms in multiple cognitive tasks are extracted (see Figure 2). In normal people or people who recovered from anxiety disorders, it is observed that the red line of [oxy-Hb] relative concentration curve is on the top, and the curve of [deoxy-Hb] relative concentration is on the bottom, with a parallel hyperbola. During the onset of depression, attention is weakened and the degree of neuronal activation is reduced. In the symptom mapping classification compared to the mapping of normal people, the phase is of inverted parallel shape, in which the blue line [deoxy-Hb] is at the top and the red line [oxy-Hb] at the bottom, showing an inverse parallel shape, representing the inefficient use of oxygen at this locus.

In the anxiety state, the brain is too sensitive to external information, with increased attention and hyperactivity, which is reflected by the high peaks in the symptom classification mapping of multiple cognitive tasks. In the compulsion state, attention is enhanced with the brain repeatedly excited on the same task; thus, the brain continues to provide energy to this region. The increased attention to a stimulus will lead to the hyperexcitation of neurons, which is manifested in the continuous increase of [oxy-Hb] concentration. On the symptom classification mapping, the superposition of waveforms is seen, with an open hyperbola. The open positive phase indicates that the relative concentration of [oxy-Hb] at this site is higher than that of [deoxy-Hb]. The open negative phase indicates that the relative concentration of [deoxy-Hb] at this site is higher than that of [oxy-Hb]. Both of which may be a localized persistent pathological state. In adolescent children with attention deficit disorder or bipolar disorder with mixed episodes of inattention, and in mixed states of anxiety and depression, crossover disordered waveforms can be observed, i.e., the relative concentration curve of [deoxy-Hb] and the relative concentration curve of [oxy-Hb] are crossed, and the hyperbolic amplitude increases significantly increased and the waveforms are disordered.

From the perspective of neural mechanism, almost all the current fNIRS research only analyzes the changes in the relative concentration of [oxy-Hb], and little is known about the effect of [deoxy-Hb] on the neurovascular coupling mechanism. Neurons, vascular smooth muscle cells/pericytes, and astrocytes are involved in neurovascular coupling. The destruction of physiological structures such as the peritubular space, blood–brain barrier, and humoral factors such as Ang can cause neurovascular coupling dysfunction. Part of the action mechanisms of different types of neurons, key neurotransmitters, receptors, and ions in related pathways are closely related to the maintenance of brain homeostasis because the neurovascular coupling mechanism widely exists in the brain and presents the characteristics of multi-structural participation and multi-channel regulation (57).

It is generally believed that neurovascular coupling is only a marker of neuronal activation, with an amplitude proportional to the degree of neuronal activation, and changes in neurovascular coupling under disease are rarely considered. Csipo et al. (58) found that the fNIRS approach can distinguish the representation of the neurovascular coupling mechanism in cognitive tasks of different difficulties. For example, in pathological states such as aging and cognitive decline, decreased clearance of metabolites in peritubular space may be one of the important pathological mechanisms of neurovascular coupling dysfunction (59). Both psychiatry and neurology need to pay attention to the changes in phase, amplitude, and waveform of the relative concentration curve of [oxy-Hb] and [deoxy-Hb] in the neurovascular coupling mechanism of the prefrontal working memory network represented by fNIRS.

Multiple cognitive tasks analyze fNIRS imaging based on neurovascular coupling mechanism through cognitive tasks with different difficulties and divide the working memory network into three cognitive-related sub-networks for the first time. The near-infrared detection of multiple cognitive tasks presents the vascular coupling mechanism of the prefrontal neural network and neural working loops. Our articles (15–17) support the idea that the intracellular signal pathway network is blocked under stress as proposed by Arnsten (18). Aided by fNIRS, the sub-systems of the working memory network are represented, namely the attentional working memory primary coordination network, the perceptual content working memory secondary network, and the emotional-behavior working memory executive network.

The subdivision of prefrontal working memory networks based on neurovascular coupling offers a novel insight into the analysis of fNIRS imaging representations, and also provides a direction for drug evaluation. This study may help expand the clinical application of fNIRS through the informed diagnosis of mental disorders and provide physicians with an objective measure that may eventually be used to personalize treatment. With the development of brain function imaging and imaging

analysis technology, such as dynamic brain atlas, a more accurate and refined representation of the working memory network will be represented.

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

YR drafted the manuscript according to PL's clinical experience and was inspired by GC's psychological accounts. PL and YR discussed the theoretical framework and went through several minor changes. PL, GC, XZ, KF, and CY approved the final version of the manuscript with their guidance and comments on the article. All authors contributed to the article and approved the submitted version.

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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frontiers | Frontiers in Psychology

TYPE Systematic Review
PUBLISHED 19 January 2023
DOI 10.3389/fpsyg.2022.968638

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychology

RECEIVED 14 June 2022
ACCEPTED 07 December 2022
PUBLISHED 19 January 2023

CITATION
Li J, Ma H, Yang H, Yu H and Zhang N (2023) Cognitive bias modification for adult's depression: A systematic review and meta-analysis.
Front. Psychol. 13:968638.
doi: 10.3389/fpsyg.2022.968638

Cognitive bias modification for adult's depression: A systematic review and meta-analysis

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Objects: This study aimed to elucidate the effect of cognitive bias modification on depression.

Methods: This research included 10 randomized studies searching four major databases: PubMed, Embase, PsycINFO, and Cochrane Library, with a total sample size of 467. Moreover, they were examined for quality and possible publication bias.

Results: Cognitive bias modification (CBM) had statistically significant results, g=−0.64, 95% CI=[−0.97−0.32]. The interpretation of cognitive bias modification shows the highest effect size, g=−1.45, 95% CI=[−2.05−0.88]. When the training place is located in the laboratory, the training effect is significant, g=−1.11, 95% CI=[−1.62−0.61]. The difference is statistically significant when the training environment was changed to home, g=−0.28, 95% CI=[−0.51−0.05]. CBM has a statistical effect on moderate-to-severe depression, g=−0.70, 95% CI=[−1.04−0.36].

Conclusion: We found that CBM had a moderate therapeutic effect on depression, whether the setting was at home or in the lab. Especially when the interpretation of cognitive bias modification (CBM-I) was used, we got the highest effect value. Furthermore, CBM has a statistical effect on moderate-to-severe depression.

KEYWORDS

depression, review, meta-analysis, cognitive bias modification, cognitive bias

1. Introduction

Depression is a common mental disorder, accounting for 5% prevalence in adults worldwide (WHO, 2021). It is a costly and disabling illness that reduces life expectancy and affects people of all ages. It is well-established that there are many symptoms of depression, such as loss of interest and anhedonia, persistent depression, insomnia, fatigue, attention deficit, problems with low self-esteem, hopelessness, and suicide (Hasin et al., 2018).

According to the cognitive theory of depression, Cognitive theory holds that different psychopathological conditions are associated with specific biases that influence how an individual incorporates and responds to new information (Beck and Dozois, 2011).

Negative attentional bias plays a significant role in developing and maintaining depression (Beck, 2008). A large body of literature has documented that depressed people selectively pay attention to negative information (Gotlib and Joormann, 2010). Furthermore, depressed individuals tend to interpret ambiguous situations negatively (Orchard et al., 2016). Some theories also suggest that attentional bias and explanatory bias jointly affect depression (Everaert et al., 2012). These attentional patterns are associated with persistent rumination of negative value information and impaired emotional regulation due to difficulty in dissociating from negative stimuli (Yaroslavsky et al., 2019). When adverse circumstances activate potential negative patterns, depressed people's belief that they are unlovable and bad will be highlighted, so that individuals may selectively pay attention to information and opinions consistent with this negative self. It is a pessimistic view not only for yourself but also for others and the world (Roiser et al., 2012).

Among them, the persistent negative effects of cognitive dysfunction, attention deviation, and MDD can be understood as partly due to the dysfunction of prefrontal cortex circuits and related obstacles in emotional cognitive control (Murrough et al., 2011). There is a lot of research on the neural structure and function of negative cognitive bias. The two basic types of cognitive dysfunction observed in MDD are cognitive bias, including information processing or attention distribution distortion of negative stimuli, and cognitive deficits, including impaired attention, short-term memory, and executive function (Darcet et al., 2016). Based on cognitive defects such as impaired attention, some intervention strategies of implicit attention training can be explored. As mentioned later in this article, the attention deviation correction program is used to intervene in depression and anxiety (Jonassen et al., 2019).

Ochsner found that depressed adults' perception bias toward negative stimulation was related to the dysfunction of the amygdala and ventromedial prefrontal lobe. These brain regions are involved in bottom-up emotional processing (Ochsner et al., 2004). Dai found in the event-related unit that depressed adults are more likely to be aroused by negative sad faces (Dai and Feng, 2012). The above two studies are based on neuroimaging and EEG techniques, respectively, which make us realize that negative cognitive bias is not only a kind of psychological bias or thinking distortion but also corresponds to the defect of neurocognitive function. In addition, Fritzsche found that the attention bias of depressed adults toward negative stimuli, especially sad stimuli, will last until the recovery period of depression (Fritzsche et al., 2010). The attention bias to negative stimuli will cause further difficulties in the life of depressed adults, such as interpersonal dysfunction, thus aggravating the development and maintenance of depression (Geerts and Bouhuys, 1998). Besides, it is more difficult for depressed adults than non-depressed adults to exclude irrelevant negative information from working memory, and when working memory shows competition for resources, depressed adults will also suffer damage in selecting relevant positive content (Levens and Gotlib, 2009).

About one-third of adults with depression receive traditional antidepressant treatment [e.g., selective 5-hydroxytryptamine reuptake inhibitors (SSRI)] but respond poorly (Aguglia et al., 2014). Another study also showed that SSRIs are usually used as the first-line treatment for MDD. However, only 42–53% of patients treated with SSRIs have improved their condition, and medication for treatment-resistant depression remains a challenge (Tanaka et al., 2022). Biased cognition and maladaptive behavior patterns are considered to be the key factors leading to the development and persistence of depression. Given the safety of cognitive-behavioral therapy (CBT) and the important role of cognitive bias in the occurrence and maintenance of depression, CBT is the most commonly sought alternative therapy (Sudak, 2012). The selective efficacy of CBT combined with antidepressants has been previously reported (Ironside et al., 2016). However, the World Health Organization has listed it as the main cause of the burden of all diseases in middle- and high-income countries. This has led to increasing demands for innovative treatments that can be delivered by computer or telephone (Simon and Ludman, 2009).

Cognitive bias modification (CBM) is an application based on computer-intervention programs and cognitive theory. The intermediary hypothesis of cognitive theory is that the way individuals think and explain events affects their emotional and behavioral responses. Cognitive change assumes that individuals can become more functional and adaptable by intentionally changing their cognitive and behavioral responses to the environment they face (Beck and Dozois, 2011). CBM aims to directly change the process of prejudice in the cognitive process, such as biased attention to threatening stimuli and biased interpretation of vague stimuli as threats (Joormann et al., 2015).

These programs aim to modify information processing through cognitive tasks, which use basic learning principles and repeated exercises to encourage a healthier way of thinking. Researchers pointed out the practical benefits provided by CBM, such as scalability and easy dissemination, which can enhance the effect of CBT (Beard and Amir, 2008). Among them, CBMI usually aims at allowing individuals to explain ambiguous situations in a benign way, to encourage more flexible thinking, and be less rigid and negative (Joormann et al., 2015). CBM technology does not need to consider the quality and cost of the individual therapist. The role of the therapist is handed over to a relatively automated process. On the other hand, patients can even do it themselves at home (Pictet et al., 2016).

A growing number of studies and reviews have reported the promise of CBM as an alternative or complementary intervention to anxiety and depression. A study reports that the interpretation of Cognitive bias modification (CBM-I) can significantly correct the negative explanations to reduce depressive symptoms and provide evidence for supporting a clinical application, particularly in mild-to-moderate depression (Nejati et al., 2018). Another study shows that attention to

Cognitive bias modification (CBM-A) showed effectiveness in reducing attentional bias to negative information, increasing attention allocation to positive stimuli, and reducing depressive symptoms (LeMoult et al., 2016). Furthermore, a pilot study provides preliminary evidence that imagery and interpretation of cognitive bias modification (i-CBMI) could provide positive clinical outcomes in an Iranian psychiatric setting, showing that i-CBMI led to significant improvements in depressive symptoms (Torkan et al., 2014). However, there are some inconsistent results. Study shows that CBM had just a small effect on anxiety and depression ($g = 0.13$); when anxiety and depression were examined separately, CBM significantly modified anxiety but not depression (Hallion and Ruscio, 2011). A meta-analysis shows that the intervention effect of CBM on depression is insufficient (Fodor et al., 2020).

The results of these studies are in contrast. We found that some studies have included both depression and anxiety, which may have confounding factors because of comorbidity (Bowler et al., 2012). Furthermore, the study shows some differences in symptoms between adolescent depression and adult depression. Studies show that the differences in how depression presents in adolescents and adults may be consistent with different pathophysiological mechanisms. For adolescents, they found that physical disturbances were common (loss of energy, appetite, and sleep changes). For adults, anhedonia, loss of interest, and concentration difficulties were more common (Rice et al., 2019). At the same time, studies have shown that attentional bias was positively associated with anhedonia. Assessing biases in multiple domains increased sensitivity to uncover relationships between emotional processing biases and anhedonia symptoms (Salem et al., 2018). Therefore, we pay more attention to the cognitive bias modification of adult depression, which may reduce the mixing factors to expect purer and more targeted results.

The purpose of this study is to explore the effectiveness of cognitive bias modification in the intervention of depression patients with different severity; Second, to explore the effect of cognitive bias modification used by depressed adults in different training places; Finally, we want to know the intervention effect of three cognitive bias modification paradigms on depression.

2. Materials and methods

2.1. Literature search

This meta-analysis was entirely guided by the PRISMA tool (Stovold et al., 2014). This study was conducted to explore the effect of CBM on depression symptoms. Two authors (JL and HY) conducted a systematic search independently in PubMed, PsycINFO, Embase, and Cochrane Library on September 17, 2021. We searched four databases and used the same search strategy "((Cognitive bias modification) OR (attention* bias modification) OR (interpret* bias modification) OR (attention training) OR (bias training) AND (depression [Mesh Terms]) OR (depressive disorder) OR (depress*))." In case of missing any research that may not be randomized controlled trials, the reference lists within published reviews on CBM for depression were also searched.

2.2. Inclusion and exclusion criteria for the literature

Studies were identified using the following inclusion criteria: (1) randomized controlled trials; (2) using CBM intervention, alone or in combination with another treatment (i.e., CBM-I, CBM-A, and imagery CBM-I); (3) adult depression participants were included; and (4) clinically relevant outcomes. Exclusion criteria included the following: (1) healthy control group; (2) children or adolescent participants; and (3) conference abstracts and non-English articles were excluded.

Two authors (JL and HY) examined the literature obtained through the search strategy. Differences were resolved through discussion, and they will be consulted by the senior author (MH) if they still exist.

2.3. Literature quality assessment and data extraction

The quality of the included studies was assessed using criteria for seven "Risk of Bias" assessment tools developed by the Cochrane Collaboration (Higgins et al., 2011): (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias.

The content of data extraction includes the following dimensions: author, publication date, sample type, sample size, female sample size, mean age, CBM training location, training session, CBM process alone or in combination, CBM type (i.e., CBM-A, CBM-I, or imagery CBM-I) outcome measures, type of control group (i.e., sham training or waiting list), and follow-up study.

2.4. Meta-analysis procedure

For each study, the correlation values of the post-test in the control group were compared [mean and standard deviations (SD)]. Considering that different samples used different self-assessment questionnaires and several studies had small sample sizes, we used hedges' *g*-value to represent the effect size (Borenstein et al., 2009).

Most of the included studies were measured using self-rated questionnaires. The Beck depression inventory-II is a self-reported measure used to assess depressive symptoms. Depression was

measured by BDI-II. The self-rating depression scale is a 20-item self-report inventory that assesses depressive symptoms in both clinical and non-clinical populations and can distinguish between different levels of severity in depression symptoms (Zung, 1973). The PHQ-9 is a nine-question instrument given to patients in a primary care setting to screen for the presence and severity of depression. It is the nine-question depression scale from the Patient Health Questionnaire (PHQ). The Center for Epidemiologic Studies Depression Scale (CES-D) is a brief self-report questionnaire developed in 1977 by Laurie Radloff to measure the severity of depressive symptoms in the general population.

TABLE 1 Description of typical cognitive bias modification interventions.

CBM paradim	Description
CBM-A[1]	Participants are typically presented with pairs of words or faces (neutral or negative) and are trained to direct their attention away from the negative stimulus. The probe was placed on neutral or positive words or faces to divert their attention from negative stimuli; Computer records the timing when they click the button. General training tasks include dot-probe and Visual Search task.
CBM-I[2]	Participants are typically presented with ambiguous situations (often realistic scenarios capturing situations occurring in daily life) and are trained to resolve them to favor neutral or positive interpretations over negative interpretations; most CBM-I paradigms target the broad range of disorder-relevant situations and cognitions, although some have a very specific focus (e.g., interpretations of one specific kind of situation or behavior.)
i-CBMI[3]	Participants are typically presented with ambiguous situations. They are trained to resolve the ambiguous situation and are instructed to generate a mental image combining the picture and the words. Sometimes we use auditory material. After each stimulus, participants were asked, "How vividly could you imagine the scenario described?" Responses were made on a scale from 1 (not at all vivid) to 5 (extremely vivid).

[1]Attention of cognitive bias modification; [2]Interpretation of cognitive bias modification; and [3]Imagery and interpretation of cognitive bias modification.

RevMan5 and STATA software were used to analyze the results. If data are insufficient, try contacting the author of the original article. Considering the CBM was divided into three similar interventions: CBM-A, CBM-I, and i-CBMI, specific methods are introduced in Table 1. The random effect model is considered to calculate the effect value, and this model assumes that the included studies are from different research groups (Riley et al., 2011). Moreover, we can easily guess the heterogeneity between studies for they use three different similar interventions. We also need to calculate the Q statistic and I^2 index to assess heterogeneity. In addition, sensitivity analysis was used for the robustness of the study. How do you analyze sensitivity? The main approach used is a step-by-step elimination method, in which one study at a time is removed and the effect size (ES) of the remaining studies is calculated to see if heterogeneity changes. If an outlier occurs, the reason behind the anomaly literature needs to be explored. Subgroup meta-analyses can also help identify the sources of heterogeneity and understand the effects of experimental interventions in different subgroups. For assessment of publication bias, the Funnel plot can be used by looking at the symmetry of the Funnel plot. Egger's test is used to test the symmetry of the funnel plot.

3. Results

3.1. Search results

We searched a total of 1,884 articles in four databases, one of them was obtained through manual retrieval of references. There are 1,885 articles; 385 duplicating papers were first removed, leaving 1,500, and then a selection of titles and abstracts was done which excluded 1,287 articles. Therefore, 213 relevant literature pieces were left for the final full-test screening, from which 203 articles were excluded. The details of full-text screening are shown in Figure 1.

3.2. Research characteristics

Table 2 shows the characteristics of the 10 studies included. Sample sizes ranged from 18 to 114, with a total sample size of 467. This meta-analysis included studies of six moderate, three mild, and one severe depression samples. CBM's session ranges from 3 to 20 times. Four of the trials used CBM-A as an independent treatment, and the last one used CBM-A and CBM-I in combination. Another five items were divided into three items of i-CBMI and two items of CBM-I intervention methods.

3.3. Risk of bias in included studies

There are few studies on the best quality. Three studies met five of the criteria and two studies met four criteria; two studies met three criteria, and three studies met only two criteria. In general, the randomization of the studies was good. However,

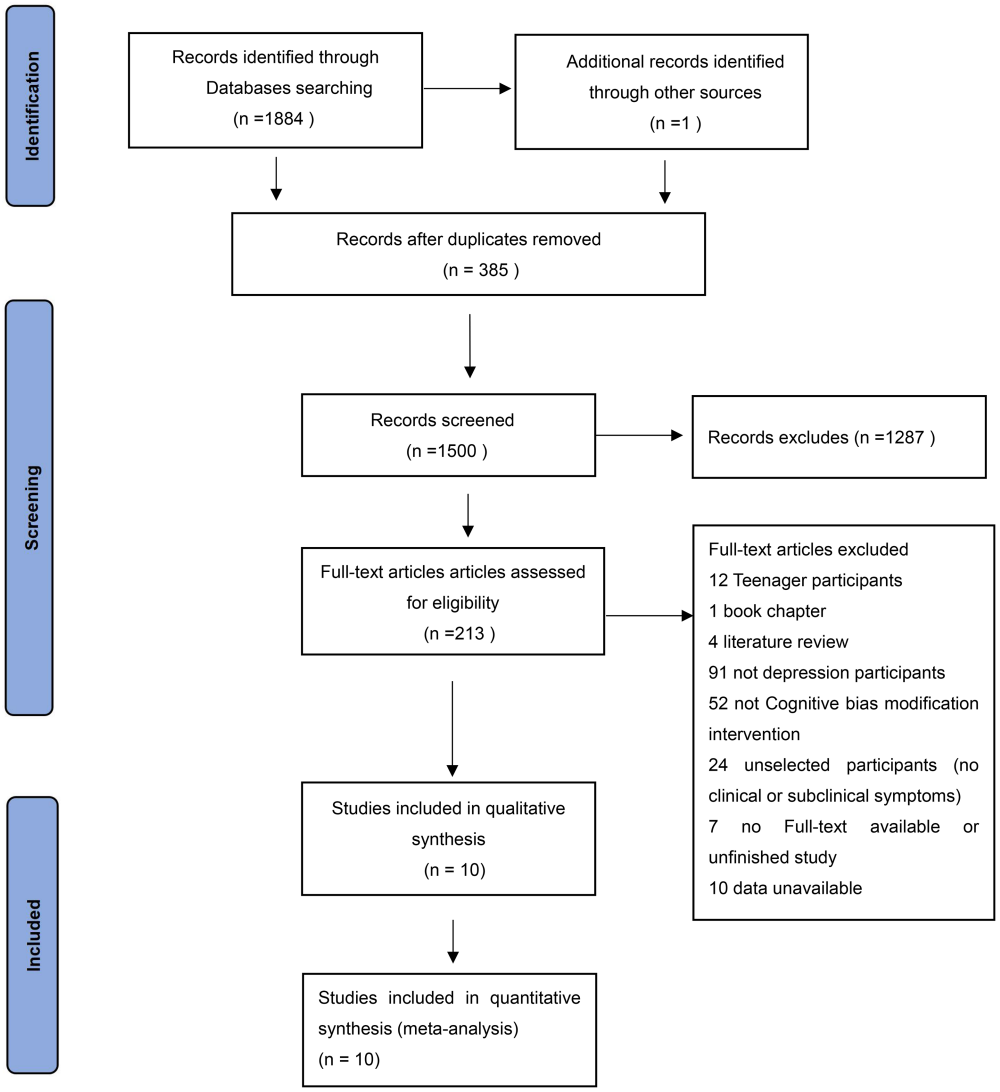

FIGURE 1
Follows the PRISMA statement. This is the flow chart included in the study.

almost all of the studies did not elaborate on how they hid the allocation, which could lead to a risk that the estimates would deviate from the true clinical outcomes. Three other studies had no follow-up and lacked complete outcome reports. Finally, some bias in other aspects mainly comes from the small sample size of the experiment, and the selection of subclinical samples is not precise enough and relatively broad, which is determined by the characteristics of mild symptoms themselves. Figure 2 is the bias diagram. In addition, there is a certain dropout rate in some studies, which may lead to inconsistency with the number of people who just started to be included, and the dropout rate may affect the reliability of outcome indicators. In addition, most of the included studies use self-assessment questionnaires, which may also lead to bias. In addition, considering that some interventions are made by patients themselves at home, there may be uncontrollable related factors, which will affect the quality of research.

3.4. Overall effect

Our study found that the analysis results of 10 studies reported the effect of CBM intervention on depression, the 95% CI (expressed numerically) of the meta-analysis results did not cross the invalid value, and both CBM significantly reduced the symptom score of depression. The total effect size was ($g = -0.64$, 95% CI = [−0.97–0.32], $N = 10$, $z = -3.84$, $p < 0.001$) and the research of heterogeneity was [Q (9) = 24.05, $p = 0.004$, I^2 (%) = 62.6; Figure 3].

TABLE 2 Study characteristics.

Study	Depression severity	*N*	Female (%)	Setting	*N* session	CBM methods	Measures	Control condition
Woolridge et al. (2022)	Moderate	40	65	Lab	3	CBM-A	BDI-II[1]	Placebo
Yang et al. (2015)	Mild	54	68.5	Lab	8	CBM-A	BDI-II	placebo
Baert et al. (2010)	Mild	18	88.8	Home	10	CBM-A	BDI-II	No training
Chen et al. (2022)	Moderate	40	95	Lab	4	CBM-I	SDS[2]	No training
Basanovic et al. (2019)	Mild	114	48.5	Home	20	CBM-I & CBM-A	PHQ-9[3]	Placebo
Lang et al. (2012)	Moderate	26	73	Home	7	i-CBMI	BDI-II	Placebo
Nejati et al. (2018)	Moderate	22	63.6	Lab	10	CBM-I	BDI-II	Placebo
Torkan et al. (2014)	Severe	26	57.6	Home	7	i-CBMI	BDI-II	No training
Krejtz et al. (2018)	Moderate	60	56.7	Home	14	CBM-A	CES-D[4]	Placebo
Pictet et al. (2016)	Moderate	67	76	Home	4	i-CBMI	BDI-II	No training

Study	Country	Mean age	IG depression score	CG depression score	Specific control condition
Woolridge et al. (2022)	Canada	44.5 ± 14.5	17.79 ± 12.2	23.45 ± 11.89	Neutral stimuli
Yang et al. (2015)	China	19.5 ± 1.3	10.96 ± 4.62	16.78 ± 5.09	Neutral (50%)
					Sad (50%)
Baert et al. (2010)	Belgium	19.4*	11 ± 6.19	13 ± 5.64	Invalid (50%)
					Valid (50%)
Chen et al. (2022)	China	21.3 ± 2.2	50.75 ± 8.07	60.63 ± 6.9	Waiting list
Basanovic et al. (2019)	Australia	60.2 ± 9.7	7.2 ± 3.67	7.24 ± 4.07	Random stimuli
Lang et al. (2012)	England	28.5 ± 9.2	19 ± 10.73	25.92 ± 9.66	Positive (50%)
					Negative (50%)
Nejati et al. (2018)	Iran	19.9 ± 1.2	7.72 ± 6.05	23.27 ± 9.93	Negative (50%)
					Ambiguous (50%)
Torkan et al. (2014)	Iran	28.5 ± 9.7	21.15 ± 10.11	26.92 ± 11.49	No training
Krejtz et al. (2018)	Poland	35.1 ± 13.0	25.67 ± 10.4	30.11 ± 11.25	Positive (50%)
					Neutral (50%)
Pictet et al. (2016)	Sweden	26.3 ± 8.9	18.66 ± 9.84	22.76 ± 10.34	Waiting list

[1]Beck Depression Inventory; [2]The Self Directed Search Questionnaire; [3]Patient Health Questionnaire-9; and [4]Center for Epidemiologic Studies Depression Scale. *None SD data; IG: Intervention group; CG: control group.

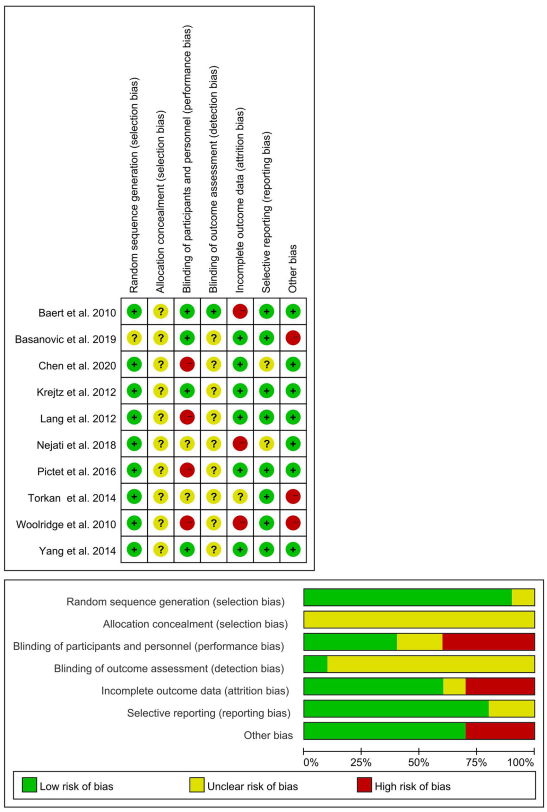

FIGURE 2
Risk of bias graph. Review authors' judgments about each risk of bias item presented as percentages across all included studies.

3.5. Subgroup analysis and meta-regression analysis

Subgroup analyses revealed that the three training methods and CBM training setting show significant statistical differences (Table 3). For different severity of depression, the results of subjects with severe depression had statistical significance. The intervention results of subjects with mild depression did not reach statistical differences. Compared to the experimental group, both the sham training and the waiting list showed significant differences. As we can see in Table 4, the meta-regressions revealed that the mean age of participants significantly moderated the post-test effect size. But there is no significant correlation between the publication year, the proportion of women, the session, and the effect value. The study found that the mean age significantly moderated the post-test effect size with younger participants benefiting more from CBM.

3.6. Sensitivity analysis and publication bias

3.6.1. Sensitivity analysis

Although most of the included studies were small sample studies, sensitivity analysis showed that the results of the random-effects model and the fixed-effects model were not significantly different; however, we decided to use the random utility model because we knew the heterogeneity of the research methods. Moreover, we found that sensitivity analysis and stepwise elimination showed no significant change in the final combined effect size. It is also proved that the result is robust.

3.6.2. Publication bias

We use review management to find out that the funnel plot is roughly asymmetric. Stata was used for trim-and-fill analysis, but we found that no trimming performed; and data unchanged. The Funnel asymmetry may be due to heterogeneity among studies. Continuity-corrected Begg's test shows marginal publication bias ($p = 0.049$) but egger's test shows publication bias ($p = 0.038$; Figure 4).

4. Discussion

4.1. Intervention effect and advantages of CBM

This is the first meta-analysis that includes three different cognitive bias modifications (CBM-A, CBM-I, and i-CBMI), and we only include depression participants. Considering the difference in cognitive symptoms between children's symptoms and depressive symptoms in adults (Rice et al., 2019), we included only adult depression studies. Heterogeneity and publication bias of the included literature was further explored. A total of 10 studies were included with a total sample size of 467 subjects. The results show that CBM has a significant effect on depression. This is different from previous studies of CBM on depression (Fodor et al., 2020).

We found that the heterogeneity of this research is high. However, the subgroup analysis we conducted later found that the different intervention mainly causes the reason. We have estimated the high heterogeneity before the analysis of this research. The experimental methods used between groups are not the same. In the subgroup analysis, we found that the heterogeneity within the three methods was very low, while the effect values and results were stable. This study shows that the combined effect size of subjects in the CBM-I group is the largest, higher than that in the CBM-A and i-CBMI groups. But we only included three CBM-I studies, one of which combined CBM-I and CBM-A. Thus, only two studies were included in the analysis, which may lead to bias. Among the three different methods, the effect size of the CBM-A value is larger than that of the i-CBMI group. The reason may be that i-CBMI requires imagination to intervene. There is a study that shows that different people may have different abilities for imagination, which will lead to confusion about this intervention (Lang et al., 2009). The method may not take into account individual differences. Some people's imagination is not prominent, thus, it may be difficult to ensure that the imagined scene is as clear as we think. However, considering the small sample size of this study, there are differences in the statistical data of the three methods, representing the efficacy of the three methods in alleviating depressive symptoms. Maybe

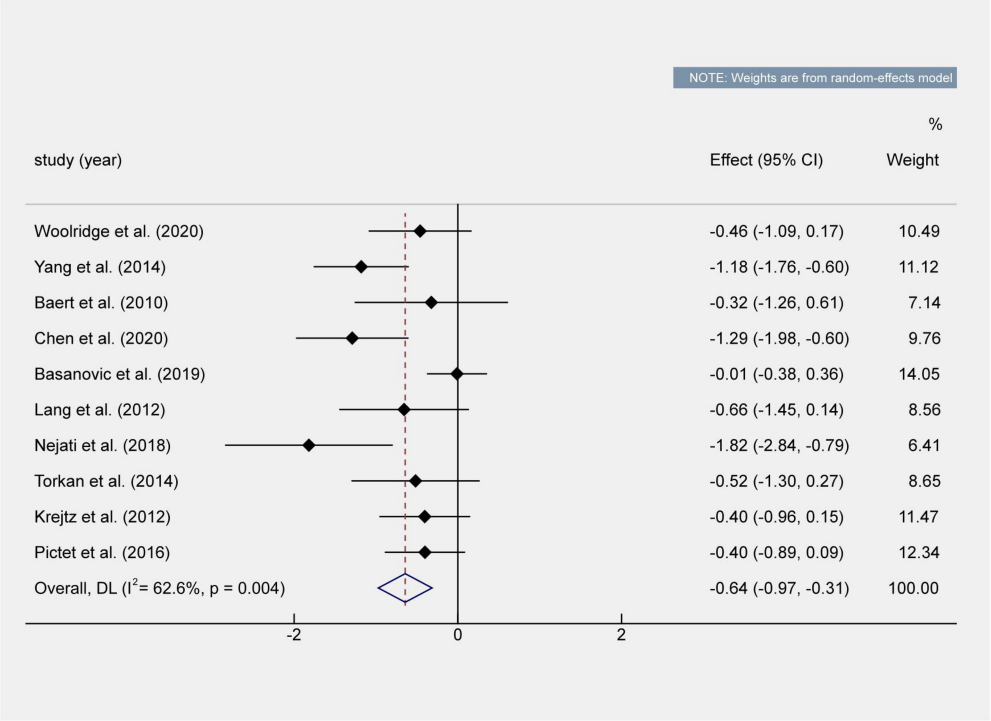

FIGURE 3
Overall effect shown in a forest plot. The total effect value shows that there are statistically significant differences. The effect value of the meta-analysis did not cross the invalid value.

TABLE 3 Subgroup analysis with categorical variables for depression symptoms at post-test.

Moderators		*N*	*g*	95% CI	Q_w	*p*	*z*	*p*
CBM methods	CBM-A	4	−0.63	[−1.04,-0.22]	4.76	0.19	−3.01	0.003
	CBM-I	2	−1.45	[−2.05,-0.88]	0.71	0.4	−4.99	0.00
	i-CBMI	3	−0.48	[−0.85,-0.11]	0.3	0.86	−2.56	0.01
Control condition	Sham training	6	−0.67	[−1.15,-0.19]	18.68	0.00	−2.72	0.006
	No training	4	−0.63	[−1.08,-0.20]	4.86	0.18	−2.83	0.005
Severity of depression	Mild	3	−0.49	[−1.31,0.31]	11.12	0.1	−1.21	0.227
	Moderate to severe	7	−0.7	[−1.04,-0.36]	10.56	0.00	−4.04	0.00
Training settiing	Lab	4	−1.11	[−1.62,-0.61]	6.19	0.1	−4.31	0.00
	Home	6	−0.28	[−0.51,-0.05]	3.72	0.59	−2.37	0.018

we should arrange CBM paradigm according to the individual differences of subjects. We can refer to future research that may focus on which method is the most suitable way for individuals. If the patients have a great imagination, we can recommend i-CBMI intervention; if the patient has good language ability, we can recommend CBM-I intervention; and we can arrange CBM-A intervention for the patient who has great facial recognition and emotional vocabulary recognition. Therefore, we can conclude that both CBM-I and CBM-A and i-CBMI can be used as potential alternative therapies for depression.

In the laboratory, CBM intervention will produce a larger experimental effect size, enabling CBM tests and intervention to be more serious in the laboratory. We speculated that low compliance at home might be the reason (Enock et al., 2014). Interventions at home may be more dependent on the patient's initiative, and the level of conscientiousness and concentration is less easily assured. In addition, the motivation of depressed adults, affected by symptoms (such as loss of interest, loss of pleasure, and energy exhaustion), is difficult for ensuring the full effect of the intervention. From this point of view, it may

TABLE 4 Regression analysis with continuous variables for depression symptoms at post-test.

Moderators	*N*	*β*	*SE*	*Z*	*P*
Mean age	10	0.02	0.01	3.81	0.00
N sessions	10	0.03	0.02	1.57	0.12
Female(%)	10	−0.16	0.01	−1.68	0.09
Year	10	−0.02	0.05	−0.38	0.71

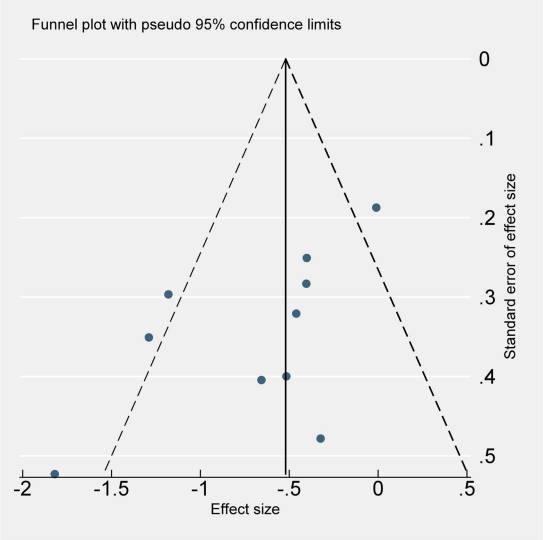

FIGURE 4
Funnel plot shows the publication bias and the heterogeneity. Scatter distribution suggests that there may be publication bias. Three studies fall outside the funnel chart, suggesting that there may be heterogeneity.

be a good plan to design a computer laboratory specifically for cognitive intervention in the future.

This study found that CBM was only effective in moderate-to-severe patients and did not achieve good results in mild patients. Nevertheless, Baert et al. found that CBM could only decrease symptom scores for those with mild depressive symptoms, while symptom scores increased for those with moderate-to-severe depression (Baert et al., 2010). Subjects with moderate-to-severe depression may have more room to lower their scores.

This research found that CBM (CBM-A, CBM-I, and i-CBMI) can significantly reduce depression symptom scores at post-test in adults. The CBM-I might be the best intervention training among the three methods. This may be because CBM-A and i-CBMI involve neurocognitive interventions, such as expression of emotion, positive/negative attention, and imagination, while CBM-I involves more top-down psychological explanation interventions. There may be some differences between them. We usually think that the neurocognitive level is the more basic part, which of course means the more difficult part to change. Moderate-to-severe depression participants and young adults tend to predict a larger effect size. It may be due to the decline of cognitive functions such as processing speed, working memory, and executive cognitive function of the elderly (Murman, 2015). CBM, as an independent treatment method, is not limited by space and can be easily intervened in homes and laboratories. Compared with other psychotherapy, it requires less effort and money, and saves a lot of resources. It can be considered as a potential complementary therapy for depression.

4.2. Limits and challenges

There are several limitations to this study. First, this study was not pre-registered, which may result in some potential bias. However, we have strictly followed the common procedures of systematic reviews. Second, there was no follow-up in some studies, and the follow-up intervals were different, which was not conducive to testing the long-term effects of CBM. Third, there are three methods of CBM, which cause heterogeneity among studies. Perhaps we need to devote all of our attention to one specific intervention paradigm in the future. Fourth, the total number of included studies is small and the sample size is relatively small, making the results of subgroup analysis less reliable, although we have used the Hedges' g as the effect value. Fifth, we only included studies published in English journals so we may have missed some studies. We hope there will be more studies with more accuracy and larger sample sizes in the future, not limited to English studies. Finally, we found that publication bias exists. This study shows that the effect of meta-analysis calculation may overestimate the efficacy of intervention measures, suggesting that we should draw conclusions cautiously. In future studies, we need to be more rigorous, ensure that the groups are masked, and reduce the experimenter effect.

Our research results of CBM on depression show that the intervention effect of CBM-I is the most obvious, so we can devote ourselves to further improving CBM-I, for example, considering individual differences and improving the training materials. The boring experimental procedure may easily lead to psychological conflict, and the training may be affected, thus affecting the effectiveness of the intervention. Maybe we should arrange intervention exercises according to the uniqueness of the subjects. Different subjects may be suitable for different training methods. In addition, cognitive bias correction is a training method that changes cognitive bias and then emotional response. However, these changed methods will not lead to people forgetting about fear or the original related situational events but will establish a new event background. When new fear clues appear, the original automatic response mode, namely negative deviation mode, may be restored. Thus, how to promote the generalization of cognitive bias correction is very important. It can be tried that the training materials should contain as many kinds of situational clues as possible, and these life situations usually reappear in reality and cause negative prejudice. The more types of situation simulation, the more helpful it is for the subjects to learn and cope. In addition, considering the individual specificity, the subjects can recognize their negative emotional reactions and record the situation and coping style at that time, such as the negative explanation of encountering vague situations. Feedback on the

recorded content was provided to scientists or psychologists in the laboratory so that the cognitive deviation correction program can be iterated and updated, and become a training version more suitable for patients themselves. In addition, some studies have shown that the fuzziness of information is an important adjustment factor for the correction of interpretation bias. If the fuzziness of information is insufficient, then no matter whether it is positive or negative stimulation, the subjects' interpretation mode can be affected (Hoppitt et al., 2010). And ambiguity of information is an important adjustment factor to correct for interpretation bias. If the ambiguity of the information is not sufficient, then it will affect the training results. (Brosan et al., 2011). On the one hand, the laboratory encourages the subjects to strictly follow the task instructions, actively pay attention to the screen, and try to respond accurately, but more consideration should also be given to how to make the cognitive deviation correction program more participatory and interactive, even by increasing the interest, reducing the subjects' conflict, and enhancing the popularization of cognitive deviation correction training, such as developing a program that combines cognitive bias modification with animation and games. Even virtual reality technology.

Because this study is based on the theoretical basis of cognitive therapy. It represents a shortcoming, which is restricted by the theory of cognitive therapy. Therefore, it may be a better way to integrate CBM with other therapies. In view of the relatively low clinical effect of cognitive bias correction therapy, while affirming its value, we also see its limitations. On the one hand, we need to further explore the improvement and perfection of cognitive bias correction programs as an independent training technique, and at the same time, we need to pay attention to the value of combining it with other therapies. For example, the explanation deviation correction training with a relatively large experimental effect amount is combined with behavior training, considering that the former is more based on the correction of thinking and explanation, while the latter is more about adjusting the emotional state of patients. The advantages of the combination of the two may be even greater, which of course needs further research to verify. However, previous studies have shown that the combination of online cognitive behavior therapy and cognitive deviation correction training can significantly improve the symptoms of patients (Yiend et al., 2005).

However, the integration alone may not be enough, if the effect of integration does not meet our expectations. Then, it may be necessary to re-examine the theoretical paradigm of depression. This study supports that cognitive processes and disease symptoms can be changed by correcting cognitive bias, and it is concluded that the effect value of cognitive bias correction training based on explanation is higher than that of the other two cognitive bias correction training methods. Studies have shown that the effect of cognitive bias correction based on interpretation can last for more than 24 h, and it is not easily affected by the individual's environment (Lang et al., 2012). But on the whole, the experimental effect of cognitive deviation correction training is only low-to-moderate. This has made us think about where the future of cognitive bias correction technology will develop. We feel that this kind of program or technology seems to have some limitations. A basic assumption of cognitive therapy and cognitive assessment of emotional disorders is that cognition plays an important role in emotional resilience and vulnerability, which is confirmed by cognitive bias correction training. However, more and more experimental studies have found that the cognitive bias correction of mental disorders is a very complicated cognitive process. For example, behind some psychological symptoms, there may be many cognitive biases. Additionally, although perception or attention is the lower part of the neural mechanism, and thinking or explanation is the higher cognitive content, they are actually closely interactive processes, and some studies also show that there are common potential mechanisms among cognitive processing systems (Mathews and MacLeod, 2005). In this regard, the ideological trend of embodied concepts sweeping the cognitive building in recent years is challenging the traditional symbolic operation or processing theory. The former closely embeds the body and cognition, emphasizing the great roles of the experience and state of the body and perceptual movement in cognition. Perhaps, in the absence of complete analysis and understanding of the pathological mechanism of depression, we can partially expand the clinical treatment of depression and enrich the cognitive theory of depression by changing theoretical paradigms, such as the treatment method of combining cognitive deviation correction procedures with physical activation training mentioned earlier and the combination of cognitive deviation correction with vivid scenes by using virtual reality technology. We hope that more effective training paradigms will appear in future, to improve the well-being of patients with clinical depression.

5. Conclusion

In our research, we found that CBM has a moderate effect on depression, whether at home or in the laboratory. The effect of CBM-I paradigm training is relatively the best. In addition, CBM has statistically significant effect on adults with moderate to severe depression. Based on the effect of CBM, the core effect of human cognitive correction on emotion is further affirmed. People can try to use such a convenient computer program to help correct their biased cognition and improve their emotional symptoms, which is an economical and effective method.

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

JL: data curation, conceptualization, data analysis, and writing an original draft. HM: supervision, method, and conceptualization. HYa: data curation. NZ: supervision. HYu: manuscript editing and

word correction. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Jiangsu Provincial key research and development program (Grant No. BE2015609).

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.968638/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Systematic Review
PUBLISHED 02 February 2023
DOI 10.3389/fpsyt.2023.1098734

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

RECEIVED 07 December 2022
ACCEPTED 16 January 2023
PUBLISHED 02 February 2023

CITATION
Khan MI, Qureshi H, Akhtar S, Bae SJ and Hassan F (2023) Prevalence of neuropsychiatric disorders in patients with systemic lupus erythematosus in Pakistan: A systematic review and meta-analysis. *Front. Psychiatry* 14:1098734. doi: 10.3389/fpsyt.2023.1098734

Prevalence of neuropsychiatric disorders in patients with systemic lupus erythematosus in Pakistan: A systematic review and meta-analysis

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Introduction: By conducting a systematic review and meta-analysis, we investigated the prevalence of neuropsychiatric (NP) symptoms among systemic lupus erythematosus (SLE) patients in Pakistan.

Methods: In this review work, three electronic databases (Web of Science, MEDLINE, and Google Scholar) and local databases were screened for 20 years from 1 January 2002 to 30 September 2022, to identify the articles evaluating the prevalence of NP symptoms in SLE patients in Pakistan. We performed a random-effects meta-analysis to estimate the prevalence of NPSLE. Statistical heterogeneity was measured by the I2 index, and subgroup meta-analyses were used to access the statistical heterogeneity. Furthermore, meta-regression models were used to examine the associations between prevalence estimates and study characteristics of interest. Three independent authors reviewed existing studies, extracted data, and rated the qualities of selected studies. This review was registered on PROSPERO (Registration no. CRD42022361798).

Results: Thirteen studies met the inclusion criteria out of the 322 studies with a total of 2,003 SLE patients for this systematic review and meta-analysis. The prevalence of NP disorders in SLE patients was estimated to be 30.42% (95% CI:18.26–44.11%), with cognitive dysfunction being the most common (31.51%; 95% CI:1.28–76.27%), followed by headache (10.22%; 95% CI: 0.00–33.43%), seizures (5.96%; 95% CI: 3.80–8.53%), psychosis (3.64%; 95% CI: 2.38–5.13%), and neuropathy is the least common (0.86%; 95% CI: 0.00–2.74%). The heterogeneity between studies was significant ($p < 0.01$). The pooled prevalence of NP disorders among SLE patients was found highest in Punjab (41.21%) and lowest in Sindh (17.60%).

Conclusion: Findings from this study revealed that SLE patients have a high prevalence of NP disorders. The most common symptoms were cognitive dysfunctions, headaches, seizures, psychosis, and neuropathy. Clinicians can manage these potentially deadly and disabling diseases more effectively if they

understand the incidence of each NP symptom in SLE patients. NP symptoms among SLE patients are at their peak in Pakistan; policymakers should devise preventive strategies to curb the disease.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=361798, identifier CRD42022361798.

KEYWORDS

meta-analysis, neuropsychiatric, Pakistan, random-effects, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is one of the most prevalent lupus types. SLE is an autoimmune disorder with a complex pathogenesis in which an immune system attacks the body's own tissues, causing inflammation and tissue damage in the organs affected (1–5). It can damage the brain, the skin, joints, kidneys, blood vessels, and the lungs (6). There are no clinical treatments available for SLE patients, but medical interventions and lifestyle changes can help manage their conditions. Women are more likely to have SLE than men, with a ratio of about six women to every male (7, 8). Patients tend to have a wide range of autoantibodies, which are often linked to different clinical signs and symptoms (9, 10).

Despite numerous therapy advancements and improved diagnosis techniques, SLE continues to cause significant morbidity and mortality (11, 12). Neuropsychiatric (NP) involvement in SLE patients is one of the disease's most dangerous side effects. It can cause negative effects on quality of life and disability (13–15). NPSLE pathogenic etiologies are likely complex (16–18), with multiple pathophysiological pathways implicated. Injury to the vascular system, blood-brain barrier (BBB), and brain parenchyma causes NPSLE symptoms (19, 20). Research shows that the damage may be caused by cytokines and autoantibodies, which can have localized or widespread effects on the central nervous system (CNS). Because the BBB does not protect the peripheral nervous system (PNS), it is vulnerable to the effects of immunological complexes, circulating autoantibodies, and other inflammatory chemicals (21). The pathophysiology of NPSLE most likely involves several antibodies (22, 23). The pathophysiological implications of NPSLE autoantibodies, which are anti-neuronal antibodies, were first investigated (24–26). NPSLE can also be caused by problems with the blood vessels, such as vasculopathy, atherosclerosis, and hypercoagulability (27, 28).

Cognitive dysfunction is a well-known sign of SLE (29–31), up to 90% patients affecting (32). Patients who do not have overt NPSLE frequently complain of cognitive issues, and rigorous neuropsychological testing commonly indicates cognitive abnormalities (33, 34). Problems with working memory, attention, and executive function are common mental abnormalities in SLE (35) and are frequently related to dysfunction in frontoparietal brain areas (36). Structural brain imaging was utilized to study these cognitive abnormalities in SLE patients (37). The results revealed structural damage to white and gray matter (38) and a higher number of white matter hyperintensities (WMHs) in SLE patients compared to healthy controls (39). This structural damage has been linked to cerebrovascular accidents, particularly in individuals with aPL autoantibodies, and breaches in the BBB, which may allow autoimmune processes to harm the brain (35, 40). WMHs have also been discovered in healthy controls, but they are much higher in SLE patients (41). These additional WMHs seen in people with SLE may cause problems with how networks connect, affecting how well people think (42).

In Pakistan, NP disorders are common in the patients with SLE. The most common disorders are depressions, anxieties, and psychoses. The other disorders include seizures, dementia, and strokes. The prevalence of NP disorders in Pakistani patients with SLE has not clearly covered. The prevalence of SLE and complications are steadily increasing in Pakistan. A number of researches (43–55) have found that NP disorders were commonly observed among SLE patients in Pakistan. To our best knowledge, there exists no official countrywide survey or national health registry for NP disorders in SLE patients in Pakistan. The goal of this work is to systematically locate, select, review, summarize, and estimate pooled prevalence of NP disorders in SLE patients using existing publications from Pakistan. The findings from this study may also contribute to the development of a management policy to lower the perceived prevalence of NP disorders in patients with SLE.

Materials and methods

This systematic review and meta-analysis was aligned with PRISMA guidelines, and the checklists were provided in the **Supplementary Table 1**. They were registered with PROPERO in October 2022 (with registration no. CRD42022361798).

Data sources and searches

Three independent authors searched Medline (*via* PubMed), Web of Sciences, Google Scholar, and local databases to identify all relevant studies published up to 5 September 2022, on the prevalence of NP disorders in SLE patients in Pakistan, regardless of language restrictions. The main used keywords were as follows: "lupus," "neuropsychiatric" or "NP," "NPSLE," "SLE" or "Systemic lupus erythematosus" combined with "ACR," "American college of rheumatology," or "American rheumatology association" or "ARA." Reference lists of relevant studies and reviews were also checked to identify additional articles.

Study selection

The studies were included in this meta-analysis if they fulfilled the following criteria. (1) The studies were published up to September 2022 and looked at how often NP problems happened in SLE patients. (2) The studies were either retrospective, prospective, or cross-sectional. Studies that did not address all NPSLE symptoms, provided duplicate data, were irrelevant, or were missed during the initial assessment of abstracts were excluded (e.g., case reports or review articles).

Data extraction

This study's authors (M.I.K., H.Q., and F.H.) worked together to create the data extraction form in Microsoft Excel. On this information extraction sheet, the initial author's name, the year the article was published, study design, total patients, positive patients, prevalence, setting, province, sex, male percentage, the working year, mean age of the patients, and classification criteria of SLE were all listed. Finally, the reliability of deleted data files was carefully reviewed, and any discrepancies between the deleted data were resolved by close discussions between the authors.

Study quality assessment

The risk of bias in selected studies was independently evaluated by two authors (S.A. and F.H.) through the JBI Critical Appraisal Checklist for Studies (11). Discrepancies in the scores assigned to various aspects of methodological quality assessments were resolved through debate and adjudication by a third investigator (M.I.). The quality score (ranging from 0 to 9) was assigned to each study. Each study presents a higher possibility of bias (1–3), a medium chance (4–6), or a lower possibility (7–9), based on the score it received.

Statistical analysis

For the pooled data, a random-effects (DerSimonian/Laird) meta-analysis model was used (56, 57), assuming the heterogeneity between the studies. Pooled results were produced at 95% confidence intervals and demonstrated with forest plots. Cochrane's *Q*-statistic

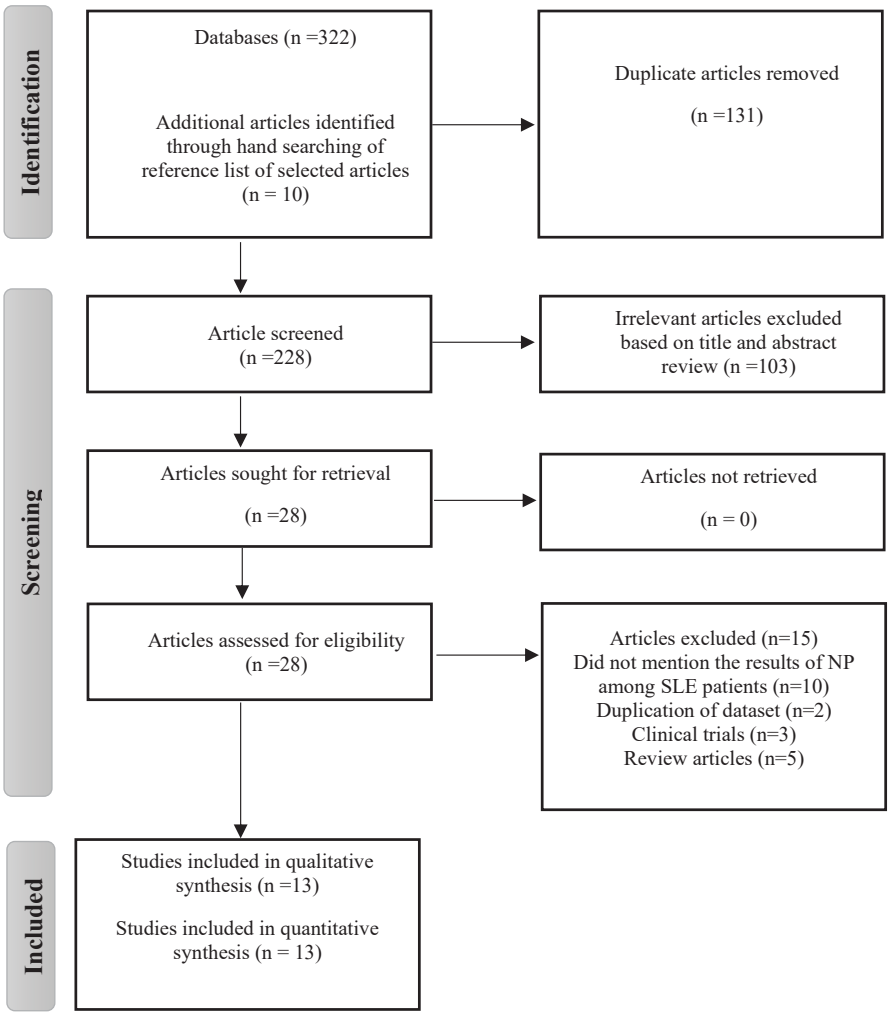

FIGURE 1
A flowchart of a PRISMA process.

was used to test whether the heterogeneity between the studies was significant, whereas I^2-index was employed to quantify it. The significance of heterogeneity was defined by the I^2 value more than 50% (58, 59). The prediction interval was computed to determine the range in which the genuine effect deviates from the mean. Funnel plot, Egger regression test, and Begg's test were conducted to investigate potential publication bias (60, 61). We conducted subgroup meta-analyses according to geographical locations, seizures, psychoses, headaches, cognitive dysfunctions, and neuropathies. To further explore the heterogeneity, univariate meta-regression models were constructed to determine the relationship between the prevalence of NP disorder in patients with SLE and the characteristics studied. The covariates in the meta-regressions included the publication year, the size of the sample, the study year, and the gender. To assess the impact of missing data from various studies on overall pooled estimates, we performed a series of sensitivity analyses in which we serially removed a study from the meta-analysis. Kappa statistic was utilized to quantify the degree of inter-rater agreement between investigators (62). All analyses were done using statistical software R (version 4.2.1).

Results

Figure 1 depicts a flowchart of the PRISMA process for including or excluding articles. A total of 322 studies were found, 311 of which were found through database searches and remaining 10 articles from reference lists. After deduplication (n = 131), 103 studies were excluded after carefully reviewing their titles and abstracts. The remaining 28 studies were given a full-text review to determine eligibility; those failing to satisfy inclusion criteria were eliminated. Thirteen articles were finally chosen in the meta analysis. Inter-rater agreement between investigators for study selection was significant (Kappa score = 0.81, $p < 0.01$).

Study characteristics

General characteristics of 13 eligible studies are described in Table 1. Selected studies were published between 2002 and 2022, along with 67% of the studies published in the past 10 years. It was noted that the period of participants' inclusion was from 1986 to 2019. Ten of these studies had a cross-sectional study design (43–46, 49–53, 55) and two studies had a prospective design (47, 54), whereas one was only retrospective (48). In total, 2003 SLE patients were included. Sample sizes of SLE patients varied from 23 to 663, with an average of 103. Average ages of SLE patients were reported in all studies, ranging from 10.5 (55) to 39.99 years (51). Pooled average age of SLE patients in 13 studies was 29.86 years. The proportion of female SLE patients in 13 studies ranged from 76% (43) to 96% (51). Among 13 studies, seven studies (43, 47, 49, 51–54) were conducted in Punjab province, five in Sindh province (44–46, 48, 55), and one in Khyber Pakhtunkhwa province (50). All of the studies were based on both urban and rural areas. Nine studies had a medium risk of bias in terms of methodological quality (43–46, 48, 49, 51, 53, 54), four had a low risk (47, 50, 52, 55), and none had a high risk. Kappa score of 0.78 (p = 0.001) indicates that the authors agreed on the extracted data.

TABLE 1 Shows the general characteristics of studies chosen for the study (n = 13).

References	Study design	Total sample	Positive cases	Prevalence %	Province	Sex	Female %	Working year	Mean age of the patients	Bias possibility	Classification criteria of SLE
Ahmed et al. (43)	Cross-sectional	50	7	14	Punjab	Both	76	2002	22.02	Medium	ARA
Rabbani et al. (44)	Cross-sectional	196	26	13.27	Sindh	Both	87.76	1986–2021	31.09	Medium	ARA
Rabbani et al. (45)	Cross-sectional	198	29	14.65	Sindh	Both	86.87	1986–2022	31.00	Medium	ARA
Rabbani et al. (46)	Cross-sectional	198	56	28.29	Sindh	Both	87.88	1992–2005	31.09	Medium	SLICC/ACR
Raza and Khan (47)	Prospective	65	20	31	Punjab	Both	93.84	2008–2011	28.45	Low	SLICC/ACR
Ishaq et al. (48)	Retrospective	105	16	15.24	Sindh	Both	94.3	2008	31.6	Medium	ARA
Batool et al. (49)	Cross-sectional	61	40	65.57	Punjab	Both	80.3	2015–2016	26.2	Medium	ACR
Khan et al. (50)	Cross-sectional	663	202	30.47	KPK	Both	91.4	2014–2016	33.09	Low	ACR
Mumtaz et al. (51)	Cross-sectional	100	84	84	Punjab	Both	96	2016	39.99	Medium	ACR
Shamim et al. (52)	Cross-sectional	23	3	13.04	Punjab	Both	91.3	2018–2019	11.00	Low	SLICC
Butt et al. (53)	Cross-sectional	43	28	65.1	Punjab	Both	95.3	2016	28.72	Medium	SLICC
Khan et al. (54)	Prospective	269	57	21.1	Punjab	NA	NA	2018–2019	27.8	Medium	ACR
Ahmed et al. (55)	Cross-sectional	32	5	15.6	Sindh	Both	87.5	2011–2015	10.5	Low	ACR

NA, not applicable; KPK, Khyber Pakhtunkhwa; KPK province 1 study included; Sindh province 5 studies included; Punjab province 7 studies included; 10 cross-sectional studies; 1 retrospective study; 2 prospective studies; ARA, American College of Rheumatology; ACR, American College of Rheumatology; SLICC, Systemic Lupus International Collaborating Clinics.

Quantitative synthesis

Pooled prevalence of NP disorders

Table 2 summarizes the subgroup meta-analysis for the pooled prevalence of NP disorders in SLE patients. The prevalence of NP disorders in the SLE patients in included studies ranges from 13.04% (95% CI: 2.78–33.59%) to 84% (95% CI: 75.32–90.57%). Among SLE patients, the pooled prevalence of NP disorders was 30.42% (95% CI: 18.26–44.11%). The 95% prediction interval was 0.001 to 84.60%. The Forest plot displayed in Figure 2. The heterogeneity level in the meta-analysis was significantly high ($I^2 = 95.7\%$; $p < 0.001$). We could not find any evidence of small-study effects or publication bias based on the visual inspection of the funnel plot (Figure 3). The results of the Egger regression test ($t = 0.53$; $p = 0.7882$) and Begg's rank test ($z = 0.55$; $p = 0.7194$) statistically support the absence of evidence for publication bias. The sensitivity analyses reveal that the pooled prevalence of NPSLE varies from 25.98% (95% CI:16.70–36.44%) to 32.14% (95% CI:19.06–46.72%) by excluding each study step by step (Supplementary Figure 1). No single study had an extreme influence on pooled NPSLE prevalence estimates.

Subgroup analysis

All subgroup analyses for the prevalence of NPSLE are shown in Table 2. The subgroup analyses show the differences in NPSLE prevalence by its disorder. Table 2 shows that cognitive dysfunctions are the most prevalent manifestation of NPSLE (31.51% CI: 1.28–76.27%), which is followed by headaches (10.22%; 95% CI: 0.00–33.43%), seizures (5.96%; 95% CI: 3.80–8.53%), psychoses (3.64%; 95% CI: 2.38–5.13%), and the least was neuropathies (0.86%; 95% CI: 0.00–2.74%). Pooled NPSLE prevalence was also found to differ by study location; the studies conducted in the Punjab province found the highest pooled prevalence estimate (41.21%; 95% CI: 6.48–81.93%), followed by Khyber Pakhtunkhwa (30.47%; 95% CI: 26.98–34.13%), and the lowest was found in Sindh 17.60% (95% CI: 8.32–29.34%). The prevalence NPSLE in significantly higher in adult population (33.35%; 95% CI: 19.38–48.96%) than pediatric population (14.50%; 95% CI: 5.99–25.47%). In the subgroup analysis, heterogeneity was high (I^2 index ranged from 0.0 to 97.4%).

Using the univariate meta-regression analysis (Table 3), we observed an increasing trend with a year of study in the prevalence of NP in SLE patients. The analysis also showed that age of SLE patient is significantly correlated with the prevalence of NP disorders in SLE patients. The results showed no statistically significant relationship between the prevalence of NP disorders in SLE patients and the year of publication, the percentage of females in the sample, diagnostic method, methodological quality or the sample size of the studies.

Discussion

We performed, to the best of our knowledge, the first systematic review and meta-analysis on the prevalence and risk factors associated with NP disorders among SLE patients in Pakistan, based on available data published from January 2002 to September 2022. The study used the data from 13 unique data sets with 2003 SLE patients from geographically diverse populations of Pakistan. Our study is purposed to provide useful information about the creation of public health measures to reduce NP disorders in SLE patients. Pooled overall prevalence of NP among SLE patients was 30.1%, indicating that approximately one out of every three SLE patients living in Pakistan is suffering from NP disorders. The findings of this meta-analysis are in line with the recent meta-analysis conducted in the Swiss lupus cohort study (28.1%) (63). However, pooled overall prevalence of NPSLE in Pakistan is significantly lower than in the studies conducted in Switzerland at 56.3% (64) and Egypt at 50.7% (65). This discrepancy could be attributed to the differences in research methodology, sample size, and universal definition of NPSLE disorders.

In our meta-analysis, as in many other studies, headaches, cognitive dysfunctions, psychoses, and seizure were the most frequent neurological disorder (66–68). The subgroup analyses show that cognitive dysfunctions was the most common NP manifestation, affecting 31.51% of SLE patients. The results are somewhat similar with another meta-analysis which showed that 39% prevalence of cognitive dysfunctions in SLE patients (33). Some studies have reported the results that persons with SLE have a greater, although extremely varied, prevalence of cognitive dysfunctions ranging from 17 to 66% (33, 69). In part, the disparities are attributed to a lack of a universal cognitive definition in many existing studies.

The subgroup analysis showed that pooled prevalence of NP disorders in SLE patients significantly varies with geographical location. The highest pooled prevalence of NP disorders was found in Punjab province at 41.42%, which was followed by Khyber Pakhtunkhwa province (30.45%) and Sindh province (17.32%). The wide disparity in prevalence between studies is due to variations in geographical location, ethnicity, sample bias, study design screening methodologies, the terminology used to define the event, the lack of specificity of NP symptoms, and the extent to which the occurrence is linked to SLE (70–72).

Admittedly, our systematic review and meta-analysis study has the following limitations. First, most of studies (69%) included in the meta-analysis had medium risk of bais and only four studies had a low risk of bias. Second, the results of the meta-analysis are only based on the data from three provinces. We have not found any articles from Baluchistan and Azad Kashmir. Even though these are the most populous provinces in the country, we should be careful in the generalization of the results to entire country. Thirdly, we limited our search to peer-reviewed studies and excluded gray literature, which may lead to some publication bias in our study. Fourth, in the included studies, we found a high level of heterogeneity in our analysis, which is commonly observed in meta-analyses of prevalence data (73, 74). This showed that of the variability in NPSLE prevalence measurements is due to the heterogeneity between the studies as opposed to chance. This is because that NPSLE is not a single disease entity (75), but rather a mixture of diverse disorders with potentially distinct pathophysiologic processes, including the production of autoantibodies (76). None of the ACR's 19 NP syndromes are specific to SLE; they have been reported in association with systemic vasculitides, antiphospholipid syndrome, Sjogren's syndrome, Behcet's disease, rheumatoid arthritis, and many other autoimmune disorders, as well as in individuals without autoimmune disease (77–80).

Even though there are some limitations, this is the first systematic study and meta-analysis to investigate how common

TABLE 2 Summary estimates from meta-analyses of NP disorders in patients with systemic lupus erythematosus in Pakistan.

Variable	No. of articles	No. of participants	No. of cases	Prevalence, (95% CI)	I^2, %	95%, prediction interval	*P*-value			
							Q test	Egger test	Begg test	Subgroup difference
NPSLE	13	2003	573	30.42 (18.26–44.11)	96	0.00–84.60	<0.001	0.7882	0.7194	
Types										
Seizures	8	1621	100	5.96 (3.80–8.53)	45	0.80–14.7	0.09			0.001
Psychoses	4	185	23	3.64 (2.38–5.13)	3.2	1.20–7.21	0.02			
Headaches	3	474	48	10.22 (0.00–33.43)	96.6	0.00– 100.0	0.03			
Cognitive dysfunctions	3	208	72	31.51 (1.28–76.27)	97.4	0.00–100.00	0.001			
Neuropathies	3	39	4	0.86 (0.00–2.74)	38.9	0.00; 45.93	0.1949			
By location										
Punjab	7	299	154	41.42 (20.14– 64.46)	97	0.00 – 100	<0.001			0.0055
Sindh	5	679	127	17.32 (11.92– 23.46)	76.8	0.00 – 55.79	<0.001			
KP	1	663	202	30.47 (26.98–34.13)						
By age										
Adult patients	11	1948	565	33.35 (19.38–48.96)	96.4	0.00–89.68	<0.001	0.3976	0.3487	0.0450
Pediatric patients	2	55	8	14.50 (5.99–25.47)	0.0					

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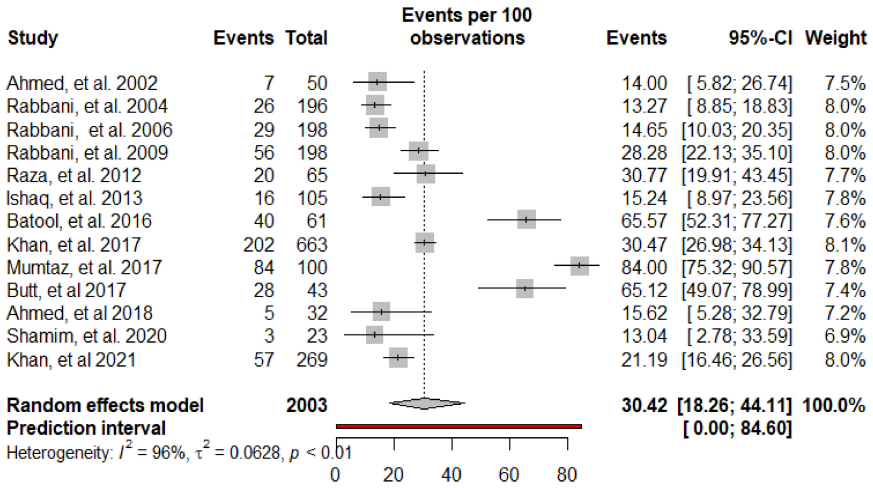

FIGURE 2
Forest plot of the prevalence of NP disorders among SLE patients in Pakistan.

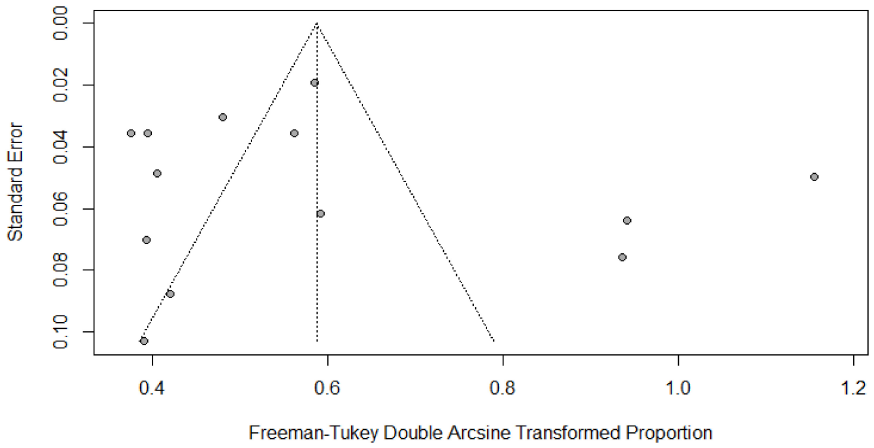

FIGURE 3
Funnel plot of the prevalence of NP disorders among SLE patients in Pakistan.

TABLE 3 Univariate meta-regression analyses.

Variable	Beta (β)	*P*-value	95% CI	R^2 %
Publication year	0.0159	0.1672	−0.0067– 0.0384	8.22
Year of investigation	0.0177	0.0490	0.0001–0.0353	23.02
Female ratio	−0.0002	0.3371	−0.001– 0.0007	0.00
Sample size	0.0028	0.0588	−0.0001– 0.0056	11.43
Diagnostic method	0.1518	0.1965	−0.0722–0.4652	8.99
Methodological quality	0.1225	0.44	−0.1894–0.4343	0.00
Age of SLE patient	0.0143	0.0939	−0.0024–0.0310	13.48

NP disorders are in SLE patients in Pakistan as a whole. Before we started the study, we published the protocol of the study that explained how we would do it. We also used scientific and statistical methods to gather and analyze the data. Different subgroup analyses and random effects meta-regression analyses were conducted to assess numerous variables that could influence our estimates. Despite the high heterogeneity, this systematic review and meta-analysis still provides useful and important information for the pooled prevalence of NP disorders in SLE patients in Pakistan. As conducting high-quality primary research on the prevalence of NP in SLE patients is often very expensive, and it can take years until the findings can finally be analysed.

Conclusion

This study provides pooled estimates of NP disorder among SLE patients in Pakistan. The figures suggest that NPSLE is a significant public health issue in Pakistan. Over the last several decades, there has been an uptick in the overall prevalence of NP symptoms in the general population in Pakistan. This upward trend is likely to continue in the foreseeable future. Since NP symptoms among SLE patients in Pakistan are on the rise, the government of Pakistan needs to work on developing an NPSLE preventative strategy and control programs that can be implemented across the entire country.

Furthermore, there is a significant variation in the prevalence of NPSLE in different provinces of Pakisan. Therefore, a countrywide study is recommended on pathogenesis of NP disorder in SLE patients in Pakistan, and to find the relative prevalence of each symptom relative to matched controls, such as individuals with other autoimmune disorders or apparently healthy subjects.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

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

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1A4A4079904) and the Korea Institute of Energy Technology Evaluation and Planning (KETEP) and the Ministry of Trade, Industry & Energy (MOTIE) of the Republic of Korea (No. 2021202090056C).

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1098734/full#supplementary-material

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 03 February 2023
DOI 10.3389/fpsyg.2023.1099257

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychology

RECEIVED 15 November 2022
ACCEPTED 06 January 2023
PUBLISHED 03 February 2023

CITATION
Gauld C and Depannemaecker D (2023) Dynamical systems in computational psychiatry: A toy-model to apprehend the dynamics of psychiatric symptoms. *Front. Psychol.* 14:1099257. doi: 10.3389/fpsyg.2023.1099257

Dynamical systems in computational psychiatry: A toy-model to apprehend the dynamics of psychiatric symptoms

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Introduction: These last years, scientific research focuses on the dynamical aspects of psychiatric disorders and their clinical significance. In this article, we proposed a theoretical framework formalized as a generic mathematical model capturing the heterogeneous individual evolutions of psychiatric symptoms. The first goal of this computational model based on differential equations is to illustrate the nonlinear dynamics of psychiatric symptoms. It offers an original approach to nonlinear dynamics to clinical psychiatrists.

Methods: In this study, we propose a 3+1 dimensions model $(x, y, z + f)$ reproducing the clinical observations encountered in clinical psychiatry with: a variable modeling environmental noise (z) on the patient's internal factors (y) with its temporal specificities (f) and symptomatology (x). This toy-model is able to integrate empirical or simulated data from the influence of perceived environmental over time, their potential importance on the internal and subjective patient-specific elements, and their interaction with the apparent intensity of symptoms.

Results: Constrained by clinical observation of case formulations, the dynamics of psychiatric symptoms is studied through four main psychiatric conditions were modeled: i) a healthy situation, ii) a kind of psychiatric disorder evolving following an outbreak (i.e., schizophrenia spectrum), iii) a kind of psychiatric disorder evolving by kindling and bursts (e.g., bipolar and related disorders); iv) and a kind of psychiatric disorder evolving due to its high susceptibility to the environment (e.g., spersistent complex bereavement disorder). Moreover, we simulate the action of treatments on different psychiatric conditions.

Discussion: We show that the challenges of dynamical systems allow to understand the interactions of psychiatric symptoms with environmental, descriptive, subjective or biological variables. Although this non-linear dynamical model has limitations (e.g., explanatory scope or discriminant validity), simulations provide at least five main interests for clinical psychiatry, such as a visualization of the potential different evolution of psychiatric disorders, formulation of clinical cases, information about attracting states and bifurcations, or the possibility of a nosological refinement of psychiatric models (e.g., staging and symptom network models).

KEYWORDS

psychiatric disorders, computational psychiatry, dynamical systems, symptoms dynamics, theoretical psychiatry

1. Introduction

Contemporary psychiatric nosology is based on categorical and static taxonomic distinctions. Thanks to the International Classification of Diseases, Eleventh Edition (ICD-11) (CIM, 2019) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Association, 2013), the operationalization of psychiatric disorders within descriptive and categorical nosographies has been one of the most important advances in contemporary psychiatry (or "psychopathology") (Kendler, 2017). Partly related to these specificities, such classification systems have major limitations that substantially impede scientific and clinical progress (Krueger and Bezdjian, 2009; Hyman, 2010). In addition to the difficulty in "carving the nature at its joints," i.e., clearly demarcated psychiatric disorder entities as discrete taxa (Kendler, 2016), a large part of these limitations stems from the conception of psychiatric disorders as categorical kinds, aka separate entities stable over time (Zachar, 2000; Haslam and Ernst, 2002). In this way, categorical psychiatric disorders as they are present in contemporary psychiatric nosography have at least three main limitations. First, they do not consider the temporal dynamics of psychiatric symptoms (Hitchcock et al., 2022). For instance, the category of schizophrenia provides an overview of the clinical picture of a patient, but fails to identify the evolution of his/her symptoms as events unfolded day after day and week after week. Secondly, categorical disorders cannot account for the intrinsic non-linearity of the evolution of disorders, as it is perceived in patients in clinical practice. There are indeed phenomenological transitions in the clinical state of a patient, sometimes slow and sometimes brutal, which are difficult to explain by a single psychiatric category (Nelson et al., 2021). Finally, these psychiatric categories cannot capture the intra-individual variability of the symptoms of a patient. For example, a series of studies have shown that there may be up to 1,030 unique symptom profiles of major depressive disorder (Fried and Nesse, 2015), or with any combination and classification, up to 636,120 ways to have a post-traumatic stress disorder (Galatzer-Levy and Bryant, 2013).

1.1. Psychiatry and dynamical systems

Psychiatric disorders are thus dynamical conditions (Demic and Cheng, 2014). They may be conceived as evolving entities, varying over time under the pressure of allostatic loads (i.e., accumulations of external factors over time), according to the evolution of symptoms (e.g., a delirium reinforcing the interpretative mechanisms) or according to subjective perceptions. A flow of current research theoretically aims to show that psychiatric disorders can be modeled dynamically (Kelso, 1995). Dynamical models aim to provide a precise outline accounting for the evolution of various psychiatric disorders or conditions over time, according to different types of temporal evolutions. For instance, Schizophrenia Spectrum (SS), Bipolar and related Disorders (BD), Major Depressive Disorders (MDD) evolve by outbreaks and oscillations. Attention Deficit/Hyperactivity Disorders (ADHD), Autism Spectrum Disorders (ASD) are considered as more continuous. Others, as Obsessive-Compulsive Disorders (OCD), normal grief or Persistent Complex Bereavement Disorder (PCBD) raise the question of an evolution influenced by various contextual factors (Association, 2013). However, despite a number of theoretical expectations on dynamical systems (Nelson et al., 2017), these theories have been under-applied in psychiatry.

1.2. Three kinds of theoretical clinical proposals

We have identified the existence of at least four main types of non-modeled clinical theoretical proposals in the psychiatric literature. The first one corresponds to the 3P model (Wright et al., 2019). The 3P model is defined as a model considering 3 factors: predisposing, precipitating and perpetuating (Spielman, 1986). Predisposing factors makes the system sensitive to a stimulus, and depends on the prior state of the system states. Precipitating factors initiate the dynamics of psychiatric disorders under the action of a trigger (named "kindling," see below). The interaction between the first two factors (the predisposing and precipitating factors) is sometimes called a "stress-diathesis" model. Perpetuating factors keep the system burnished despite the absence of stimuli. The 3P model allows to understand the evolution of patients from the early stages of neurodevelopment, and to visualize their evolution over the life-course as a function of the influence of the three aforementioned factors. To our knowledge, however, the 3P model has never been mathematized.

The second kind of clinical theoretical proposal corresponds to the kindling model. This clinical formulation, from the field of epilepsy, explains the manifestations of a relatively short stage of a psychiatric disorder. At a during fleeting moments of susceptibility (e.g., from a few hours to a few weeks), a triggering factor would lead to expressing the manifestations of this disorder. This psychiatric disorder bursts by successive acute manifestations on a relatively short time scale (Adamec, 1990). When the system is above a certain threshold, the kindling formulation brings together two parameters: an increase in the frequency of cycles of bursting, and a triggering of these cycles more and more independently of environmental factors (i.e., reflecting a phenomenon of sensitization).

The third kind of clinical theoretical proposal corresponds to staging models. Staging models are defined as psychiatric models aimed at distinguishing subgroups evolving by (successive) stages (McGorry et al., 2014). However, this proposal remains based on a linear conception of psychiatric disorders (Nelson et al., 2017). We insist on these notions of linearity and non-linearity because we are going to propose a model which is by definition non-linear. Non-linearity is used to describe a situation where there is no direct relationship between an independent variable (e.g., "the depression") and a dependent variable (e.g., "anhedonia"), i.e., where it cannot be drawn a "straight-line" between them.

Finally, the fourth kind of clinical theoretical proposal corresponds to the conception of psychiatric disorders through the prism of dynamical systems, as we are going to explain, develop and use in this work.

1.3. Case formulations

In this article, we propose to use dynamical systems in order to build a computational model to apprehend the dynamics of

psychiatric symptoms. Three methodological anchors allow this development: case formulations, wealth of dynamic systems and desire for a manipulable model.

First, the main goal of the use of dynamical systems is to computationally validate empirical observations made by clinicians and researchers of the psychiatric field. This computational model is based on case formulations of different psychiatric disorders and conditions and aggregated symptoms. We define (stereotyped) case formulations as the psychiatric disorders and conditions of a given patient. These are typical cases of clinical observation. Case formulations aim to model the characteristics of specific individuals, e.g., "an individual with an autism spectrum disorder." This computational model is thus designed in a contingent way to exemplify the phenotypes of psychiatric disorders. These stereotyped case formulations are those described in the textbook of clinical psychiatry and transmitted to any clinician in his/her elementary formation, and as he/she can then observe it in his/her daily practice (corresponding to irrefutable and prototypical cases of dynamical evolutions of psychiatric disorders). Such case formulations serve as tools that help organize complex and contradictory information about a person (Eells et al., 1998). Thus, case formulations help to describethe stereotypical description of the temporal evolution of psychiatric disorders, and phenomenologically reproduce the empirical or simulated dynamics of psychiatric disorders (e.g., the clinically observed relationships between the psychiatric variables), as described in the empirical and historical descriptions of clinicians and researchers.

Such dynamical model will allow to learn about non-linear phenomena and instability, major variations related to fluctuations in initial conditions, phenomena of resilience and fragility or the attainment of tipping points (transitions) and steady states, attractors and oscillations between multiple stability in response to internal conditions or external stressors. It also incorporates the elements mentioned in the three previous kinds of clinical modeling, e.g., predisposing, precipitating and perpetuating factors, consideration of different time frames, sensitization (kindling) and stages (staging models) of psychiatric disorders.

First, current computational models found in the literature integrate biological factors, can be predictive, are interested in different time scales, but rare are the models that allow the common integration of all these variables. Studies are restricted to parameters such as noise from the environment (e.g., psychosocial stress) (Huber et al., 2000) or monovariable approaches (unlike our 4 variables) (Demic and Cheng, 2014). Moreover, computational psychiatry models also rarely integrate symptoms. Secondly, a common joke in the field of computational psychiatry reports that the number of articles promoting the theoretical promises of the field has exceeded the number of its empirical articles. Complex dynamical systems theories have been used to metaphorically explore psychiatric disorders (e.g., depression which can be understood as a metaphorical "stuck state" of emotional processing) (King et al., 1983; Boldrini et al., 1998; Bystritsky et al., 2012; Hayes et al., 2015; Sulis, 2021). However, this metaphor has largely remained highly theoretical and has only marginally resulted in a manipulable model based on the dynamical system (Durstewitz et al., 2021).

1.4. Main goals

Based on these theoretical considerations, no computational model considering both symptomatology, internal factors, environment and temporality (i.e., the four variables of the model presented below) seems to exist in the scientific literature. We seek to go beyond theoretical contributions by proposing a variable modeling environmental noise (z) acting on the patient's internal elements (y) with its temporal specificities (f) and symptomatology (x).

Here, we propose such a dynamical model as a structure able to receive simulated or empirical data, reproducing the phenomenological dynamics of psychiatric disorders. The whole interest of such a model is precisely to be able to get away from the traditional diagnostic categories to apprehend a multitude of empirical or simulated symptoms in a transdiagnostic way. The "toolbox" constituted by this model can, for instance, integrate both anhedonia and low mood (major depressive disorder category) and acoustico-verbal hallucinations (schizophrenia category). We believe that this granularity at the scale of the symptom is particularly important for clinical psychiatry.

Moreover, because of its desire to be generalizable to different types of disorders and adaptable to different datasets, this toy-model differs from a certain number of other dynamic models of psychiatric disorders found in the scientific literature (Durstewitz et al., 2021).

We propose here a toy-model to study the dynamics of psychiatric symptoms, which reduces complexity by considering aggregates of non-linear relationships between a limited number of variables depending on time: environment, internal elements (e.g., subjective phenomenological experiences or biology) and symptoms. Such a model is based on equations intended to reproduce case formulations. It produces an abstract representation of patients. It is not built on empirical data collected in research. Such a computational model is thus called a toy-model. In a toy-model, abstract values correspond to qualitative behaviors empirically perceived in clinical practice. As we will discuss, such a toy-model could only serve to apprehend, understand, or support debates on the possible dynamics of psychiatric disorders. As its name indicates, a toy-model is deliberately used to explain and make practical a behavioral function, like a box containing balls, which is considered as a toy-model allowing to understand, in a simplified way, both the solar system and the interactions between atoms. As has already been proposed in the context of epilepsy (Depannemaecker et al., 2021) under the name of *"epileptor"* (Jirsa et al., 2014) (which accounts for electrophysiological brain activity), this dynamical modeling of psychiatric symptoms, internal elements and environment could thus be qualified as a *"psychiator."*

2. Methods

2.1. Research methodology

We propose a model based on dynamical system for psychiatric disorders. This model is based on the theory of dynamical systems, which offers a framework for modeling the evolution of variables as a function of time. We used a structure, able to receive simulated data, reproducing the phenomenological

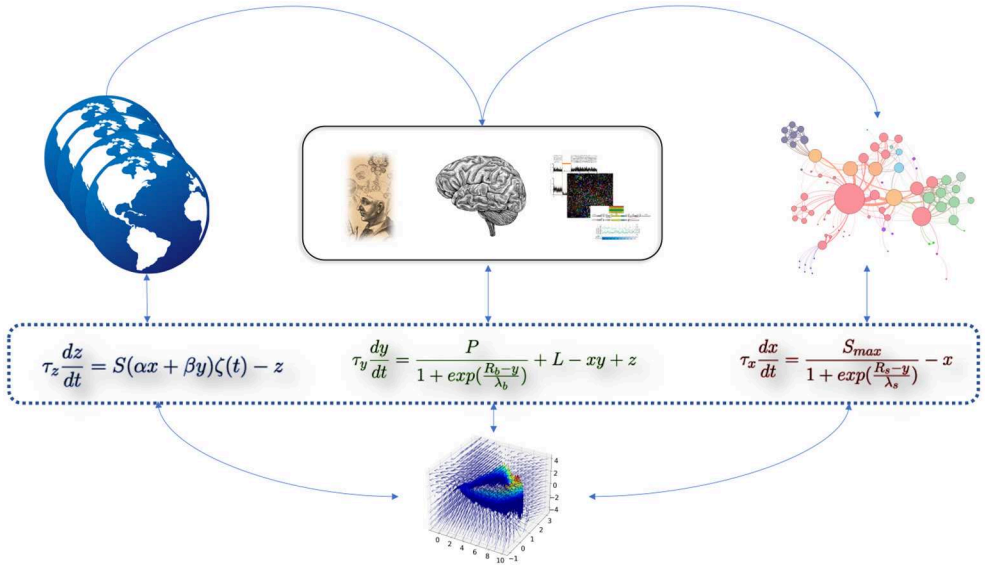

FIGURE 1
Cartoon representation of the computational dynamical toy-model of psychiatric disorders. The three equations are intrinsically linked by their interacting variables. The equation on the left (variable *z*) represents the effect of the external environment as perceived by the patient. The equation in the middle (variable *y*) represents the aggregation of internal elements (e.g., biological). The equation on the right (variable *x*) represents the intensity of symptoms. Empirical or simulated data can be "included" in these abstract variables (i.e., their precise identification does not change the model and its dynamics). The 3-dimensional phase space at the bottom of the figure corresponds to the toy-model presented in this study.

dynamics of psychiatric disorders. In order to avoid starting from psychiatric categories, we isolated variables from case formulations of different psychiatric disorders and conditions and aggregates of symptoms.

The model captures the temporal evolution of a phenomenon using mathematical differential equations, which intrinsically integrate temporality. Differential equations allow to calculate next states given a current state, depending on time. In a first-order differential system, the state of a variable at a time t is calculated based on its variation with respect to time t-Δt. The rate of amplitude changes over time will determine the time scale. Each equation composing the system can vary according to its own time scale. This notion of time scales is an important consideration in psychiatric disorders because psychiatric acute events occur on a much shorter scale (minutes, hour, day, weeks) than the longer time scale of the development and consequences of a psychiatric disorder (months, years, decades). Thus, to model psychiatric disorders, a fast sub-system helps to switch from a basic (healthy or already pathologically latent) state to a state with high level of symptoms. A slower system is needed to drive the transition between these states. Therefore, a slow-fast system is proposed, including these different time scales, in which an external input drives the transition between states.

We seek to infer the dynamical relationships that exist between the variables producing a psychiatric phenomenon. Thus, we describe the expected temporal trajectory of the variables, by including different relevant psychiatric aspects into the equations to obtain the desired phenomenological characteristics. The parameters are identify in order that the simulation dynamics correspond to clinical observations. The modeling of psychiatric disorders could have been carried out in other ways. Our primary goal is to computationally match clinical observations.

2.2. General presentation of the model

As schematized in Figure 1, the set of elements which should be integrated into the model, in order to account for the observed evolution of the psychiatric disorders modeled, should be: 1) A first variable *x*, which correspond to the intensity (or "apparent level") of symptoms; 2) A second variable *y*, which aggregate the internal elements of a patient, interacting with the intensity of symptoms. This variable could refer to his/her "subjective state," or "phenomenological state," but also to biological elements (e.g., genetic data or brain morphological data). It is thus called a "potentiation variable," because it potentializes the intensity of symptoms; 3) A third variable *z*, which correspond to the external environment as it is perceived and filtered by the patient. In addition to these variables, we add a fourth variable *f*, corresponding to the slow temporal fluctuations. This variable depends on *y* because the onset of symptoms depends primarily on the "subjective state" of the patient, i.e., its potentiation. In other words, there can be temporal fluctuations only if the patient describes subjective states, which are themselves at the origin of a potentiation of the symptomatology. In this computational model, we hypothesize that a slow accumulation in *f* allow a (slow) transition toward the pathological state. We seek to model the interactions between variables *x*, *y*, *z* (see Results for details of the effects of these interactions). The variables in the toy-model do not in any way prejudge any (top-down or bottom-up) causality, but rather are dependent variables interacting in a coupled way.

TABLE 1 Description of the parameters of the toy-model.

$\tau_{x,y,z,f}$	Time scales of the four equations.
S_{max}	Maximal level of symptoms.
R_s and R_b	Sensitivity: the difficulty in triggering the system. Rs refers to sensitivity in terms of symptoms. Rb refers to sensitivity in terms of internal elements (or potentiation).
λ_s and λ_b	Slope of the symptom and internal elements (or potentiation) curves. λ_s corresponds to the increase in the intensity of symptoms x as a function of the subjective state of the patient y. λ_b corresponds to the increase in the internal elements (or potentiation) y as a function of the environment z.
P	Maximal rate of internal elements of the systems: the aggregation of biological, psychological or subjective/phenomenological elements. It refers to the fabrication of the semantic configuration of a phenotype from a set of biological signals. It is an element of potentiation of symptoms.
L	Level of predisposing factors: it contributes to a permanent shift in the internal elements (potentiation).
λ_f	Scaling factor of the slow evolution of the fluctuations affecting L
S	Overall sensitivity level to the environment.
α and β	Weight of the effect of the variable x and y on the perception of the environment

The computational toy-model is thus described by the following system of equations:

$$\begin{cases} \tau_x \frac{dx}{dt} = \frac{S_{max}}{1+exp(\frac{R_s-y}{\lambda_s})} - x \\ \tau_y \frac{dy}{dt} = \frac{P}{1+exp(\frac{R_b-y}{\lambda_b})} + fL - xy - z \\ \tau_z \frac{dz}{dt} = S(\alpha x + \beta y)\zeta(t) - z \\ \tau_f \frac{df}{dt} = y - \lambda_f f \end{cases}$$

The literal descriptions of the parameters of the toy-model are given in Table 1.

2.3. Equation 1: Modeling of symptom intensity

The first Equation (1) can be understood as: "The intensity of symptoms increases due to subjective state y of the patient, and saturate to a maximal value S_{max}" (i.e., referring to a model with sigmoïdal function).

$$\tau_x \frac{dx}{dt} = \frac{S_{max}}{1 + exp(\frac{R_s-y}{\lambda_s})} - x \quad (1)$$

If nothing participates to maintain high intensity of symptoms, the intensity of symptoms decreases over time (modeled with the exponential decay $-x$). The evolution of the intensity of symptoms occurs with the time scale of τ_x. The R_s parameter corresponds to the sensitivity, i.e., the difficulty in triggering the system in terms of potentiation (i.e., if R_s is high, the appearance of symptoms occurs only for a very high value of the variable y). It can be seen as a form of sensitivity (or propensity) to develop symptoms depending on the internal elements. The λ_s parameter corresponds to the increase in the intensity of symptoms x as a function of the internal elements of the patient y, which is therefore almost linear in the middle of the curve (λ_s is the slope of the symptom curve where the sigmoïd is centered).

2.4. Equation 2: Modeling of internal elements

$$\tau_y \frac{dy}{dt} = \frac{P}{1 + exp(\frac{R_b-y}{\lambda_b})} + L - xy - z \quad (2)$$

The second Equation (2) refers to the internal elements of a patient. The variable y evolves on the time scale τ_y, and depends on the elements described below. The first term $(\frac{P}{1+exp(\frac{R_b-y}{\lambda_b})})$ may be seen as the effect of the aggregate of internal elements underlying elements which have a dynamical effect depending on the state of the patient. A maximal fixed level of potentiation P corresponds to the subjective level of a patient allowing the existence of symptoms. In the Cambridge model, it could be seen as the "primordial soup," i.e., the making of the semantic configuration of a phenotype from a set of biological signals (Berrios and Chen, 1993). In other words, P refers to the influence of the internal elements on the expression of symptoms through the variable y. The R_b and λ_b parameter are interpreted as for the intensity of symptoms but regarding internal elements (i.e., in terms of potentiation). The parameter L corresponds to the level of predisposing factors that contribute as a permanent shift in the potentiation. This parameter gives the baseline of predisposition for a psychiatric disorder. It corresponds to the basic level toward which the system tends when the intensity of symptoms diminished. The decay in time of this state potentiation being faster soon after paroxysmal symptomatic period, the decay is model by $(-xy)$. Finally, the variable y is influenced by the perceived environment through z.

2.5. Equation 3: Modeling of perceived environment

$$\tau_z \frac{dz}{dt} = S(\alpha x + \beta y)\zeta(t) - z \quad (3)$$

The third equation refers to the environment (or external world) perceived by a patient, modeled by the variable z (Equation 3), which evolves with a time constant τ_z. It depends on the overal sensitivity level S, and the joint effects of symptoms x and the potentiation y respectively pondered by factor α and β. The factors α and β may be positive or negative depending on the type of psychiatric disease considered. The perceived environment integrates the equation as external noise $\zeta(t)$, set between –1 and 1 with Gaussian distribution. The release occurs with an exponential decay $(-z)$.

2.6. Equation 4: Modeling of temporal specificities

A fourth equation can be added to model slower processes of psychiatric disorders. This equation is equivalent to a change of a parameter over time to capture elements on a much longer timescale, especially at the scale of a lifetime (Equation 4):

$$\tau_f \frac{df}{dt} = y - \lambda_f f \tag{4}$$

This equation could be adapted according to the fluctuations of the values of λ_f). These fluctuations can create oscillations, or slow evolutions of other variables over the long term. This is a variable of slowness, which interacts at a longer time with the other three variables evolving more rapidly. The variable depends on the internal potentiation y, and affect the latter as a multiplicative factor of L, the level of predisposing factors. Thus, the differential equation of y become (Equation 5):

$$\tau_y \frac{dy}{dt} = \frac{P}{1 + exp(\frac{R_b - y}{\lambda_b})} + fL - xy - z \tag{5}$$

2.7. Set of constraints applied to the model

Due to the structure of these equations, we have to consider a set of constraints.

First, we are looking for a system representing several states, accounting for phase transitions: 1) of psychiatric states below a first threshold delimiting a state of health and a pathological state; 2) of psychiatric states above the threshold of psychiatric disorders; 3) of psychiatric states corresponding to the maximum intensity of symptoms, i.e., the most intense state of crisis describable for a disorder.

Secondly, configurations containing negative x (the intensity of symptoms) and y (the "subjective state" of the patient, a variable of potentiation) are not considered, as they are not (patho)physiologically plausible.

Thirdly, the rate of the noise $\zeta(t)$ is chosen at 0.01, meaning that the perceived environment variable z changes every 0.01 days (noise will be generated every 14.4 min). It is a compromise between the duration of variability of the symptoms of psychiatric disorders and their environment (i.e., considering a psychological state change every 14.4 min). In other words, the model provides a smoothness of 14.4 min, i.e., informs about potential changes in its variables approximately every quarter of an hour. This contingent choice captures most symptomatic variations of psychiatric disorders, but it does not record environmental noise without clinical value. For instance, a longer time (e.g., 12 h) would have missed potentially important information like mood variations during the day in the case of cyclothymia or behavioral disorders, while a shorter time (e.g., 10 s) would have captured too much noise without clinical value like emotional reactions to any life event.

Fourthly, the S_{max} parameter is fixed on a Likert scale (steps from 0 to 10). In the simulations, we saturate the scale to 10, to challenge the system to design maximum symptom intensity. Conversely, the other parameters cannot be quantified or bounded, because they depend on each patient specifically.

We use an Euler integration method with $dt = 0.01$ for the simulations given in the Results section.

2.8. Presentation of the simulations

In the following section, we will perform four simulations based on four case formulations to verify that the model captures the following stereotypical dynamics of psychiatric conditions: a healthy condition, a schizophrenia spectrum disorder, a rapidly cycling bipolar disorder, and a persistent complex bereavement disorder.

From the observed dynamics of simulations of these four case formulations of psychiatric disorders, conditions and aggregates of symptoms, and based on this set of equations, we will propose to identify contingent relative threshold values (maximum and minimum) for each of the 13 parameters of the x, y, z equations of model. These values will be identified empirically to be consistent with clinical observations. We will add for each of these simulations an external event that acts as an environmental trigger, not related to the patient. We consider a practical model which includes variations between its limit cycles and its fixed points, with an influence of the noise varying the characteristics of the system, and potentially several bifurcations.

Finally, in addition to these four simulations, we will propose a fifth simulation in which we visualize the effect of a therapeutic action according to knowledge and stereotyped case formulations.

3. Results

We used a toy-model built on differential equations to simulate the dynamics of psychiatric conditions and disorders through case formulations. Depending on the variability of the parameters handled in this toy-model, various dynamics of different psychiatric disorder could be modeled. If empirical data from research has been incorporated into the model, although each of these conditions tends to be as stereotyped as possible relative to empirical observations of clinical practice, each condition could be dynamically different according to the interindividual variations of the patients. Thus, in each of the following case formulations, based on observation of stereotypical cases, we can identify that each dynamic could be observed when the value of a parameter increases or decreases.

3.1. Identification parameter values for the simulations

Constrained by clinical observations, simulations of the four following psychiatric conditions (named here Figures 2A–D) provide relative parameter values which correspond to the maximum and minimum thresholds found empirically in order to obtain variable behavior in the simulations which are consistent with case formulations (Table 2).

3.2. Dynamics of psychiatric disorders: Simulation results

3.2.1. Case formulation 1: Healthy situation

In this case formulation, described in the panel (a) of the Figure 2, the modeled patient through the toy-model is in one possible healthy state. The corresponding parameters are given in Table 2, which

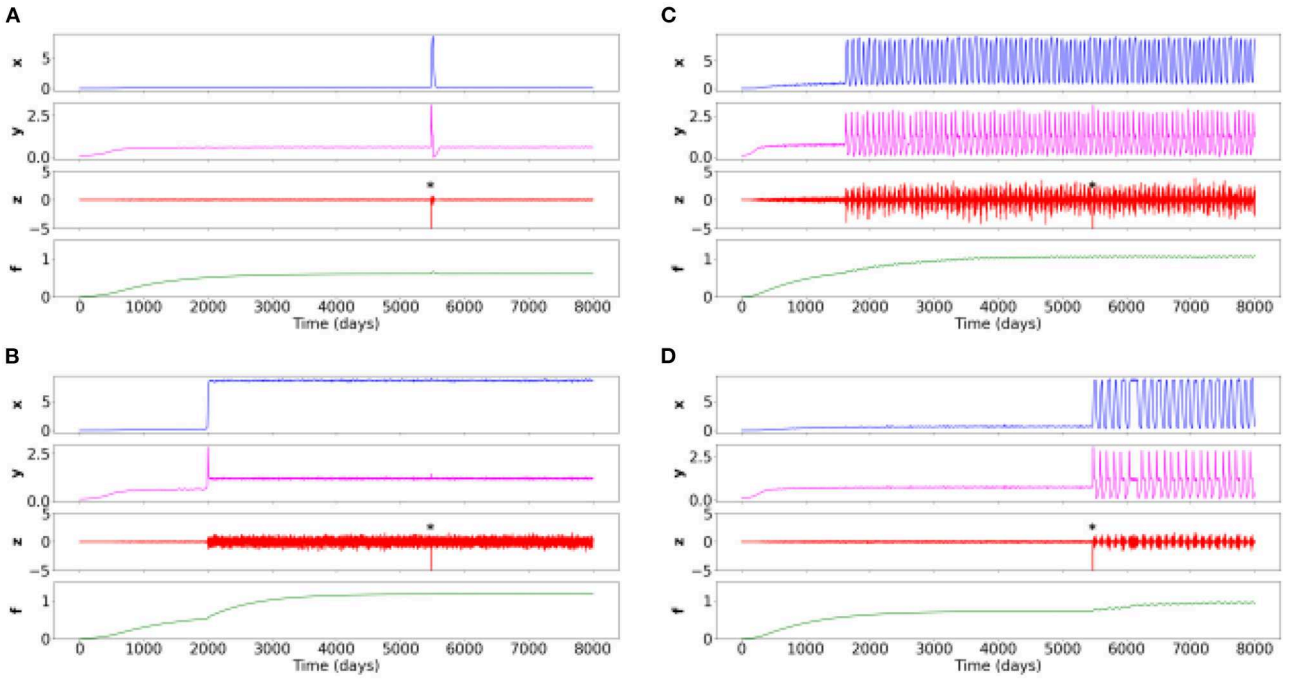

FIGURE 2
Time series of the four simulations for different sets of parameters. Negative events from the environment (variable z) are labeled with an asterisk. **(A)** Healthy situation: the negative event creates transient symptoms (x), potentiation of internal elements (y), and environmental sensitivity, and then returns to the baseline healthy level. **(B)** Constant symptom pathology (e.g., schizophrenia spectrum): symptoms appear at some point in life when potentiation has increased due to slowly changing accumulation variable f. The pathology is strongly expressed when the negative event occurs, and weakly affects the other variables. **(C)** Oscillating symptom pathology (rapid cycling in bipolar disorder): symptoms appear at some point in life when potentiation has increased due to a slow changing accumulation variable f. The disorder is strongly expressed when the negative event occurs which weakly affects the other variables. **(D)** A disorder based on oscillating symptoms (persistent complex grief disorder): a negative event triggers and stabilizes the oscillations despite the disappearance of this event.

TABLE 2 Values of the 13 parameters for the 4 simulations (or case formulations).

	S_{max}	R_s	λ_s	τ_x	P	R_b	λ_b	L	τ_y	S	α	β	τ_z
Figure 2A	10	1	0.1	14	10	1.04	0.05	0.2	14	4	0.5	0.5	1
Figure 2B	10	1	0.1	14	10	0.904	0.05	0.2	14	4	0.5	0.5	1
Figure 2C	10	1	0.1	14	10	1.04	0.05	1.01	14	10	0.5	0.5	1
Figure 2D	10	1	0.1	14	10	1	0.05	0.6	14	4.5	0.5	0.5	1

For all simulations $\lambda_f = 1$ and $\tau_f = 720$.

thus provide the basic relative threshold values from which other psychiatric conditions will evolve.

At a random time of 5,500 days (about 15 years), a potentially destabilizing life event occurs. It could be, for instance, the death of a loved one. However, given the healthy characteristics of the modeled patient (depending on its different values of x and y), this event causes at most a normal grief, with a brief resolution of the symptoms. After the effect of the perturbation, all variables come back to their healthy initial level.

3.2.2. Case formulation 2: Schizophrenia spectrum

In this case formulation, described in the panel (b) of the Figure 2, the patient would be diagnosed with a schizophrenia spectrum.

We identify that these dynamics could be observed when the R_b decreases, corresponding to a decrease in resistance. Thus, less resistance leads to an increase in the potentiation (y) and thus to a more intense development of symptoms (x).

At the random time of 5,500 days, in the absence of any intervention, a potentially destabilizing life event occurs. After this event, the symptoms persist due to different patient parameters simulated. We observe the complete absence of responsiveness to environmental stimuli.

3.2.3. Case formulation 3: Rapid cycles in bipolar disorder

In this case formulation, described in the panel (c) of the Figure 2, the patient would be diagnosed with a rapidly cycling bipolar disorder.

Here, the R_b (i.e., sensitivity or resistance) is different from the formulation box (b), but identical to (a). However, the P (i.e., base level of potentiation) is much higher in this formulation case. This

difference leads to the occurrence of rapid cycles. Moreover, the S (overall sensitivity level to the environment) is very high: the individual perceives his/her environment in a very senstive way.

Each complete cycle lasts approximately 100 days, with a symptom plateau lasting approximately 15 days, similar to what can be found in clinical practice. Finally, we retrieve that despite the presence of an intense life event, there is no change in the patient's sensitivity to his/her environment or in the intensity of the symptoms.

3.2.4. Case formulation 4: Persistent complex bereavement disorder

In this case formulation, described in the panel (d) of the Figure 2, the patient would be diagnosed with a Persistent Complex Bereavement Disorder (PCBD).

In the PCBD, it is precisely the onset of an intense life event that causes this disorder. However, unlike the situation (a) in which the intensity of symptoms and the sensitivity to the environment returns to the threshold of normality over time, the patient modeled in this case formulation continues to have mood fluctuations.

This case formulation is thus close to the healthy situation, except for the P which is slightly higher, with a slightly lower resistance R_b: this slight shift leads to the non-return to the healthy state.

3.2.5. Action of psychiatric therapeutics on different psychiatric disorders

In the Figures 3A, B, correspond to the Figure 2B, aka to the schizophrenia spectrum. In the Figure 3A, the given treatment is relatively efficient, but its effect is transient after some oscillations. This is the stereotypical case of antipsychotic treatments in schizophrenia, which take effect after several weeks and require adjustments related to early relapses.

In the Figure 3B, the treatment does not work well but enable brief moments of improvement and a slightly lower overall symptom intensity.

In the Figure 3C, the high intensity of symptoms present at the beginning of the period immediately decreases (on/off effect). This case formulation has a symptomatology which appears from birth, as is the case with, for instance, attention deficit disorders with or without hyperactivity. It could then be a treatment with (for instance) methylphenydate, having a rapid efficacy in this disorder/condition.

In the Figure 3D, corresponds to Figure 2C, i.e., rapid cycling bipolar disorder. We find with the treatment (e.g., lithium) an increase of healthy state over time. Note however that the treatment is insufficient, but it still changes the frequency, regularity and intensity of cycles.

4. Discussion

In this simulation study, we proposed a toy-model (the "psychiator") that can phenomenologically reproduce the time evolution of the intensity of psychiatric symptoms, interacting with the internal elements and his/her perceived external environmental inputs, while considering different time scales. This computational model enables to understand the effects of non-linear relations between different psychiatric disorders' determinants. It has a set of strengths and limitations that we will detail. The Figure 4 helps to show the importance of such simulations by offering a comparison of the time series of the four variables, the cyclic trajectory in the phase space of the three fast variables, and the phase plane of a subspace of the system (i.e., what "draw" the equations in space, with the visualization of the different dynamic objects of the system such as the stable or unstable fixed points).

4.1. Main interests

We retrieve at least five main interests of such a computational toy-model.

First, by varying the values of the parameters, such a model allows visualization of simulations of different case formulations of psychiatric conditions and disorders and aggregates of symptoms. Such visualizations allow to find potentially new endpoints for clinical and research purposes, which in themselves enables computational models to be refined. This model allows to show that the interactions between three relatively simplified variables lead to behaviors that are very difficult to intuitively interpret. This complexity thus demonstrates the need to consider non-linear relationships rather than single variable-phenotype relationships at the clinical level. For instance, for psychotherapy, such non-linear formalization of the patient behaviors can help guide indications for specific drug therapy. It can also constitute a didactic and pedagogical tool to help the patients to understand the (non-linear) factors at the origin of their distress (Burger et al., 2020; Fried and Robinaugh, 2020).

Secondly, this model provides a high flexibility, allowing a large number of concepts to be discussed and made practical. Indeed, its interest lies in the possibility of using a large number of different empirical data from research in psychiatry, clinical psychology or neuroscience, with different actions on the parameters of the toy-model, to observe in particular the inter- and intra-individual differences of psychiatric disorders. For instance, this model is sufficiently generic to be interpreted for different type of symptoms. Moreover, the versatility of this model (i.e., the model can be adapted to many different psychiatric disorders and psychological conditions) allows to compare the differential evolutions of these disorders. This comparison could help to specify their phenotypes and refine precision medicine. Psychiatry is struggling with the issues of differential diagnoses (i.e., distinguishing two disorders whose symptoms overlap) and with the issues of comorbidity (i.e., assessing the need to distinguish two conditions or to combine two of them into one). In recent decades, no diagnostic biomarker, neither predictive nor endotype have been identified to clearly define the boundaries of psychiatric disorders: in this way, hopes lies in the differential evolution of psychiatric disorders themselves, potentially evaluable with such a computational model. The very large number of possible combinations refers to the infinite number of phenotypic variations in psychiatry. Such a model provides access to the variability of psychiatric phenotypes for a same disorder.

Thirdly, on the therapeutic level, such a toy-model provides information on the attracting states (i.e., the states to which the system gravitates). This result allows to understand what stabilizes the patient in a given (healthy) state. The warning signals leading to this attracting state can thus be detected upstream (Hayes and Andrews, 2020).

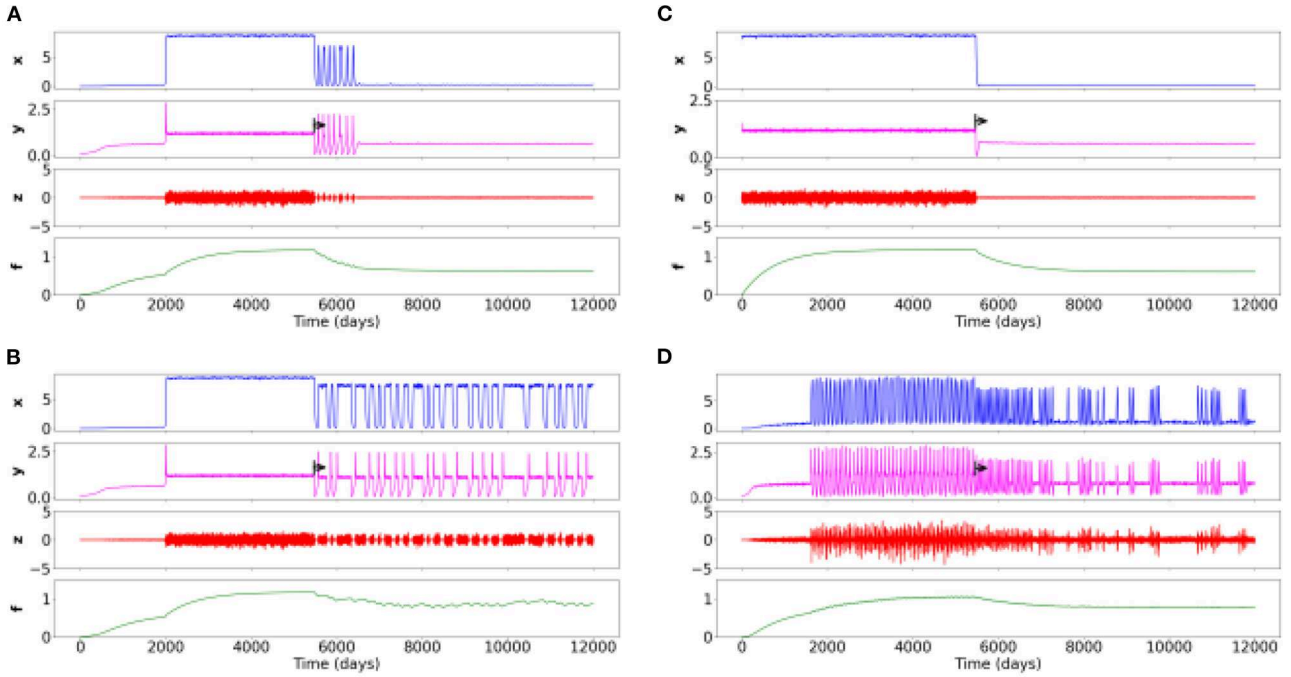

FIGURE 3
Time series of four simulations for different sets of parameters with a therapeutic action on different psychiatric disorders. The black arrow corresponds to the beginning of the treatment. **(A)** Schizophrenia spectrum with effective treatment. **(B)** Schizophrenia spectrum with insufficient treatment. **(C)** Childhood-onset disorder (e.g., neurodevelopmental disorder) treated with a fast-acting drug (e.g., methylphenidate) or another therapy. **(D)** Rapid cycling bipolar disorder with an ineffective treatment but with an action on the frequency, regularity and intensity of cycles.

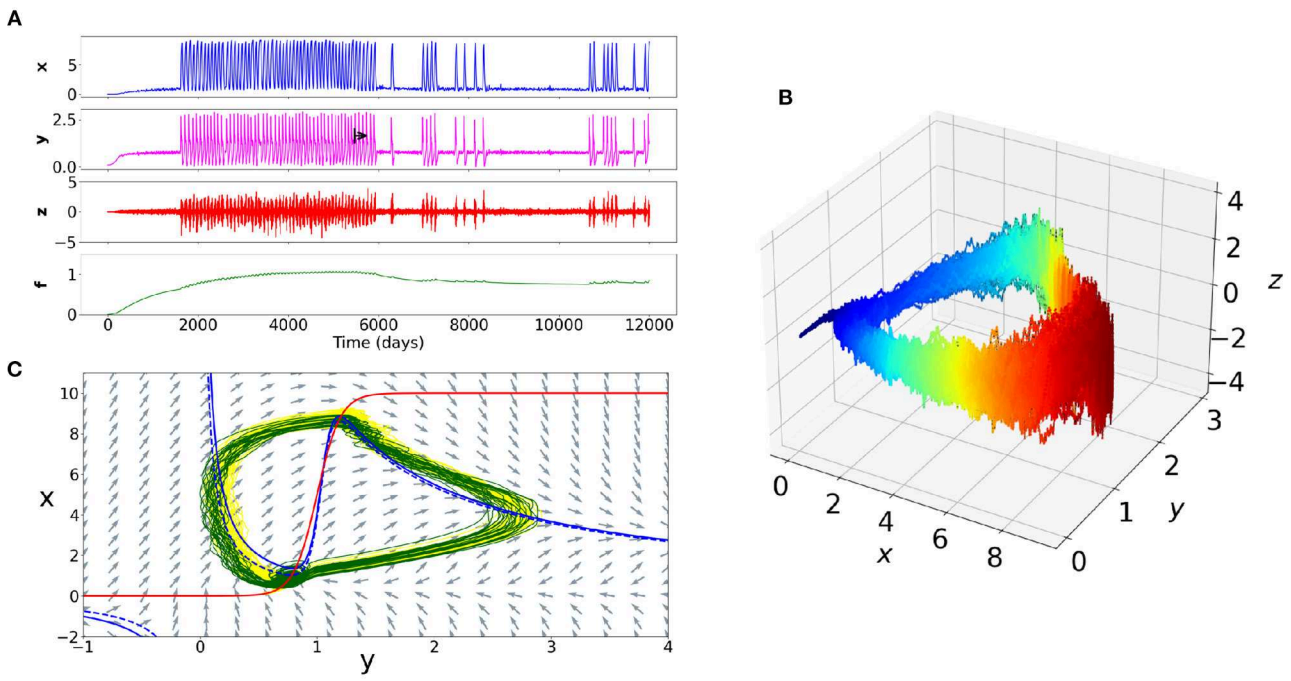

FIGURE 4
Example of the dynamics of a simulation of a rapid cycling bipolar disorder. **(A)** Time series of the four variables. The black arrow corresponds to a therapeutic action on the internal elements of the patient (e.g., on neurotransmitters). The intensity of the symptoms becomes thus less frequent. **(B)** Trajectory in the phase space of the variables x, y, z. The blue color corresponds to a decrease in symptoms and the red color to an increase in symptoms. The cyclic nature of the trajectory appears clearly. The path at the onset of the peak of symptoms intensity is different than at the offset. **(C)** Plane of a subspace of the system. The NullClines of the equations x and y appear respectively in red and blue colors. The blue dotted line corresponds to the y NullCline after the change in the value of one of the parameters of the internal elements y. The difference between the dotted blue line and the solid blue line accounts the important change of dynamics between the yellow trajectory (before treatment) and the green trajectory (after treatment).

Fourthly, this model proposes a dynamically theoretical framework allowing to constitute longitudinal studies and the use of assessment tools in daily life. This model provides a flexible framework allowing to integrate a large number of heterogeneous data, distinguishing patient-dependent factors, her/his subjective experience and the environment. Certainly, the absence of large cohorts of longitudinal data in psychiatry is due to numerous economic or organizational factors. However, they also relate to a lack of methodological tools. In other words, such a framework constitutes a prerequisite for the collection of longitudinal data in psychiatry. Such methods may be integrated into moment-to-moment ecological macro- or micro-level assessment (depending on the period), and especially a widely used methods such as ecological momentary assessment or joint modeling of time-to-event outcome with time-dependent predictors (i.e., given the temporal nature necessary to predict the onset of a disorder) (McGorry et al., 2014). In turn, data offered by such techniques would allow to confirm and validate this model in terms of predictivity. Regarding the clinical utility, based on these repeated evaluations in ecological daily life, individual predictions allow a patient to be informed of her/his level of risk and of the (natural or under treatment) course of her/his psychiatric disorder.

Fifthly, such a model could refine at least two kinds of nosological psychiatric models: staging models (McGorry et al., 2014) and symptom network models of psychopathology (Borsboom, 2017). One of the criticisms of these proposals is that stable and static clinical pictures at any given time could not be predicted on the basis of a sampling of cross-sectional data (McGorry et al., 2014). Cross-sectional data at a single point in time cannot provide predictions about the future emergence of a psychiatric disorder. Having multiple sets of cross-sectional data requires dynamic models to deal with the nonlinearity (i.e., the absence of the direct association between variables) (McGorry and van Os, 2013; van Os, 2013). Sets of snapshots of clinical states can be integrated in our model to provide information on the dynamic course of psychiatric disorders, in a non-linear manner. For example, symptoms networks could be modeled based on our computational dynamical model. In symptom network models, a psychiatric disorder is defined as the steady frozen state of a strongly connected network. A dynamic component could be added to this definition, especially by providing a notion of threshold corresponding to a bifurcation of the model. The evolutions and interactions between heterogeneous variables (objective, subjective or environmental) can be considered in dynamical symptom network models (e.g., based on multi-level vector autoregression models using time-series data) (Haslbeck et al., 2021).

Finally, such a ubiquitous and abstract toy-model, in future works, would allow to propose new classifications of psychiatric disorders according to their dynamics. We would find some disorders particularly sensitive to the environment (e.g., OCD), others presenting a rapid rhythmic activity (e.g., rapid cycles in bipolarity), or others with abrupt bifurcations in their trajectory.

4.2. Limitations

This toy-model also has several limitations.

First, the explanatory scope of this model remains limited. There could have been an infinity of models, impeding this model from being considered as predictive. Comparable dynamics could be found with completely different set of parameters, or even with different ordinary equations. Nowadays, the absolute values of parameters are not representative of any physically measurable elements. Indeed, it is important to note that the terms of the equation are contingent, and could have been defined differently. In other words, there could have been several ways of defining the dynamics of a psychiatric disorder, and this model is only one of the answers allowing to visualize their evolution over time. For example, mathematical solutions could be found to reduce the number of model parameters. However, we choose to keep it under this form to maintain intuitive clinical interpretability. To be predictive for a given patient, the model should incorporate her/his specific collected longitudinal values. Unlike digital twins (i.e., data-driven mathematical models of patients that allow for more precise and effective medical interventions), this toy-model is not built, at first, to be personalized. However, the objective of this study is not to select the best model (in terms of the equation structuring), but to propose a systematic formulation of an observed phenotypic behavior, based on the clinically relevant variables and parameters.

Secondly, this model seems reductionist regarding clinical practice. However, it integrates in an original way non-linear relations between qualitatively and clinically interpretable equations. Indeed, we have proposed a model in which it is not the biological mechanistic structures that are modeled, but behaviors (Marr, 2010). Moreover, we do not aim to directly capture internal biological elements, but rather the resulting output interacting with the symptoms and perceived environmental variables, at a very coarse level (Sulis, 2021).

Thirdly, it turns out that this model should be tested with experimental data to ensure its discriminative, construct and/or predictive validity. We hypothesize that research in psychiatry waited for such a robust model to collect empirical data, and conversely that no robust model could be built due to a lack of empirical data. The absence of measurements of such values is largely due to the absence of a model as we propose it. We are thus seeking to break this vicious circle with such a toy-model. After empirical validation, the structure of this computational model could serve as an optimized framework for simulating behavior and predicting the course of disorders. In order to choose whether certain other methods could allow to model psychiatric disorders in the same way, a set of models similar to this one should be constructed, with a sorting of these models by an analysis of the choice of the best model (in terms of choice of the free parameters). Future studies will aim to identify the maximum and minimum ranks of the (13) parameter values described in the Table 2.

Fourthly, the representation of x corresponds to the intensity of the symptoms, and that the model corresponds to an abstract representation of psychiatric disorders. It could be necessary to refine the model to have different kinds of symptoms. Indeed, in this model, only the symptom intensity is discussed, but not the nature of symptoms forming the dynamics. For instance, it is not possible to distinguish the effect of delirium vs. acoustico-verbal hallucinations in schizophrenia. The fluctuations do not allow to affirm whether these are depressive or maniac episodes. However, this computational model aims to model the characteristics of specific individuals (e.g., "an individual with an autism spectrum disorder"), and not a psychiatric category (e.g., "autism spectrum disorders"). Thus, the

absence of characterization of the nature of the symptoms is of little importance, because our approach remains idiographic: for some individuals, the dynamic model will evolve toward a characteristic psychotic break, and for others, it will evolve toward a return to the previous state, according to the individual characteristics of the different variables.

Fifthly, a last limit concerns the potential difficulty to interpret the dynamics of the models. Indeed, the incorporated variables account for non-linear phenomena, which could be not intuitively explainable to a clinician. More precisely, it could be difficult to know why some stressors and triggers have or not an action on the system (e.g., inducing a dissociation), why certain nonlinear effects occur at particular times (e.g., fluctuations of affective states) or how interactions between certain symptoms occur (e.g., low mood and overeating or anorexia). Clinical inference from this kind of model should be very careful. By extension, it will be necessary to ensure that these individual-level models are not naively transferred to group-level models.

5. Conclusion

In the history of clinical psychology and psychiatry, predicting the occurrence of disorders and symptoms has focused on the evaluation of a spectrum of variables – ranging from genetics to the environment, including neurocognitive measurements or subjective feelings. These conditions are particularly difficult to model, and this difficulty is largely due to the lack of dynamic modeling to model them, despite a growing theoretical literature advancing such promises for at least several decades (Nelson et al., 2021). In order to shift from this research, we propose with this "psychiator" to dynamically modelize human behaviors and (subjective and biological) internal elements in a non-linear way, while maintaining clinical, phenomenological and biological plausibility useful to the clinician. Although this model is only a toy-model, it offers a conceptual basis for data acquisition, and can serve as a starting point based on dynamic systems for establishing a theoretical definition of psychiatric disorders and sustain nosology.

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/s. An example code of an implementation of the model presented in this paper is available at https://github.com/ddadep/ModelPsy.

Author contributions

CG and DD were the principal investigators and study supervisors and interpreted the results and wrote the manuscript. CG conceptualized and supervised the analysis. DD made the mathematical equation formalization and run the simulations. Both authors approved the final version.

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.

Publisher's note

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 15 March 2023
DOI 10.3389/fpsyt.2023.1080668

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

RECEIVED 26 October 2022
ACCEPTED 21 February 2023
PUBLISHED 15 March 2023

CITATION
Soda T, Ahmadi A, Tani J, Honda M, Hanakawa T and Yamashita Y (2023) Simulating developmental diversity: Impact of neural stochasticity on atypical flexibility and hierarchy. *Front. Psychiatry* 14:1080668. doi: 10.3389/fpsyt.2023.1080668

Simulating developmental diversity: Impact of neural stochasticity on atypical flexibility and hierarchy

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Introduction: Investigating the pathological mechanisms of developmental disorders is a challenge because the symptoms are a result of complex and dynamic factors such as neural networks, cognitive behavior, environment, and developmental learning. Recently, computational methods have started to provide a unified framework for understanding developmental disorders, enabling us to describe the interactions among those multiple factors underlying symptoms. However, this approach is still limited because most studies to date have focused on cross-sectional task performance and lacked the perspectives of developmental learning. Here, we proposed a new research method for understanding the mechanisms of the acquisition and its failures in hierarchical Bayesian representations using a state-of-the-art computational model, referred to as in silico neurodevelopment framework for atypical representation learning.

Methods: Simple simulation experiments were conducted using the proposed framework to examine whether manipulating the neural stochasticity and noise levels in external environments during the learning process can lead to the altered acquisition of hierarchical Bayesian representation and reduced flexibility.

Results: Networks with normal neural stochasticity acquired hierarchical representations that reflected the underlying probabilistic structures in the environment, including higher-order representation, and exhibited good behavioral and cognitive flexibility. When the neural stochasticity was high during learning, top-down generation using higher-order representation became atypical, although the flexibility did not differ from that of the normal stochasticity settings. However, when the neural stochasticity was low in the learning process, the networks demonstrated reduced flexibility and altered hierarchical representation. Notably, this altered acquisition of higher-order representation and flexibility was ameliorated by increasing the level of noises in external stimuli.

Discussion: These results demonstrated that the proposed method assists in modeling developmental disorders by bridging between multiple factors, such as the inherent characteristics of neural dynamics, acquisitions of hierarchical representation, flexible behavior, and external environment.

KEYWORDS

autism spectrum disorder (ASD), computational psychiatry, predictive coding, flexibility, representation learning, neural noise, Bayesian brain, neural network

1. Introduction

Developmental disorders, such as autism spectrum disorders (ASDs), represent various symptoms involving perceptual, behavioral, cognitive, and social dysfunctions, and elucidating their pathological mechanisms is a challenging task. A fundamental difficulty in understanding developmental disorders is the fact that their symptoms are the results of complex and dynamic processes involving multiple factors, including neural systems, cognitive behavior, environment, and development learning. At the levels of cognition and behavior, in addition to their symptoms, people with ASD were reported to show reduced performance in a wide range of cognitive and behavioral tasks (1–4). At the level of the neural system, there are many findings related to the pathology of ASD, such as imbalance of neural excitations and inhibitions (5), altered variability in neural dynamics (6, 7), alterations in alpha oscillations (8), and abnormalities in subcortical areas including frontolimbic circuit, brainstem including superior colliculus, and autonomic nervous system (9–15). At the external environment level, it has been known that cognitive-behavioral interventions, such as structuring the environment and reducing stimulus ambiguity, alleviate symptoms of ASD (16, 17). However, despite the accumulation of these findings, existing theories of atypical development remain fragmentary because the target symptoms and the levels of explanations for each of these findings are different (18).

To address this issue, computational study has been expected to play a key role (18–21). This is because computational models can provide explanations bridging multiple levels in complex dynamical systems of the brain through quantitative simulations of the processes of neural, cognitive, and behavioral interactions that are difficult to observe and manipulate in actual biological systems.

One of the promising computational theories for developmental disorders is Bayesian brain hypothesis (22), also referred to as predictive coding theory (23, 24), Bayesian cognitive modeling (25–27), and free energy principle (28). In Bayesian brain hypothesis, the brain is considered to have the hierarchical Bayesian model that reflects the probabilistic structures in environment, and a hierarchical and probabilistic predictive process enables adaptive cognition and behavior. From the aspect of Bayesian brain hypothesis, it is proposed that symptoms of ASD are failures in Bayesian inference and abnormal acquisition of a hierarchical Bayesian model. Furthermore, the Bayesian brain hypothesis argued that these failures in inference and acquisition result from circular interactions between external stimuli and the internal brain dynamics in short- and long-term timescales (29–32). However, most ASD studies using the Bayesian brain hypothesis have focused on cross-sectional (i.e., short-term) behavioral measures such as reasoning and decision making, and there have been few studies focusing on long-term effects of environmental interactions and the acquisition/developmental learning process. For example, some studies attempted to fit theoretically driven hierarchical Bayesian models to behavioral data, and group differences in estimated values of model parameters between healthy and atypical developmental groups were investigated (33–35). In those studies, because a hierarchical Bayesian model has been constructed by researchers a priori, the process of acquiring a hierarchical Bayesian representation has not been examined.

Artificial neural networks, one of the computational modeling methods for brain function (36–38), could help investigate the developmental learning process because neural network models acquired internal representation reflecting external environment through synapse updating (39–43). In particular, a hierarchical recurrent neural network (RNN) model (44–46) has been widely applied for modeling higher cognitive function in the brain because this model has high similarity to the hierarchical system of the brain and capacity to reproduce complex dynamics. In addition to typical development (47–49), some studies investigated developmental disorders (50–53) and schizophrenia (54) as failures in the hierarchical neural system using hierarchical RNNs, and examined behavioral phenotypes and its relations to representations acquired in neural networks. These studies, referred to as neurorobotics, are promising for psychiatric research because they investigated the acquisition process of higher-order representations based on realistic and multidimensional sensorimotor sequence with the interaction of physical environment using a humanoid robot driven by an RNN (50–52, 54).

Recently, a neural network model that combines the properties of a hierarchical Bayesian model and RNN, referred to as predictive-coding-inspired variational recurrent neural network (PV-RNN), has been proposed (55). PV-RNN can embed complex stochastic sensorimotor signals in neural dynamics as a hierarchical Bayesian model through the developmental learning process. Therefore, PV-RNN can be considered a powerful tool for investigating the Bayesian brain hypothesis. Indeed, PV-RNN was useful for modeling uncertainty estimations (55), goal-oriented behavior (56), sensory attenuation (57), and social interaction (58–60).

In this study, we propose a novel and useful framework using PV-RNN for the understanding of typical and atypical developmental process, referred to as "*in silico* neurodevelopment framework for atypical representation learning" (Figure 1). The key point of the proposed framework is the integration of computational theory of hierarchical Bayesian models and neural network models as dynamical systems from the perspective of developmental learning. Specifically, in this framework, the developmental learning process of an agent is simulated in which the neural system acquires a hierarchical Bayesian representation in a self-organizing manner thorough interacting with the environment (Figure 1A). Furthermore, by manipulating the inherent characteristics of neural dynamics and environmental factors, this framework can reproduce the diversity in the developmental process, including typical and atypical development and possible interventions (Figure 1B). Namely, in the simulations, the environment generated observable signals based on the unobserved hierarchical and probabilistic generative process reflecting cognitive behavioral tasks. Through the developmental learning in this environment, the agent is needed to acquire hierarchical Bayesian models reflecting the environment structures under various conditions. After this process, the performance of the agent in the cognitive behavioral tasks and the effects of manipulations are evaluated. In these ways, the relationships between the inherent characteristics of neural

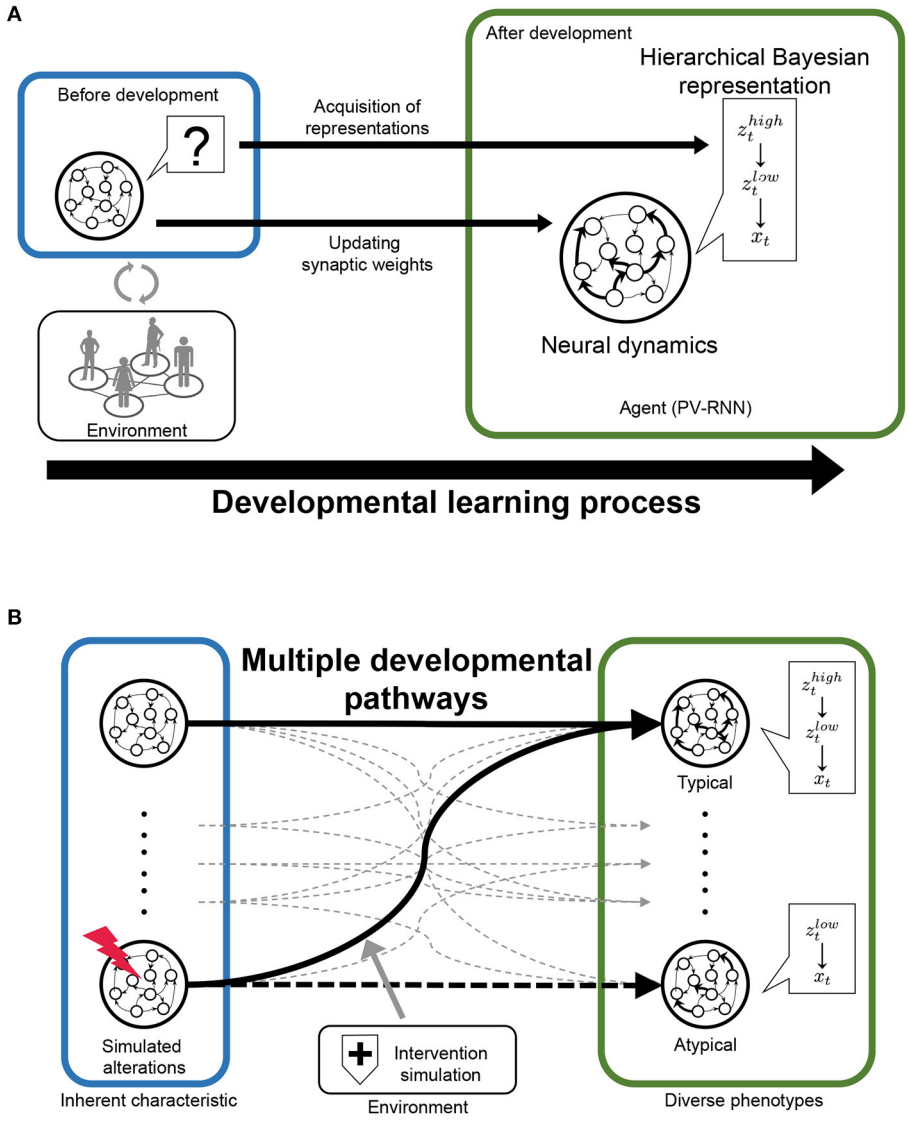

FIGURE 1
The scheme of "'*in silico* neurodevelopment framework for atypical representation learning" proposed in this study. **(A)** The agent modeled by the hierarchical Bayesian neural network model (PV-RNN) must learn the hierarchical and probabilistic structure hidden in the observations in the developmental learning process. **(B)** The inherent characteristics of neural dynamics and environmental factors are simulated as experimental manipulation to understand divergence in the developmental process. z_t and x_t represent latent and observed variables, respectively.

dynamics, acquisitions of hierarchical Bayesian representation, behavioral phenotypes, and the effects of environmental factors including possible interventions can be quantitatively analyzed.

As a proof of concept, we conducted a simulation experiment using the '*in silico* neurodevelopment framework for atypical representation learning framework (Figure 2). Specifically, we focused on the relationship between the acquisition of hierarchical and probabilistic representations reflecting environment structures and "reduced flexibility." Indeed, reduced flexibility is one of the representative cognitive-behavioral phenotypes in ASD (2, 61, 62). Although many neural foundations related to reduced flexibility have been reported (2, 62), the mechanism between these neural alterations and the reduced inflexibility has not been well known. Therefore, in the simulations, we examined: (1) whether manipulating inherent characteristics of neural dynamics and external environment induces reduced flexibility; (2) whether these manipulations lead to the normal/abnormal acquisition of hierarchical Bayesian representations; (3) how the abnormalities in hierarchical Bayesian representation are related to reduced flexibility.

2. Materials and methods

2.1. Overview

The simulation experiments based on the proposed framework consisted of two components including an environment (left side in Figure 2A) and an agent (right side in Figure 2A). The environment generated observable signals following the

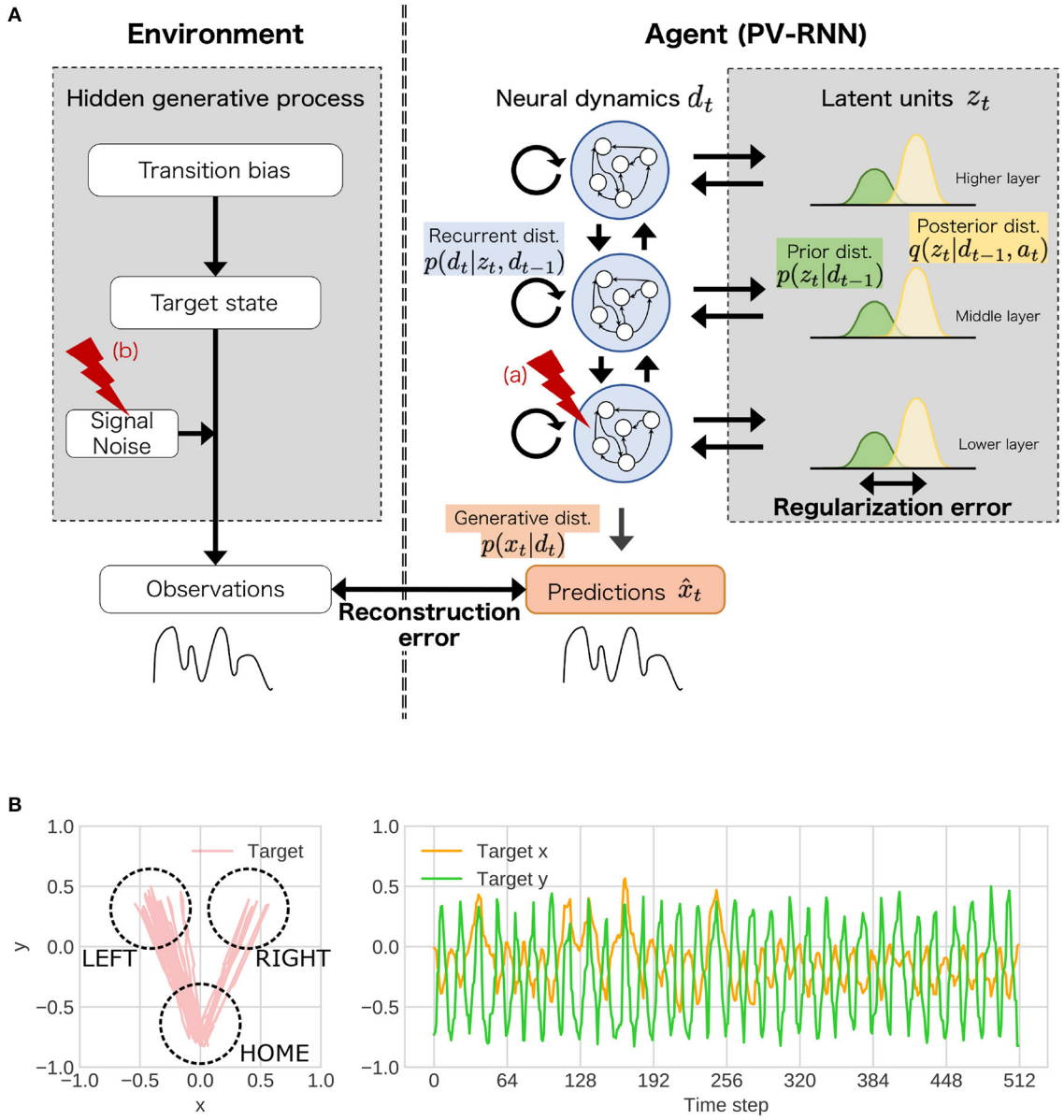

FIGURE 2
(A) The simulation experiments based on the proposed framework. In the experiments, as behavioral and cognitive task, flexibility task was used. To understand atypical developmental process, (a) the stochasticity in neural dynamics of lower layer, (b) noise level of observation signal was manipulated. *dist.* represents distribution. **(B)** An example of training sequences in the simulation experiments. These sequences repeated state transitions to LEFT or RIGHT ("target state"). The probability that the transition from HOME to LEFT is likely to occur is determined by "transition bias." Transition bias was set to 0.76 (LEFT-biased sequences), and "signal noise" was set to low (stable environment condition) in the presented sequence. In the test phase, the transition bias switched at the middle point in the sequence to quantify flexibility.

unobserved hierarchical and probabilistic generative process, which is designed to measure flexibility. The agent was required to embed the covert hierarchical structures of environment into neural dynamics using only the observed signals through the developmental learning process. After the learning process, the ability of flexibility was tested in this environment. In the experiments, stochasticity in the neural networks (i.e., agent side) and noise level of the observation signals (i.e., environment side) in the learning process were manipulated as inherent characteristics and external environmental factor, respectively. Then, we investigated whether the changes in these factors impacted on the acquisition of hierarchical representations and flexibility.

2.2. Environmental stimuli and task setting

The observable signals were two-dimensional trajectories of objects that mimic reaching movements (Figure 2B) and were

generated by three unobservable, hierarchical, and stochastic variables: "transition bias," "target state," and "signal noise" (left side of Figure 2A). Specifically, these sequences repeated the state transitions from HOME to LEFT or RIGHT (target) and return to HOME from LEFT or RIGHT. The transition bias represented the probability of the transition from HOME to LEFT, as a highest-order context in the environment. The target states (LEFT or RIGHT) were sampled from Bernoulli distributions parameterized by transition bias. The observable goal positions in one reaching movement were sampled from Gaussian distributions whose mean parameter corresponded to a central coordination of each target state and variance parameter corresponded to signal noise.

For the training, two sets of nine sequences (18 sequences in total) with 512 steps were generated with nine different transition probabilities (0.98, 0.87, 0.76, 0.65, 0.54, 0.43, 0.32, 0.21, and 0.10). Asymmetry of transition bias was used to improve the divergence of variances in the sequences. The agent learned to reproduce these sequences with diverse transition probabilities through the developmental learning process. In the test phase, the "flexibility" of the agent was tested using unknown test sequences whose transition bias was switched at the middle of the sequences. Namely, for the test sequences, two sequences with different transition biases (256 steps) were connected in which the transition bias in the second half of the test sequence was randomly sampled from the values in opposite directions to the transition bias of the first half.

The flexibility of the agent was evaluated in terms of the capability to perceive and follow change in the observations and unobservable context (i.e., transition bias) in these unknown test sequences. This quantification was inspired by flexibility tasks, such as the Wisconsin card sorting task (61), in which participants are required to detect changes of a rule or context throughout the task. The flexibility of the agent was evaluated by using two types of performance measures: 1) how accurately the network predicted observations (behavioral flexibility) and 2) how accurately the network inferred unobservable transition bias of the current sequence (cognitive flexibility). The details of the signal generation and quantification methods are shown in Supplementary Methods 1.1, 1.2, respectively.

The task settings presented here were designed to integrate motor control tasks and Wisconsin card sorting tasks. People with ASD have been reported to have alterations in sensorimotor processing (3, 4, 63), including the altered performance in the reaching movement task (3, 63). Based on these findings, observation signals in the current task were synthetically created to mimic reaching behavior, including seeing an object, predicting the movements of the object, and reaching the object. The observation signals in our task setting correspond to the moves of the target object, and the outputs of the neural network model correspond to visual and proprioceptive signals. In addition, the current task also includes a component of cognitive function measured by the Wisconsin card sorting tasks, i.e., flexibility. Indeed, individuals with ASD have been also reported to have reduced performance in the flexibility task (2, 61, 62). This component was implemented in the form that rules of object transitions (i.e., the transition bias) were switched without any notifications, and the agent needs to discover the switch.

2.3. Neurocognitive model

2.3.1. Architecture of PV-RNN

The task for the agent was to acquire an internal representation that reflects the abovementioned hidden environment structure and flexibly adapt to unknown sequences. According to the Bayesian brain hypothesis, this problem for the agent can be described as follows. The agent constructs the statistical model $p(x_{\leq T}) = p(x_1, x_2, \ldots, x_T)$ approximating the true data distribution of the environment in which x and T represent the observed signals and length of sequences, respectively. The model of agent, PV-RNN (55), factorizes this distribution by introducing two latent variables, neural dynamic units d_t and probabilistic latent state units z_t (right side in Figure 2A).

$$\begin{aligned} p(x_{\leq T}) &= \int \cdots \int p(x_{\leq T}, d_{\leq T}, z_{\leq T}) dd_{\leq T} dz_{\leq T} \\ &= \int \cdots \int p(x_1|d_1)p(d_1)p(z_1) \\ &\quad \prod_{t=2}^{T} p(x_t|d_t)p(d_t|d_{t-1}, z_t)p(z_t|d_{t-1}) dd_{\leq T} dz_{\leq T} \end{aligned}$$

This equation indicates that the PV-RNN constructs $p(x_{\leq T})$ using three components: prior distribution $p(z_t|d_{t-1})$, recurrent distribution $p(d_t|d_{t-1}, z_t)$, and generative distribution $p(x_t|d_t)$. In addition, to estimate the latent states based on observations, approximate posterior (inference) distribution $q(z_t|d_{t-1}, a_t)$ was introduced. It should be noted that adaptive variables a_t are learnable parameters and save the error information about each training sequence. For the approximate posterior, the PV-RNN (55) uses $q(z_t|d_{t-1}, a_t)$, instead of $q(z_t|d_{t-1}, x_t)$ used in the variational recurrent neural network model (64). The use of $q(z_t|d_{t-1}, a_t)$ is inspired by the predictive coding theory (24), namely the posterior of latent states is inferred not directly based on external inputs x_t, but based on prediction error.

These probabilistic distributions of mapping from the inputs to outputs were implemented in neural network models and refined through the learning (update of synaptic weights). For example, prior distribution $p(z_t|d_{t-1})$ assumed to follow the Gaussian distribution was represented using the mean and variance units (top-right in Figure 3). The neural network model corresponding to prior distribution inferred the mean and variance of latent units z_t using neural dynamics of d_t.

The neural network corresponding to recurrent distribution $p(d_t|d_{t-1}, z_t)$ has a key role in the top-down and bottom-up flows of information in a hierarchical network (bottom-right in Figure 3). It is well known that the brain has hierarchical properties such as differed intrinsic neural timescales and distinctive anatomical connections, and the hierarchy may contribute to the complex cognitive functions (65, 66). The hierarchical nature of the PV-RNN was implemented to imitate these biological findings by providing different time constants for each layer and restricting the connections between the higher and lower layer units [multiple timescale RNN: MTRNN (46, 54)]. In addition, prior distribution $p(z_t|d_{t-1})$ and posterior distribution $q(z_t|d_{t-1}, a_t)$ have similar restrictions of the connections between the layers. For example, z_t units in the higher layer are inferred only using d_t units in

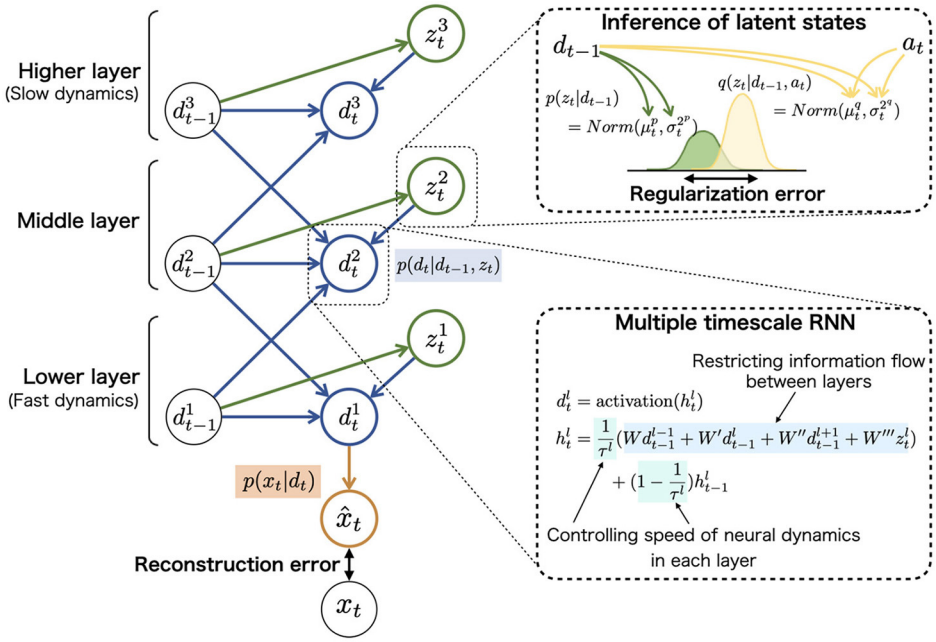

FIGURE 3
The graphical representation of PV-RNN architecture **(left)**. PV-RNN constructs hierarchical generation process in which the higher layer has larger time constant (slow neural dynamics) while the lower layer has smaller time constant (fast neural dynamics), as shown in **(bottom-right)**. In **(top-right)**, the inference process of z_t is illustrated. The right superscripts of symbols (i.e., p and q) are used to distinguish prior and approximate posterior distributions. The inference of posterior latent units z_t^q is performed by propagating the errors in the reverse direction of arrows and updating the adaptive variables a_t. This figure is simplified to improve readability, and detailed and accurate information of PV-RNN is shown in Supplementary Methods 1.3, 1.4.

the higher layer. Considering this hierarchy, the data distribution $p(x_{\leq T})$ constructed by PV-RNN is factorized as follows (left side in Figure 3):

$$
\begin{aligned}
p(x_{\leq T}) = \int \cdots \int & p(x_1|d_1^1) \prod_{l=1}^{L} p(d_1^l) \prod_{l=1}^{L} p(z_1^l) \\
& \prod_{t=2}^{T} \Big\{ p(x_t|d_t^1) \\
& \{ p(d_t^1|d_{t-1}^1, d_{t-1}^2, z_t^1) p(d_t^L|d_{t-1}^{L-1}, d_{t-1}^L, z_t^L) \\
& \prod_{l=2}^{L-1} p(d_t^l|d_{t-1}^{l-1}, d_{t-1}^l, d_{t-1}^{l+1}, z_t^l) \} \\
& \{ \prod_{l=1}^{L} p(z_t^l|d_{t-1}^l) \} \Big\} dd_{\leq T} dz_{\leq T}
\end{aligned}
$$

In this study, the number of layers was set to three. The number of d_t neural units and z_t units were set to (20, 10, 10) and (2, 2, 2), respectively, with the time constant at (2, 8, 32). Because d_t was used as deterministic variables, the integral of d_t was omitted in the following. The detailed architecture and generative processes are provided in the Supplementary Method 1.3.

2.3.2. Loss function in the learning and test phase

Updates of synaptic weights in the learning phase and inference of latent states in the test phase follow the unified principle of minimizing the loss function. In the learning phase, losses were minimized by iteratively updating the synaptic weights and adaptive variables a_t. As a result of learning, PV-RNN was expected to acquire efficient mapping from observed sensorimotor signals to hierarchical Bayesian representations. On the other hand, during the test phase, inference of latent states in posterior distribution was performed through modification of the adaptive variables a_t based on minimizing of the losses with fixing synaptic weights, called "error regression" (49).

In mathematical terms, the model parameters, such as synaptic weights and adaptive variables, were adjusted to maximize the similarity between the statistical model $p(x_{\leq T})$ and the true data distribution of the environment. This is achieved by minimizing the negative of marginal log likelihood $-\log p(x)$. Using variational inference (67),

$$
\begin{aligned}
-\log p(x) \leq & \underbrace{-\sum_{t=1}^{T} E_{q(z_t|d_{t-1}, a_t)}[\log p(x_t|d_t)]}_{\text{Reconstruction errors}} \\
& + \underbrace{\sum_{t=1}^{T} D_{KL}[q(z_t|d_{t-1}, a_t) || p(z_t|d_{t-1})]}_{\text{Regularization errors}}.
\end{aligned}
$$

The right-hand side in this inequality is called variational free energy, and its negative is equivalent to the evidence lower bound (55, 68, 69). The first term, also called the reconstruction

errors, is the negative log likelihood and reflects the differences between the data observations and predictions generated by the model. The second term, in which D_{KL} represents Kullback-Leibuler divergence, reflects the similarity between the prior distribution and posterior distribution and was proposed to have a regularization role (55). In PV-RNN, the weighting factor w^l for each hierarchy l was introduced to control the similarity between the prior distribution and posterior distribution as follows:

$$Loss = -\sum_{t=1}^{T} E_{q(z_t|d_{t-1},a_t)}[\log p(x_t|d_t^1)] + \sum_{t=1}^{T}\sum_{l=1}^{L} w^l D_{KL}[q(z_t^l|d_{t-1}^l, a_t^l)||p(z_t^l|d_{t-1}^l)].$$

The weighting factor w^l, referred to as "meta-prior," was considered to control the stochasticity of neural dynamics (Supplementary Figures S1, S2) through the developmental learning process (55). In the developmental learning process, the neural dynamics is stochastic when the meta-prior is weak, while that is deterministic when the meta-prior is strong. In the test phase, the meta-prior plays a role in controlling the impact of the prior on the posterior; That is, a high meta-prior in the test phase leads to a strong effect of the prior on the posterior, while a low meta-prior weakens the effect. It is noted that the effects of meta-prior differ in the learning and test phase because synaptic weights are fixed in the test phase, and only inferred latent units in the posterior were updated. All parameters of PV-RNN (the synaptic weight and adaptive variables a_t) were optimized using backpropagation through time by minimizing the loss function. As an optimizer, Adam (70) was used. The detail of loss deviation is provided in Supplementary Method 1.4.

2.4. Simulations of diversity in neural development

We manipulated several parameters in the simulation of the learning phase to investigate the relationships between inherent characteristics of neural dynamics, hierarchical Bayesian representation, behavioral and cognitive flexibility, and external environmental factors. First, as the inherent characteristics of neural dynamics, the stochasticity of the network in the developmental learning process was manipulated; This was implemented by changing the value of the meta-prior that controls the balance of two terms (reconstruction errors and regularization errors) in the loss function. This manipulation was attempted based on the previous theoretical studies suggesting that the stochasticity of the network (high or low neural noise) contributes to autistic symptoms (71, 72). In fact, some non-invasive studies have reported that participants with ASD showed altered neural noise (6, 7, 73, 74). Based on these findings and hypotheses, we expected that autistic-like phenomena, i.e., reduced flexibility, would be observed under both weak (high stochasticity) and strong (low stochasticity) meta-prior conditions, and the reduced flexibility would be induced by an abnormality in acquired hierarchical Bayesian representation. As a specific simulation setting, the meta-prior in the lower layer was set to 0.1, 1.0, and 10 as the weak, normal, and strong meta-prior conditions, respectively; the meta-prior in other layers was set to 1.0.

The second manipulated parameter was the level of noises included in the environmental stimulus during the developmental learning process; This is motivated by the well-known observations that reducing ambiguity in stimulations and the structuring environment promotes learning and improve behavioral and cognitive functions in children with ASD (16, 17). The large noise condition and small noise condition were tested by changing the levels of signal noise corresponding to the changes in the ambiguity of the states (LEFT, RIGHT, and HOME). Based on the findings related to interventions for people with ASD (16, 17), we hypothesized that less flexibility and alterations in the hierarchical Bayesian representations would be observed under large noise condition (noisy environment) than small noise condition (stable environment).

2.5. Implementation and statistical analysis

Python and PyTorch (75) were used in the experimental simulation to generate training and test sequences and implement the neural network model. Both R (76) and Python were used for visualization and statistical analysis. The 20 networks were trained in each condition. In each analysis, values outside of 1.5 times the quantile range in each condition were removed as outliers. Therefore, the number of conditions was inconsistent in each analysis. To compare between meta-prior conditions, analyses of variance (ANOVA) between-subject were used (three levels, normal, strong, and weak meta-prior). The interaction effects of meta-prior and signal noise were analyzed using a three (meta-prior conditions) × two (stable and noisy environments) ANOVA. In *post-hoc* multiple comparison, Shaffer's modified sequentially rejective Bonferroni procedure was used.

3. Results

3.1. Behavioral and cognitive flexibility in hierarchical Bayesian RNN

The representative example of generation of behavioral sequence and neural activities with the value of meta-prior referred to as the "normal meta-prior" condition was presented in Figure 4. The output sequences of RNN and test sequences were seemingly concordant not only at the observation signal (xy-coordinate) level, but also at the state transition level (i.e., HOME/LEFT/RIGHT). This indicated that the network successfully predicted unknown observations and adapted to the changes in the observation signals based on hierarchical internal representations acquired through the developmental learning.

Qualitative inspection indicated that the hierarchical representation of each latent unit played a different functional role. For example, the activities of latent units of the lower layer (unit0 and unit1) were synchronized with the y-axis in

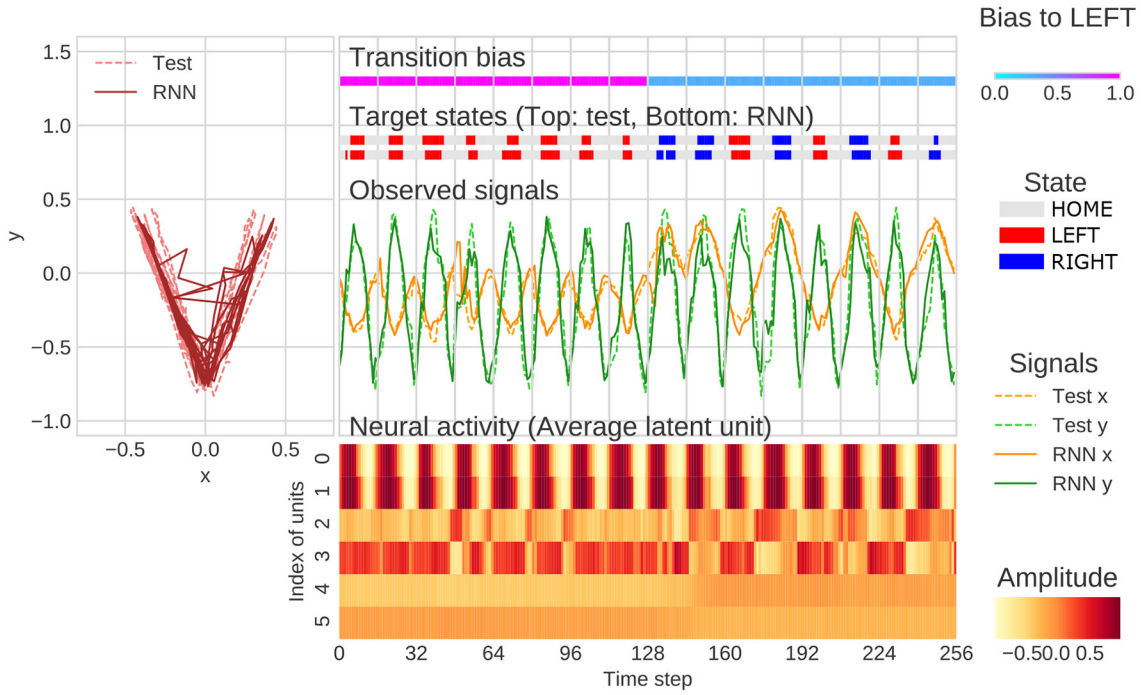

FIGURE 4
An example of flexibility tasks under normal meta-prior condition. In the top of figure, RNN generations and test sequence are plotted on two-dimensional plane **(left)** and along time axis **(right)**. The unit0 and unit1, unit2 and unit3, and unit4 and unit5 reflect the lower layer, middle layer, and higher layer, respectively. The latent units coding mean parameters of Gaussian distributions are plotted in the figure rather than z_t itself. In the figure, only the 128 steps before and after switching of the transition bias are plotted.

the behavioral trajectories. In the middle layer, unit2 was active when target states moved to RIGHT and unit3 was active in the opposite direction. The higher layer units, such as unit4 and unit5, appeared to be related to the probability of transitions to LEFT and RIGHT. Specifically, unit5 was active in generating LEFT-biased sequence (first half of Figure 4), and unit4 was active in generating RIGHT-biased sequence (last half of Figure 4). The distinct role of the middle layer and higher layer can be clearly observed in the last half of Figure 4. In this period, unit4 was continuously active because of RIGHT-biased generation even when LEFT-transition occurred (probabilistic effect on outputs). In contrast, unit3 was only active when LEFT-transition occurred (direct effects on target states). These observations indicated that the PV-RNN with normal meta-prior condition acquired hierarchical representation, which reflected the structures of environment and were flexible enough to adapt not only to the observable stimulus changes but also to the unobservable context switching.

Under the strong meta-prior condition, the network failed to accurately predict the observations in the test phase. For example, movement timing of generated sequence did not match to a test sequence (arrowheads in Figure 5A). In addition, the network under strong meta-prior condition was unable to respond to the changes in context (probability of transitions) in the target states and repeated previous output patterns (perseveration errors; arrows in Figure 5A). Indeed, activities of higher layer units (unit4 and unit5) did not change at the point when transition bias switched in the test sequence. On the other hand, these failures in behavior including perseverative errors were not observed under the weak meta-prior condition (Figure 5B). However, neural activities seemed to be relatively noisy and unstable, and the functional roles of each layer of latent units were not clear compared to the normal meta-prior.

To confirm this qualitative evaluation, two types of measure were introduced: behavioral and cognitive flexibility. Behavioral flexibility was the ability to accurately adapt to observable signal changes and quantified using the percentage of the agreement between the states of observations and the states of predictions by the networks. On the other hand, cognitive flexibility was evaluated using the correlations between true values of transition bias in the test sequences and the activities of latent units in the higher layer of the networks. Therefore, cognitive flexibility reflects the efficacy of representation learning in terms of passive inference for higher-order context and the "insight" for changes of higher-order hidden context (transition bias) in the environment.

Consistent with the qualitative evaluations, the behavioral flexibility was declined under strong meta-prior condition [$F_{(2,51)}$ = 152.5871; $p < 0.0001$ using ANOVA, and $t_{(51)}$ = 15.0647; $p < 0.0001$ at normal > strong, and $t_{(51)}$ = 14.9831; $p < 0.0001$ at weak > strong in *post-hoc* tests; Figure 6A]. Furthermore, cognitive flexibility declined more in strong meta-prior condition than weak and normal prior conditions [$F_{(2,56)}$ = 15.6619; $p < 0.0001$ using ANOVA, and $t_{(56)}$ = 4.6497; $p < 0.0001$ at normal > strong, $t_{(56)}$ = 5.0041; $p < 0.0001$ at weak > strong in *post-hoc* tests; Figure 6B].

3.2. Hierarchical and probabilistic representation for active generation

To further examine the functional role of the latent units in each layer of PV-RNN, we adapt deep learning technique called "latent space traversal (LST)." In the LST, the changes in the network predictions were investigated when the activity of single target latent unit was intentionally manipulated (77, 78). This makes it possible to functionally, causally, and operationally examine whether neural units code output information and to

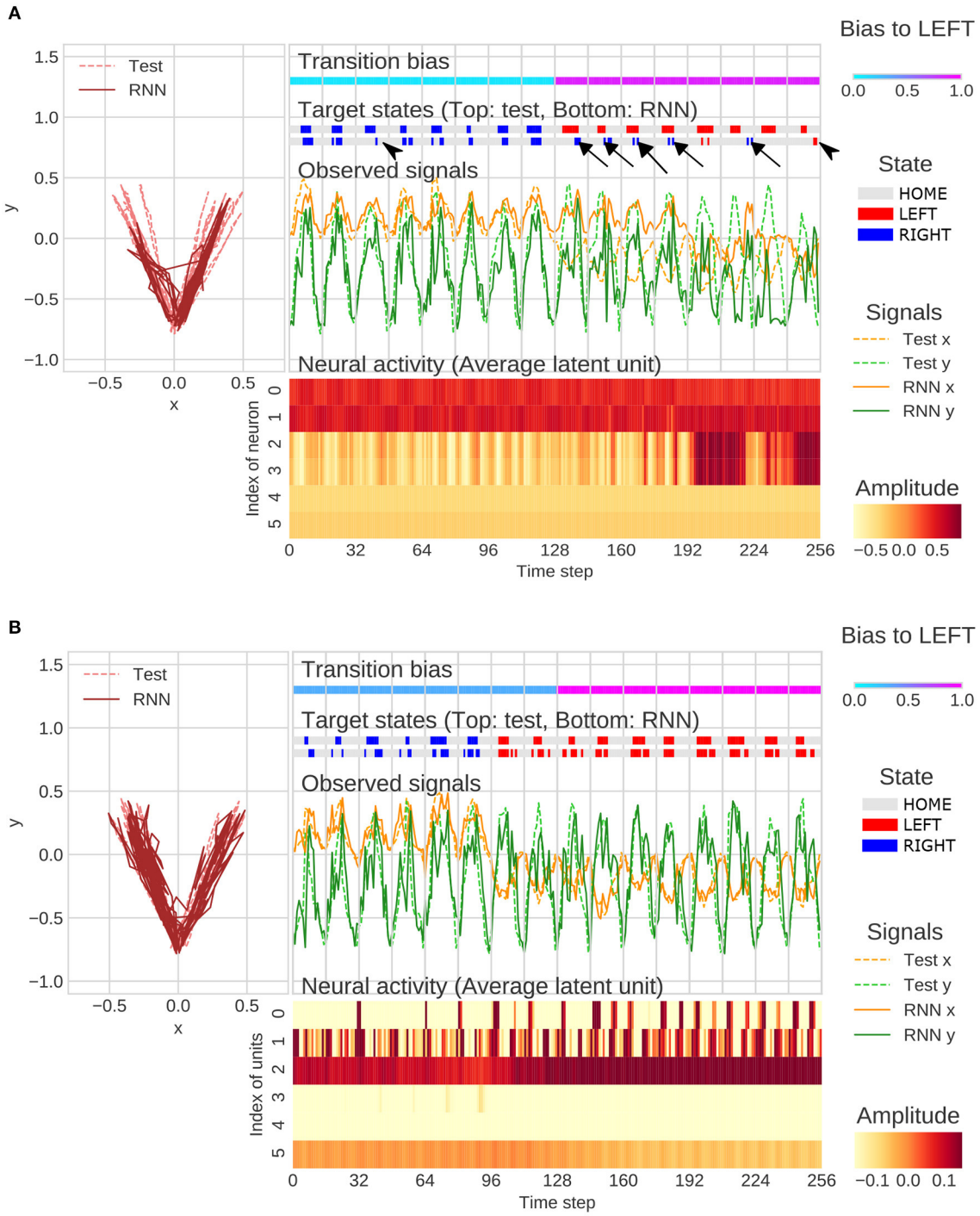

FIGURE 5
(A) Example of flexibility tasks under strong meta-prior condition. The arrows and arrowheads represent perseveration errors and timing mismatches, respectively. The latent units coding mean parameters of Gaussian distributions were plotted in figure rather than z_t itself. **(B)** Example of flexibility tasks under weak meta-prior condition. The range of color plot adjusted to activities of higher latent units although the max and min values in lower- and middle-units surpassed the ranges of those plotted. In the figures **(A, B)**, only the 128 steps before and after switching of the transition bias are plotted.

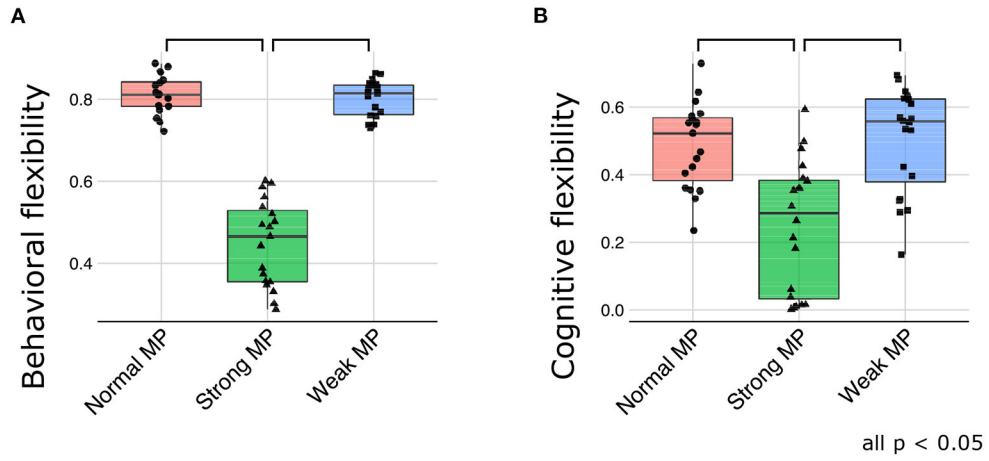

FIGURE 6
The quantitative evaluation about behavioral flexibility **(A)** and cognitive flexibility **(B)**. MP represents meta-prior.

reject the possibility that the activity of higher layer units is passively responding to bottom-up signals. Therefore, the LST method focused on the decoding (active generation) ability while cognitive flexibility focused on the encoding ability (passive inference), although both were used for evaluation of representation learning.

The LST analysis was conducted as follows. One sequence of 1,024 time steps was generated by setting the activity of the target latent unit at a particular fixing value. This process was repeated by changing the fixing values ranging from −1.0 to 1.0. Properties of the generated sequences were evaluated in terms of the ratios of time steps staying with HOME and the number of LEFT transitions, and so on. Examples of generated sequences using LST were shown in Supplementary Figure S3.

The LST under normal meta-prior condition demonstrated that the lower the activities in unit0 and unit1, the more time steps staying with HOME state (Figure 7A), suggesting that the lower layer units (unit0 and unit1) coded the y-axis movement. Similarly, the manipulations in the activities of middle layer units (unit2 and unit3) and higher layer units (unit4) lead the changes in the transition to the LEFT state, suggesting that these units coded LEFT/RIGHT transitions (Figure 7B). Note that the slope of the changes in the number of LEFT transitions induced by the higher layer unit manipulations is shallower than those induced by the middle layer unit manipulations. This observation suggests that the activity of the higher layer unit likely codes probabilistic information (i.e., transition bias), while the activities of middle layer units directly were associated with target state (i.e., LEFT or RIGHT) with an all-or-nothing manner. In addition, LST analysis applied to the variance units demonstrated that the variances of generated sequences increased as the activities of variance unit in the lower layers increased (Figure 7C). This unit seemed to code the amount of noise in the predicted signals (i.e., signal noise). These results suggested that the PV-RNN under the normal meta-prior condition could acquire hidden hierarchical and probabilistic structures of the environment in terms of not only passive inference but also active generation.

The LST analysis with different meta-prior setting conditions demonstrated altered hierarchical representations. For example, under the strong meta-prior condition, lower layer units and higher layer units did not have distinct roles, and several levels of functions are intermingled in the middle layer. Namely, the activities of unit0 and unit1 (lower layer) did not have the effects on steps staying in HOME state and the number of LEFT transitions (Figures 8A, B). The activities of unit4 (higher layer) did not have clear effects on the sequence generations (i.e., association of activities and properties of generated sequences have several outliers) (Figure 8B). On the other hand, changes in unit2 and unit3 (middle layer) had effects on the time steps staying HOME state (Figure 8A) and in the LEFT transitions (Figure 8B). These observations suggested that under the strong meta-prior condition, the representations in each layer were not good, which was consistent with the observations of poor behavioral and cognitive flexibilities.

On the other hand, under the weak meta-prior condition, unit1 and unit0 had very clear effects on the y-axis movements (Figure 8C) and LEFT transition (Figure 8D), respectively. However, unit2, unit3 (middle layer), unit4, and unit5 (higher layer) had no effects on generated sequences. Therefore, under weak meta-prior condition, it seemed that latent representations in the lower layer were effective, but those in higher layer were ineffective.

To quantitatively confirm these findings, we defined a measure referred to as "generative hierarchy," which represents the total amount of the causal effect of a network in terms of active generation. Namely, the latent units of the network have stronger causal effects for output sequences when the generative hierarchy of a network is high. The detailed procedure is as follows: first, in the LST analysis, correlations between the manipulated values of a particular latent unit (horizontal axis in Figures 7, 8) and behavioral properties of generated sequences including the number of transitions to each state, the number of stay steps in each state, and the variance in each state (i.e., the vertical axis in Figures 7, 8) were calculated. The maximum value of the correlations over all properties was calculated based on the assumption that this value

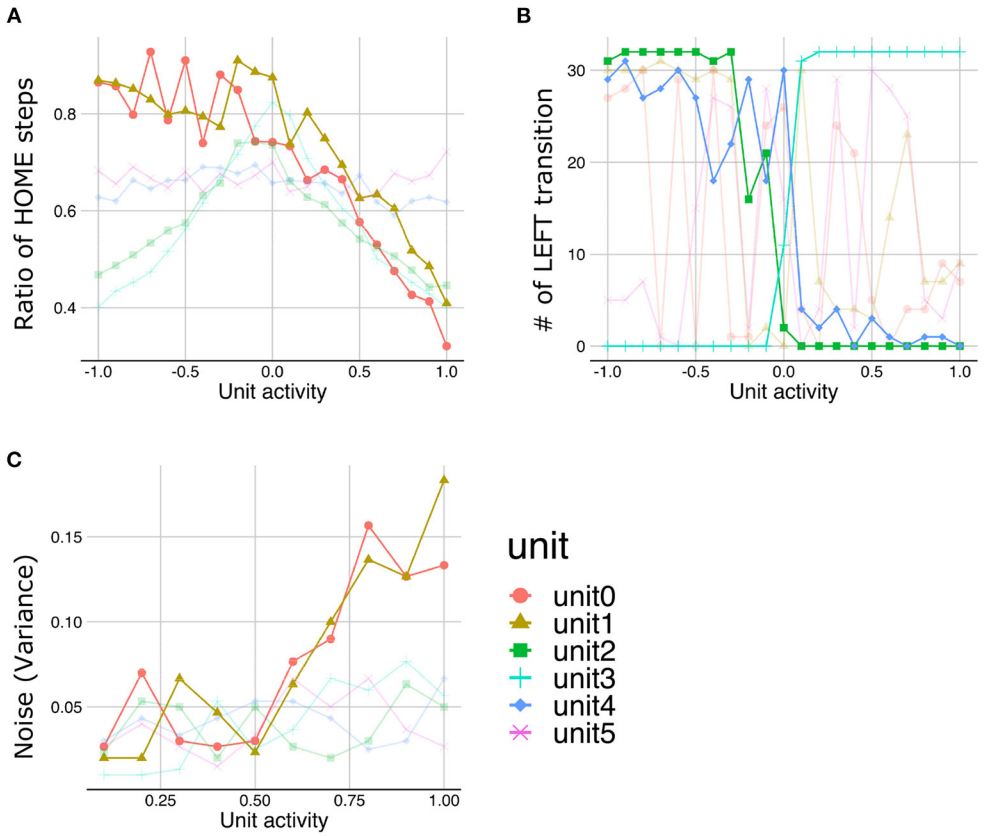

FIGURE 7
The results of latent space traversal under normal meta-prior condition. The properties of generated sequences (y-axis) changed depending on fixed activation values (x-axis) of one particular unit. Changes in the number of steps staying with HOME states **(A)** and the numbers of transition to LEFT states **(B)** were plotted. **(C)** Changes in the variances of generations were plotted when activities of units inferring variances of latent units were fixed. Irrelevant lines are plotted in a pale color to improve readability.

represents the efficacy of each latent unit on behavioral generation. Finally, the average of the efficacy of the latent units in each layer was used as the generative hierarchy of each layer in one network.

Figure 9 depicts the generative hierarchy under each meta-prior condition. As expected, to sum up all the layers, generative hierarchy of the latent representations in normal meta-prior conditions seemed to be better than in other conditions. On the other hand, under weak meta-prior condition, the generative hierarchy in the middle and higher layer was poor, although that in the lower layer was comparable to normal meta-prior condition. The generative hierarchy under strong meta-prior condition was reduced in all layers compared to normal meta-prior condition except for noise representations of variance units.

These observations were confirmed by the following statistical analyses. The generative hierarchy was best under weak meta-prior condition in the lower layer [Figure 9A; $F_{(2,56)} = 361.8663$; $p < 0.0001$, $t_{(56)} = 3.4104$; $p = 0.0012$ at weak > normal, $t_{(56)} = 24.8918$; $p < 0.0001$ at weak > strong, and $t_{(56)} = 21.1603$; $p < 0.0001$ at normal > strong]. However, in the middle layer (Figure 9B), generative hierarchy was the best in normal meta-prior condition than strong and weak meta-prior conditions [$F_{(2,53)} = 33.5184$; $p < 0.0001$, $t_{(53)} = 8.1367$; $p < 0.0001$ at normal > weak, $t_{(53)} = 3.5753$; $p = 0.0008$ at normal > strong, $t_{(53)} = 4.7977$; $p < 0.0001$ at strong > weak]. Similar to the middle layer, in the higher layer (Figure 9C), the normal meta-prior condition showed the best generative hierarchy [$F_{(2,54)} = 24.3196$; $p < 0.0001$, $t_{(54)} = 6.9503$; $p < 0.0001$ at normal > weak, $t_{(54)} = 3.2721$; $p = 0.0019$ at normal >strong, and $t_{(54)} = 3.8371$; $p = 0.0003$ at strong >weak]. The differences in the generative hierarchy of variance units were not significant [Figure 9D; $F_{(2,57)} = 0.0769$; $p = 0.9261$].

These results suggested that the networks under a weak meta-prior condition generated using only lower layers; it did not have sufficient hierarchical and disentangled representations in term of active generation, and the hierarchical representations were effective only during passive inference. On the other hand, the networks under a strong meta-prior condition showed the abnormalities in hierarchical representations in terms of both active generation and passive inference.

3.3. The buffering effect of environment on representation learning

As an external environmental factor during the developmental learning process, the noise level of the observation signals was

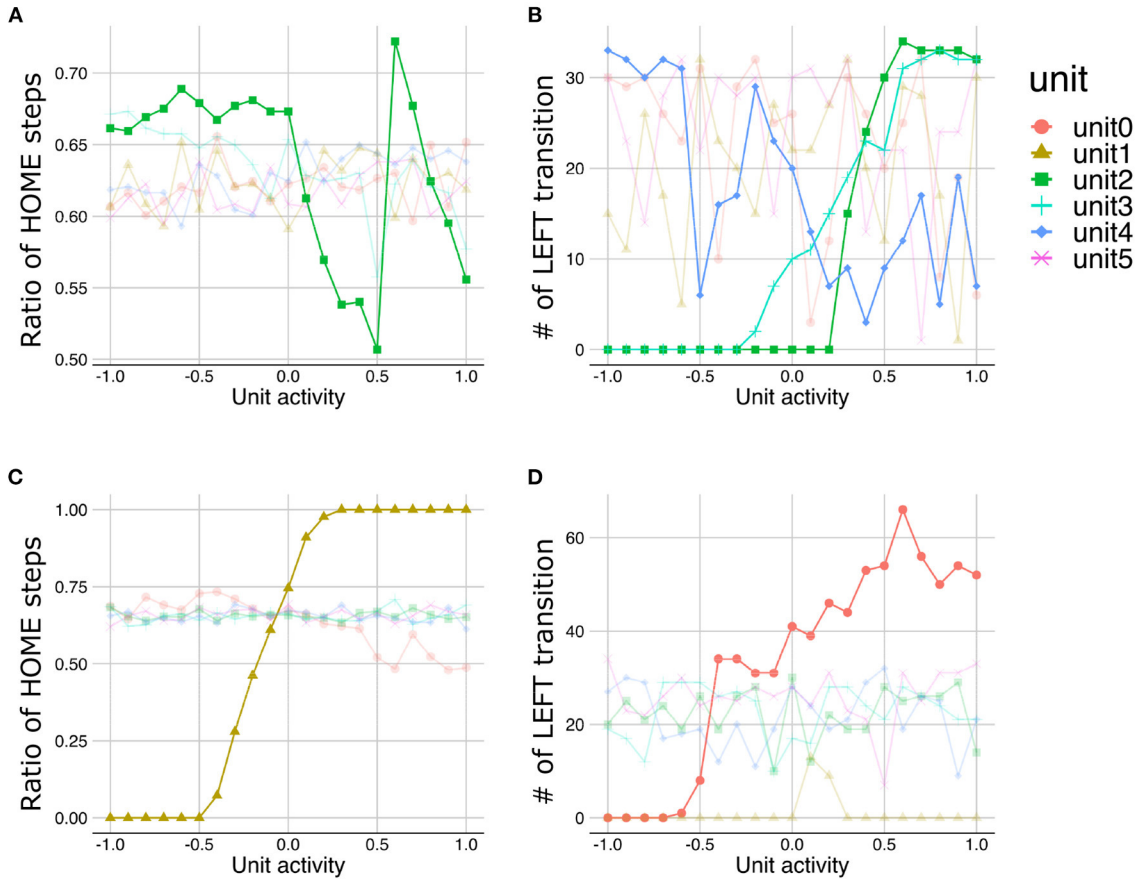

FIGURE 8
The results of latent space traversal under strong **(A, B)** and weak meta-prior condition **(C, D)**. Irrelevant lines are plotted in a pale color to improve readability.

manipulated. This experiment is motivated by the well-known phenomenon in education and support for children with ASD, namely that reducing ambiguity in stimulations and the structuring environment promote learning and improve behavioral and cognitive functions (16, 17). In this experiment, we manipulated the signal noise level included in the training and test sequences and examined the interaction effect between meta-prior and noise level on the representation learning. Figure 10A illustrated a representative example of behavioral sequence for training under the "noisy" environment condition in which LEFT and RIGHT states were not clearly distinguishable, in contrast to "stable" signal noise condition (Figure 2B).

As described earlier, strong meta-prior condition showed reduced flexibilities (behavioral and cognitive: Figure 6) and poor generative hierarchy (Figure 9). However, in the noisy environment condition, the behavioral flexibility under strong meta-prior conditions was improved (Figure 10B). Furthermore, the networks under strong meta-prior and noisy environment condition partly acquired the hierarchical representations, specifically in the middle (Figure 10D) and higher layer (Figure 10E). However, noisy environment under strong meta-prior condition did not induce the improvement of generative hierarchy in the lower layer (Figure 10C).

These observations were confirmed by the following statistical analyses. There were significant main effects of meta-prior and environment [$F_{(2,105)} = 116.4491$; $p < 0.0001$ in meta-prior, $F_{(1,105)} = 90.8178$, $p < 0.0001$ in environment]. In addition, the interaction effect between the environment and meta-prior on behavioral flexibility was significant [interaction effect $F_{(2,105)} = 72.7390$, $p < 0.0001$]. Furthermore, the difference of behavioral flexibility between environment conditions was significant under strong meta-prior condition [the simple effect of environment on strong meta-prior condition $F_{(1,105)} = 222.8984$; $p < 0.0001$]. However, the interaction effects on cognitive flexibility were not significant [$F_{(2,112)} = 1.7649$; $p = 0.1759$], although main effects of meta-prior [$F_{(2,112)} = 28.7819$; $p < 0.0001$] and noise level of environment [$F_{(1,112)} = 5.5784$; $p = 0.0199$] were significant. Moreover, the strong meta-prior condition under noisy environment improved generative hierarchy in the middle layer [interaction effect $F_{(2,107)} = 6.3325$; $p = 0.0025$, and simple effect of environment on strong meta-prior $F_{(1,107)} = 16.1836$; $p = 0.0001$] and in the higher layer [interaction effect $F_{(2,106)} = 7.1059$; $p = 0.0013$, and simple effect of environment on strong meta-prior $F_{(1,106)} = 14.5995$; $p = 0.0002$]. The interaction effect between the environment and meta-prior on lower representations was not significant [$F_{(2,111)} = 0.3530$, $p = 0.7033$].

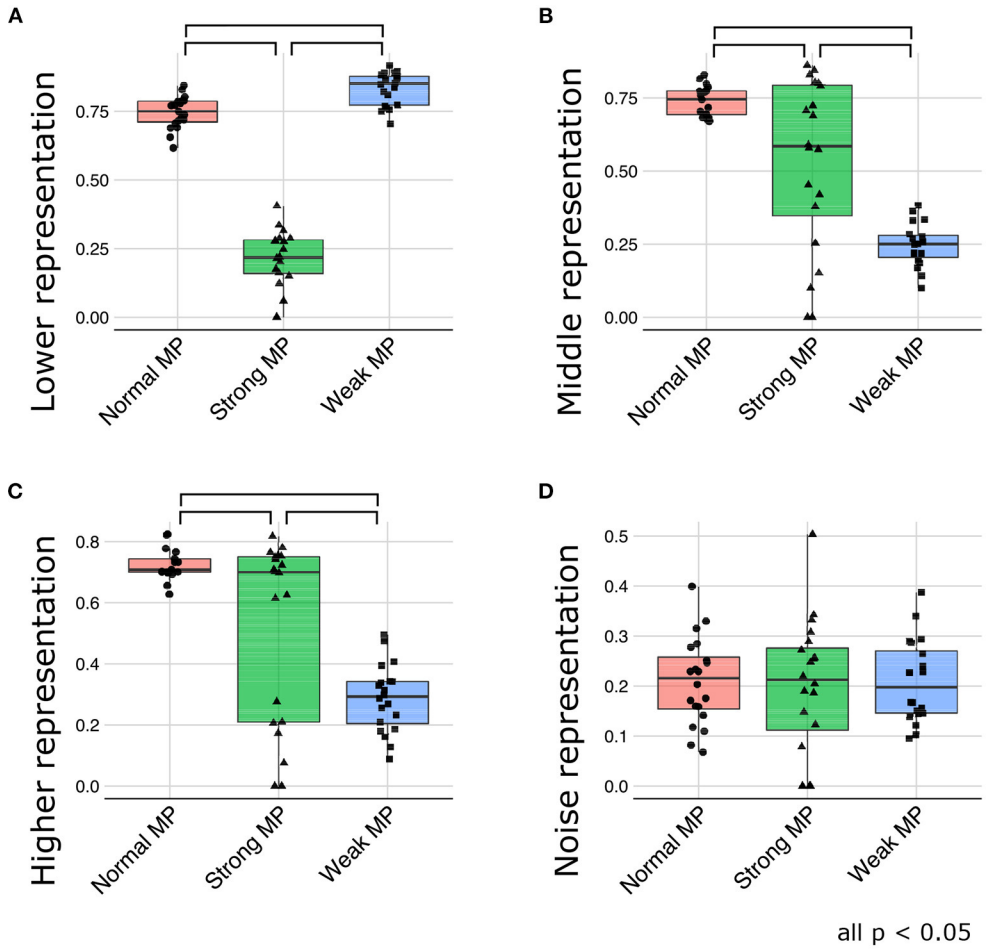

FIGURE 9
(A–D) The generative hierarchy under each condition. MP represents meta-prior.

Therefore, under the strong meta-prior condition, increased signal noise improved the behavioral flexibility and acquisition of the hierarchical Bayesian representation.

4. Discussion

In this study, we proposed a new research framework for understanding the pathological mechanisms of the atypical developmental process, using state-of-the-art computational model, PV-RNN. This framework comprehensively includes simulations of the multiple factors related to developmental disorders, for example, the neural dynamics, hierarchical Bayesian representation, cognitive-behavioral phenotypes, developmental learning processes, and the environment. In this framework, these factors could be manipulated without any restriction and analyzed quantitatively.

As an example, in experiments using this framework, we analyzed the relationships between inherent characteristics of neural dynamics, hierarchical Bayesian representation, the properties of external stimulus, and inflexibility, which is cognitive-behavioral phenotype observed in patients with ASD. Particularly, this study investigated: (1) whether manipulating inherent characteristics of neural dynamics and external environment induces reduced flexibility; (2) whether these manipulations lead to the normal/abnormal acquisition of hierarchical Bayesian representations; and (3) how the abnormalities in hierarchical Bayesian representations are related to reduced flexibility. Figure 11 summarizes the results for these questions.

4.1. Reduced flexibility and pathology of ASD

The normal and weak (high stochasticity) meta-prior conditions did not show reduced flexibility regardless of external environment condition. In contrast, the networks with strong meta-prior (low stochasticity) condition showed less behavioral and cognitive flexibility in the stable environment. On the other hand, the noisy environment improved the behavioral flexibility under strong meta-prior condition.

This result of reduced flexibility under strong meta-prior condition is consistent with the finding reported by Wirkuttis and Tani (59) that the PV-RNN with higher meta-prior had stronger

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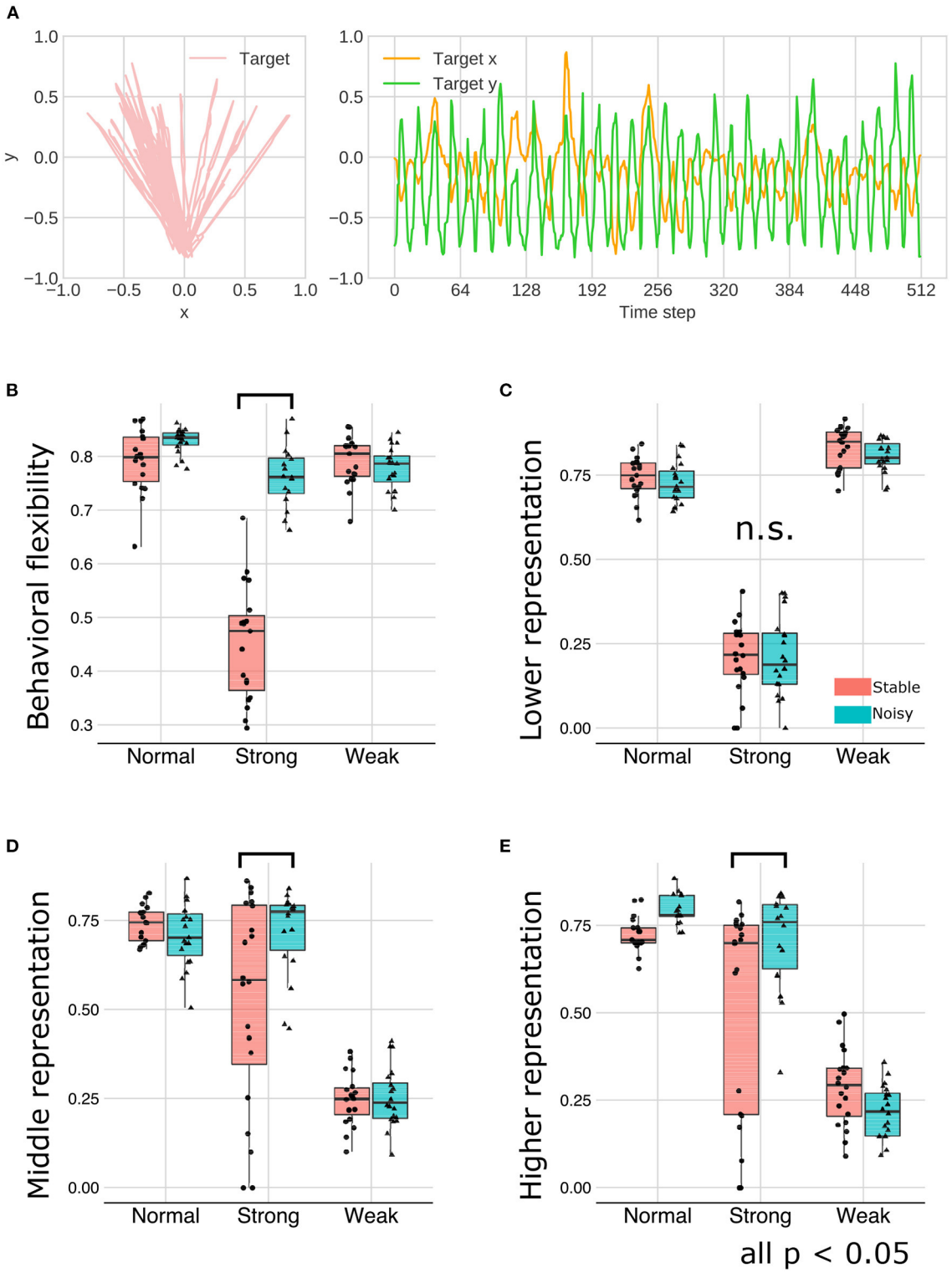

FIGURE 10
(A) The training sequence in noisy environment condition in which transition bias was set to 0.76 (LEFT-biased sequences). **(B–E)** The interaction effect between the environment and meta-prior. The results of statistical test were showed under only strong meta-prior condition.

intention and less flexible interaction with others because the top-down prior belief had more effects on generated behaviors than bottom-up sensory signals. In addition to reproducing this finding, we found that behavioral flexibility was improved by increasing stimulus noise under the strong meta-prior condition. From an information theory view of PV-RNN, the

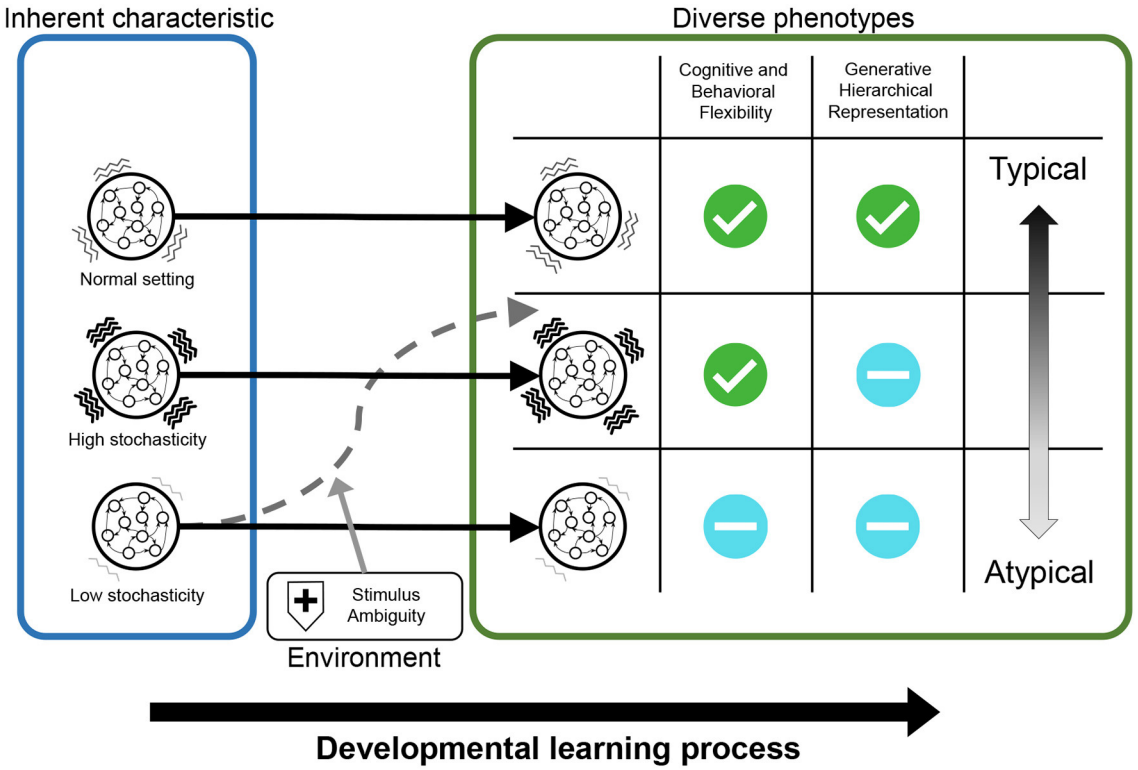

FIGURE 11
The results of simulation experiments were graphically summarized. The networks with normal neural stochasticity were able to acquire hierarchical representations, including higher-order representation, and exhibited good behavioral and cognitive flexibility. When the neural stochasticity was high in the learning process, top-down generation using higher-order representation (i.e., generative hierarchy) was impaired, although the flexibility did not differ from that of the normal settings. On the other hand, when the neural stochasticity was low in the learning process, the networks demonstrated reduced flexibility and abnormal hierarchical representation. However, this altered acquisition of higher-order representation and flexibility was ameliorated by increasing the level of noises in external stimuli.

network with strong meta-prior condition underestimates the reconstruction errors and overestimates the regularization errors in the loss function compared to the other conditions. The reason why the flexibility improved under noisy environment was that increasing stimulus noise led to an increase of reconstruction errors, resulting in amelioration of the balance between the reconstruction and regularization errors. Therefore, the combination of appropriate meta-prior and noise levels in the environment seems to be important for the flexible behavior. An alternative explanation for this amelioration effect is that increasing stimulus noise worked similar to the machine learning techniques to improve generalization capability such as augmentation (79) or denoising (80).

The findings that low stochasticity dynamics was related to reduced flexibility may provide new insights into the hypothesis that neural noise is involved in the formation of ASD. Previous theoretical studies have proposed conflicting hypotheses: one is there is more noise in the brain of people with ASD (72) and another is low noise in the brain of people with ASD (71). Our results support the hypothesis that low neural noise is associated with ASD. Furthermore, these results are consistent with the experimental findings using magnetic resonance imaging and electroencephalography that lower neural noise was associated with worse task performance in a typical developmental group (81, 82) and that lower neural noise was observed in ASD (73, 74). Moreover, in the Supplementary Results 2.3, we reported that some networks with low stochasticity dynamics generated sequences similar to restrictive and repeated behaviors. However, some studies have reported high neural noise in ASD (6, 7). Indeed, much noise intuitively seemed to lead to unstable and chaotic predictions and reduced task performance. The reason why the network with lower stochastic dynamics did not show inflexibility is that the flexibility task demanded to predict only one-step-ahead. For this reason, even if the disturbance of network dynamics by neural noise occurred, the network could sufficiently modify the predictions using observations. If the networks were required to predict a more longer future than one step, the noise would accumulate in the neural network, and the performance of the task is likely to deteriorate (55). It remains unclear why the higher neural noise induced better task performance in typical development but more severe symptoms in ASD, and refining experimental settings may contribute to solve this question.

In addition, the amelioration effect of environmental noise for flexibility was a novel finding of the current study. Indeed, although the effects of environment in developmental learning in ASD has been clinically well known (16, 17), there are few studies directly testing this topic from the computational aspect. For example, some studies discussed the environmental effects

on mental disorders using computational theories only at the conceptual level (30, 31, 83). Our study demonstrated empirically that if the networks possessed risks for reduced flexibility, such as low stochasticity in neural dynamics, they could be ameliorated by increasing ambiguity in the external environment. On the other hand, clinical findings suggest that structuring the environment and removing ambiguity in stimulus were effective for people with ASD (16, 17). Although these findings may seem contradictory, our findings do not necessarily conflict with clinical findings, because many exposure methods for anxiety disorders have suggested that increasing prediction errors was important for correcting mislearning (84). Given the hypothesis that ASDs have a higher aversion to prediction errors, it is possible that these interventions, such as structuring the environment, do not contribute to learning, but only to emotional stabilization.

4.2. Acquisition of hierarchical and probabilistic representation

The current study demonstrated that stochasticity of neural dynamics (controlled by the level of meta-prior) was indeed associated with acquisition of the internal representations reflecting hierarchical and probabilistic environment structures. The neural network model under normal meta-prior condition could acquire the hierarchical and probabilistic representations in terms of passive inference (cognitive flexibility) and active generation (generative hierarchy). However, under weak meta-prior condition, there was an anomaly in the active decoding process rather than in the passive encoding process; namely, cognitive flexibility showed good performance, although the generative hierarchy in the higher layer showed poor scores. This may be because the learning of the prior distribution (used in the LST) did not progress as well as the posterior distribution (used in the test phase). As the properties of PV-RNN, the posterior distribution learns more easily and quickly than the prior distribution because the posterior distribution can use adaptive variables a_t in addition to neural dynamics units d_t. Furthermore, under weak meta-prior condition, excessive neural noise might interfere information transmission to the higher layer from the lower layer and inhibit learning in the higher layer.

These results of simulation experiments can provide several insights for understanding the altered uncertainty estimation process assumed in ASD (29–32). The current experiment demonstrated that the mean unit in PV-RNN encoded higher-order probability (transition bias) in data sequences, and the variance units in the lower-order layer encoded sensorimotor noises (signal noise). This is not perfectly consistent with the predictive coding theory suggesting that the human brain represents uncertainty in the environment using the precision (inverse of variance) of Gaussian distribution (24). This inconsistency may be simply because of the fact that the higher-order hidden variables in the environment followed Bernoulli distribution and therefore neural networks did not need to use the variance units. However, there is still a possibility that the role of precision, as indicated by predictive coding theory, may be too normative. In fact, in a hierarchical neural network, estimation of precision can have broader effects beyond the weighting of information values assumed in the conceptual level of predictive coding theory such as disturbing neural dynamics observed in the weak meta-prior condition. Investigations using neural network implementation of predictive coding theory can contribute to further understanding of the roles of precision estimation and its alternation in developmental disorders.

The hierarchical Bayesian model has been treated as a very general and rational cognitive model for performing numerous tasks (26, 27). However, a hierarchical Bayesian model has been constructed by researchers a priori, and acquisition of representations reflecting the hierarchical Bayesian model have not been sufficiently addressed in cognitive neuroscience (33–35). In the area of machine learning and neurorobotics, although some studies focused on acquisition of hierarchical or probabilistic representations, these have some limitations. For example, some studies focusing on hierarchical representations did not assume sequential data because of using a variational auto-encoder (78, 85, 86) and did not use stochastic dynamics in RNN (42). Although there is research investigating internal representation using PV-RNN, the previous studies used lower-order probability (e.g., target state and signal noise) and did not consider explicitly higher-order probabilistic variables such as transition bias (55–60). The current result showing that artificial neural network models can acquire hierarchical Bayesian representations in a self-organizing manner is a crucial step to understanding underlying mechanisms for embedding the hierarchical Bayesian model into the brain system through developmental learning. Furthermore, our proposed research framework has applicability to a wide range of behavioral and cognitive phenotypes if its latent cognitive processes can be described using the Bayesian method (25, 26), for example, signal detection theory and drift-diffusion model in decision-making tasks.

4.3. Relationships between multiple developmental factors

It was observed that changes in the acquisition of hierarchical Bayesian representation did not necessarily induce inflexibility. Indeed, additional analysis demonstrated that the positive association between hierarchical representations (generative hierarchy) and behavioral flexibility was found only under strong meta-prior condition (Supplementary Results 2.1). However, under weak meta-prior condition, the behavioral and cognitive flexibility was comparable to normal meta-prior condition, but generative hierarchy in the higher layer was significantly lower.

This coexistence of good task performance and poor representation in the weak meta-prior condition is remarkable because the observable phenomena in performing tasks was equivalent while the underlying mechanism behind performing tasks was different between normal and weak meta-prior conditions. This finding is conceptualized as the issue of "equifinality" and "multifinality," which are fundamental difficulties in understanding neurodevelopmental disorders (87). In particular, multiple factors leading to one developmental disorder exist (equifinality, for example, genetically distinct individuals may develop common social dysfunction), and

conversely, the same cause may result in diverse and heterogeneous phenotypes (multifinality, for example, a particular gene can be associated with distinct psychiatric disorders).

From the aspect of equifinality, possible pathways other than the manipulations of meta-prior and signal noise leading to inflexibility were investigated (Supplementary Results 2.2–2.4). Specifically, the effects of different learning lengths were tested, motivated by the theoretical hypothesis that autistic characteristics in perception and cognition can be understood as "over-learning/over-fitting" (88). This additional experiment showed that the excessive learning length led to reductions in behavioral and cognitive flexibility (Supplementary Results 2.2, 2.3). Furthermore, from the aspect of episodic psychiatric disorders, even after normal development of hierarchical representation, altered flexibility can occur. To simulate this situation, we confirmed that hyper- and hypo-prior distributions (89) in the test phase can also induce inflexibility (Supplementary Results 2.4). Therefore, the reduced flexibility was caused both by alterations in the long-term developmental learning process (alterations of meta-prior, signal noise, and the learning length) and by abnormal prior influences in the short-term test phase. These simulations may contribute to constructing a unified explanation of inflexibility, which is a transdiagnostic phenotype observed in not only developmental disorders but also episodic mental disorders such as depression and schizophrenia.

It is also important that the simulations under strong meta-prior condition suggested that our proposed method can provide computational simulation frameworks for investigating multifinal phenomenon including treatment effects. Namely, the differences in external environmental stimulus induced the differences in generative hierarchy and flexibility under strong meta-prior condition, although settings of the individual network between environmental conditions were the same.

Equifinality and multifinality are widespread not only in developmental disorders but also in mental disorders and threaten the validity of the current diagnosis classification system (90). Resolving this problem may lead to the development of an effective intervention strategy that considers the individual differences (precision psychiatry), and the research handling equifinal and multifinal nature has been desirable. We are convinced that the proposed research framework contributes to understanding the multiple pathways leading to mental disorders.

4.4. Limitation and future directions

The simulation experiments had some limitations, which should be investigated in future research. First, the proposed framework is limited to '*in silico* simulation, and the findings obtained in the proposed framework are exploratory hypotheses. Therefore, the findings '*in silico* simulation should be verified with real data. For example, findings in the current experiments suggest that flexibility and/or hierarchical representation are impaired under strong and weak meta-prior conditions, suggesting that ASD may be a heterogeneous disorder. Given that flexibility was significantly reduced and hierarchical representation learning was impaired under the strong meta-prior condition, the neural dynamics with severe ASD may be low stochastic (highly deterministic). Conversely, mild ASD individuals, whose performance in flexibility task are close to the typical development group and who do not explicitly exhibit restrictive and repeated behaviors, may have high stochasticity in neural dynamics and may have problems with top-down predictions. These exploratory hypotheses could be verified using real data to refine the proposed framework.

The proposed framework has the potential to be extended for more diverse experimental settings beyond the simulations conducted in this study. For example, as mentioned above, cognitive-behavioral tasks other than the flexibility task are also applicable to the proposed framework. Furthermore, the direct effects of altered biological features other than meta-prior must be investigated in our framework as prior works on ASD and schizophrenia using neural network model utilized various virtual lesion to neural system (51–54). Moreover, the sequential data also has room for improvement. In the current study, the sequential data was two-dimensional and insufficient to reflect the real environment and sensorimotor signals. To overcome this problem, using neurorobotics experiments in which humanoid robots are used to interact with the external world to collect sensorimotor (e.g., vision and proprioception) signals would be useful (51, 52, 54, 91). Although the simulation experiments were still simple and were not sufficient to describe the interactions between multiple factors, these extended experiments based on the proposed framework will contribute to a deeper understanding of complex developmental processes.

In the simulation experiments, there were several technical issues. For example, the meta-prior, which was manipulated in experiments, was used as the hyper-parameter, which controls the stochasticity in neural dynamics. The relationship between meta-prior and stochasticity was confirmed in prior research (55) and in our simulations (Supplementary Figures S1, S2). However, meta-prior affects neural dynamics through mediating loss function rather than directly. Therefore, the process that meta-prior affected neural dynamics was more complex, and the roles of manipulating meta-prior required more careful discussion.

It was also unclear how to decide the meta-prior in the test phase, which affected the strength of prior belief. These values were decided by experimenter's trial and error in our study. The experimental results suggest that appropriate prior strength is required for good performance in both behavioral and cognitive flexibility (Supplementary Results 2.4); This is probably because it is better to ignore the prior information and use a copy of the last observations to enhance only behavioral flexibility. On the other hand, when inferring latent states, such as cognitive flexibility, both higher-order prior knowledge and observation are important to avoid adapting to accidental changes rather than true context switching. Therefore, there was a trade-off between behavioral and cognitive flexibility, and the system controlling exact prior strength may exist in humans and animals. Mathematically, this calculation may be automatically executed using Bayesian optimization or the prediction errors in the previous time step, such as deep active inference (39).

Furthermore, the variances of metrics, particularly cognitive flexibility and generative hierarchy, were big even in the same condition. The unstable results of learning were reported in the

deep learning domain and often observed in the representation learning (92). Reducing these high variances is a new and important topic that needs to be discussed in both artificial neural networks and cognitive neuroscience domains.

4.5. Conclusion

In this study, to understand the relationships among hierarchical Bayesian representation, neural dynamics, the environment, and behavioral phenotype in developmental disorders, we proposed a new framework combining PV-RNN and the environment with hierarchical generative process. Through the experiments using this framework, we investigated whether inflexibility resulted from various factors (e.g., stochasticity in neural dynamics and the level of noises included in the environmental stimulus) with focus on hierarchical Bayesian representation learning. As a result, we found that the networks with normal stochastic dynamics acquired hierarchical and probabilistic representation reflecting the environmental structures and adapted flexibly to the new environment. Furthermore, we found that even if the networks possessed risks for reduced flexibility, such as low stochasticity in neural dynamics, they could be ameliorated by increasing ambiguity in the external environment. The networks with high stochastic dynamics had the hierarchical representations in terms of passive inference but did not have sufficient hierarchical and disentangled representations in terms of active generation. Therefore, our proposed method is useful for understanding atypical development such as reduced flexibility observed in ASD by bridging multiple factors including the neural dynamics, acquisitions of hierarchical representation, and the external environment.

Data availability statement

The data presented in the study are deposited in the Github repository, which could be accessed via https://github.com/ncnp-cpsy/SimulatingDevelopmentalDiversity.git.

Author contributions

TS, JT, and YY designed the experiment and analysis. TS performed the experiment and analyzed the data. AA developed the model and advised on the programming of the experiment. TS, AA, JT, MH, TH, and YY wrote the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was partly supported by JSPS KAKENHI (JP20H00001 and JP20H00625), JST CREST (JPMJCR16E2 and JPMJCR21P4), JST Moonshot R&D (JPMJMS2031), JST SPRING (JPMJSP2120), and Intramural Research Grant (3-9 and 4-6) for Neurological and Psychiatric Disorders of NCNP.

Conflict of interest

AA was employed by Geobotica.

The remaining 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1080668/full#supplementary-material

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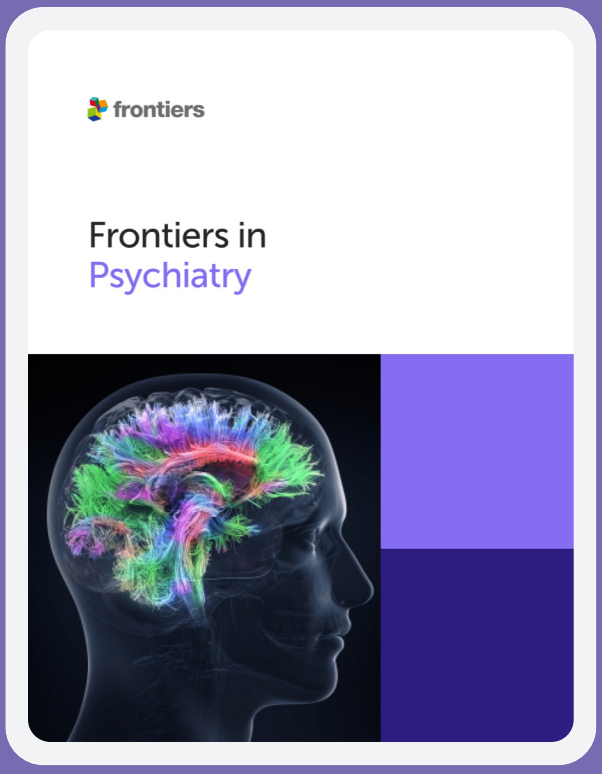

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