

Methods and applications in psychology for clinical settings

Edited by

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and Tindara Capri

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Methods and applications in psychology for clinical settings

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Editorial: Methods and applications in Psychology for Clinical Settings

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Psychology for Clinical Settings, experimental techniques, technology, methods, general psychology

Editorial on the Research Topic

Methods and applications in Psychology for Clinical Settings

The main aim of this Research Topic was to highlight the latest experimental techniques and methods used to investigate relevant questions in Psychology for Clinical Settings. This Research Topic includes 11 papers, six original research articles, two opinion articles, one mini review, and one brief research report, which include recent techniques and up-to-date methods that contribute to advancing the science of Psychology for Clinical Settings.

The first study (Jerković et al.) examined the factor structure, internal consistency, and correlates of the Croatian version of the Hospital Anxiety and Depression Scale (HADS) for patients with multiple sclerosis (MS). A total of 179 patients with MS and 999 healthy subjects completed the HADS. The results of this study demonstrated that the HADS is a reliable and valid self-assessment scale and suggested that it be used in the clinical monitoring of the psychiatric and psychological status of patients with MS.

The second study (Cobo et al.) investigated whether motor anticipation in handwriting can be an indicator of motor dysfunction in schizophrenia. A total of 24 subjects with a diagnosis of schizophrenia and 24 healthy subjects performed an easy and brief handwriting task. The authors used three measures to evaluate motor anticipation: the time per stroke (duration), the path of the pen for each stroke (trajectory), and the number of velocity peaks (disfluency). The results indicated that patients with schizophrenia did not exhibit any signs of motor anticipation. This study supported the idea of using handwriting analysis as a quantitative, objective, and reliable tool to detect motor alterations in schizophrenia.

Two studies included in this Research Topic described the effects of two different therapeutic techniques used during the COVID-19 pandemic. The first study (Zwilling et al.) examined the wellbeing level of mothers of girls and women with Rett Syndrome (RTT) who were involved in a home-based, remotely supervised motor rehabilitation program before and during the Italian COVID-19 lockdown. In total, 40 subjects with RTT were randomly assigned to two groups: Group 1 received the intervention immediately before the lockdown, and Group 2 received it during the lockdown. The motor rehabilitation program consisted of an individualized daily physical activity program carried out for 12 weeks by the participants' parents and supervised every two weeks through Skype calls to plan, monitor, and accommodate individual activities to the participants' home lives. The results showed that the participants' mothers' wellbeing was similar in the two groups, indicating that the

lockdown influenced the effect of the rehabilitation program. Thus, this study proposed that the motor intervention helped the mothers of patients with RTT to manage the new daily routine at home.

The second study, by Tao et al., described a new therapeutic technique to reduce psychological symptoms during the COVID-19 pandemic in China. This technique was the “Moving to Emptiness Technique” (MET), which combined traditional Chinese culture with relaxation and the operational process of Cognitive Behavioral Therapy (CBT). A total of 17 therapists treated 107 subjects using the MET. The participants were subdivided into two groups: a high-frequency symptom group and a low-frequency symptom group. The results showed that symptoms decreased significantly in both groups after the intervention, indicating that MET is a good therapeutic technique. However, the authors suggested caution in the interpretation of their results due to the small sample size.

Another study by Huang et al. examined the effects of hospital culture, self-efficacy, and achievement motivation on healthcare workers' perceived delivery of patient-centered care (PCC). In total, 1,612 healthcare workers from different levels of public hospitals completed a survey interview. The results suggested that self-efficacy, achievement motivation, and hospital culture were necessary to promote the use of PCC among healthcare workers.

The last research article (Ho et al.) included in this Research Topic investigated the effects of virtual reality nature experiences on the psychological and physiological stress of furniture factory employees. A total of 35 factory workers were assigned to two groups: an experimental group and a comparison group. The experimental group received virtual reality experiences consisting of 30-min nature-based 360° videos played in a headset. The intervention was conducted once a week for 12 weeks. The comparison group received no intervention; participants in this group freely performed their activities during their afternoon break. The results indicated that the experimental group showed an improvement in distress, depression, and anxiety compared to the comparison group.

With reference to two opinion articles included in the present Research Topic, the first by Metcalfe discussed practical considerations for behavioral health researchers when using open science. The author encouraged researchers to consider open science practices for their projects in pediatric medicine because they can be a viable tool for data reporting and connecting families and peers within pediatric-focused institutions. The second opinion article (Stasolla et al.) discussed the use of technology in the evaluation and recovery of post-coma and altered consciousness patients. In particular, the authors proposed the integration of assistive technology-based devices and virtual reality setups for both assessment and recovery purposes.

A mini-review (Wen et al.) examined the state of the art in Life Design Counseling (LDC), showing the lack of attention

to clients from diverse backgrounds and professional counselors, the lack of different methods in the intervention process, and the lack of research on LDC. Abdel-Wahab et al. wrote a brief report to introduce clinical guidelines for the treatment of resistant depression in Egyptian patients. The guidelines were consistent with international recommendations and were the first in Egypt. However, the proposed guidelines had a limitation related to the fact that the panel consisted of only eight doctors.

The present Research Topic offers an overview of the latest experimental techniques and methods used to investigate fundamental issues in Psychology for Clinical Settings. The studies and opinion articles included in this Research Topic were conducted in different clinical populations and settings, which may represent a strength for the audience, researchers, and health professionals. Given the collected findings and the worldwide high prevalence of mental illness (World Health Organization, 2022a), continuous efforts to explore new clinical intervention and evaluation methodologies must be strongly encouraged. The latter is of special relevance after the impact of the pandemic (World Health Organization, 2022b).

Author contributions

TC drafted the first version of this editorial. All authors contributed to and approved the final version.

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Psychometric Properties of the HADS Measure of Anxiety and Depression Among Multiple Sclerosis Patients in Croatia

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Depression and anxiety are common complaints in patients with multiple sclerosis (MS). The study objective was to investigate the factor structure, internal consistency, and correlates of the Croatian version of the Hospital Anxiety and Depression Scale (HADS) in patients with MS. A total of 179 patients with MS and 999 controls were included in the online survey. All subjects completed the HADS and self-administered questionnaires capturing information of demographic, education level, disease-related variables, and the Multiple Sclerosis Impact Scale-29 (MSIS-29). Psychometric properties were examined by estimating the validity, reliability, and factor structure of the HADS in patients with MS. The two HADS subscales (anxiety and depression) had excellent internal consistencies (Cronbach's α value 0.82–0.83), and factor analysis confirmed a two-factor structure. The convergent validity of the HADS subscales appeared to be good due to the significant correlations between HADS and MSIS-29. Receiver operating characteristic (ROC) analysis indicates that the HADS subscales have a significant diagnostic validity for group differentiation. Hierarchical regression analysis using MSIS-29 subscales as criterion variables showed consistent evidence for the incremental validity of the HADS. The HADS is a reliable and valid self-assessment scale in patients with MS and is suggested to be used in clinical monitoring of the psychiatric and psychological status of patients with MS.

Keywords: Hospital Anxiety and Depression Scale (HADS), psychometrics, depression, multiple sclerosis, anxiety

INTRODUCTION

Multiple sclerosis (MS) has a high prevalence of depression, anxiety, and stress comorbidities (Marrie et al., 2018; Karimi et al., 2020). Comorbid depression and anxiety disorders affect more than 20% of the MS population (Beiske et al., 2008; Fiest et al., 2015; Marrie et al., 2015, 2018; Karimi et al., 2020). Various screening instruments have been used to evaluate depression, anxiety, and

stress in a clinical population of people with MS (pwMS) and non-clinical populations, including the Beck Depression Inventory-II (BDI-II) (Beck and Steer, 1990; Watson et al., 2014), Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Honarmand and Feinstein, 2009), and Depression, Anxiety, and Stress Scale-21 (DASS-21) (Lovibond P.F. and Lovibond S.H., 1995; Lovibond S.H. and Lovibond P.F., 1995; Rogić Vidaković et al., 2021). The HADS is one of the most commonly used scales for assessing anxiety and depression among patients in a general hospital setting (Zigmond and Snaith, 1983; Mitchell et al., 2010). Watson et al. (2014) validated anxiety and depression measures in pwMS, confirming HADS as an appropriate questionnaire to assess depression and anxiety in pwMS. Recently Rogić Vidaković et al. (2021) reported psychometric properties of the DASS-21 scale in pwMS. The normative data for the HADS in pwMS were provided in pwMS in different languages (Honarmand and Feinstein, 2009; Atkins et al., 2012; Watson et al., 2014; Marrie et al., 2018; Pais-Ribeiro et al., 2018). A systematic review of the structure of the HADS (Cosco et al., 2012) found inconsistencies in the latent structure of the scale, which were mainly related to the different latent variable analysis methods [exploratory factor analysis and confirmatory factor analysis (CFA)] used for HADS. Regarding factor structure of HADS in pwMS MS, Pais-Ribeiro et al. (2018) conducted CFA and exploratory factor analysis providing support for a two-factor HADS structure in pwMS. There have also been specific problems in the translated versions and cross-cultural use of the HADS (i.e., authors from the same country do not apply the identical versions of HADS translations) (Wichowicz and Wiecezorek, 2011; Maters et al., 2013; Watrowski and Rohde, 2014). The HADS has been validated in a diverse group of subjects, including those in primary care patients (el-Rufaie and Absood, 1995), geriatric patients (Flint and Rifat, 1996), or cancer patients (Mitchell et al., 2010). In addition, specific HADS cut-off points have been established for patients with cancer (Ibbotson et al., 1994), gynecological disorders (Abiodun, 1994), stroke (Johnson et al., 1995), and for pwMS (Honarmand and Feinstein, 2009). In previous studies conducted in Croatia, the HADS has been used in medical conditions other than MS (Filipovic-Grcic et al., 2010; Vuletić et al., 2011; Ostojić et al., 2014; Pokrajac-Bulian et al., 2015; Miljanović et al., 2017), but no study determined psychometric properties for the Croatian version of the HADS in pwMS. Two studies conducted in Croatia with HADS stated the origin of the Croatian version of HADS (Miljanović et al., 2017; Galić et al., 2020), and so far, only Miljanović et al. (2017) investigated metric properties of HADS in terminal cancer patients but having relatively smaller convenient sample size without a control group.

OBJECTIVE

The purpose of this online survey, was to evaluate the metric properties of the Croatian version of the HADS in terms of validity, reliability, and factor structure in pwMS. The study compared HADS subscales with a non-clinical population (control healthy subjects) and published data in

pwMS (Watson et al., 2014; Pais-Ribeiro et al., 2018). The study also investigated the incremental validity of HADS using the Multiple Sclerosis Impact Scale-29 (MSIS-29) (Hobart et al., 2001) and relevant demographic and disease-related variables as the criterion variables.

MATERIALS AND METHODS

Study Population and Procedure

The subjects with MS were recruited by advertising through the Association of Multiple Sclerosis Societies of Croatia (AMSSC). A total of 179 pwMS and 999 control subjects were included in the online survey. The demographic factors, education level, and disease-related factors for pwMS and control subjects are presented in **Table 1**. In the group of pwMS, 84% were women with a mean age of 41.3 ± 11.5 years, and 16% were men with a mean age of 42.7 ± 9.9 years. Most pwMS were right-handed (92.7%) and 35–49 years old (49%). Most pwMS had high school degrees (49.1%) and graduate university degrees (23.5%). Most of the pwMS were diagnosed with MS disease between 0 and 5 years (41.4%), 26.7% were diagnosed between 6 and 11 years, and 31.8% reported having MS over 11 years. The mean duration of the disease for pwMS was 8.7 ± 7.2. A majority of the people declared to have relapsing-remitting MS (RRMS) (70.4%), while others reported having secondary progressive MS (SPMS) (7.8%) and primary progressive MS (PPMS) (10.6%). Some pwMS (11.2%) did not provide information on the type of MS. The median Expanded Disability Status Scale (EDSS) score for all pwMS was 3.5 ± 3.5. Of the 179 pwMS, 51.8% had comorbidities, of which the most common were endocrine, nutritional, and metabolic diseases (9.9%) and diseases of the circulatory system (7.8%).

In the group of control subjects, 81% of participants were women with a mean age of 39.8 ± 10.3 years, and 19 percent (19%) were men with a mean age of 40.3 ± 10.1 years. Most of the controls were right-handed (93.4%) and between 35 and 49 years old (51%), and most of them had graduate university degrees (43.7%) and high school degrees (25.6%). Of a total, 27.6% of people had comorbidities, of which the most common were endocrine, nutritional, and metabolic diseases (8.2%) and diseases of the circulatory system (5.2%).

The data were collected *via* a Google Forms survey from December 16, 2020, until January 13, 2021.

Measurements and Data Collection

Demographic Information and Disease-Related Variables

The participants were characterized by demographic information (age, sex, and handedness), educational, and disease-related factors, including duration of the disease, MS type (Lublin et al., 2014), and the score on the EDSS (McDonald et al., 2001).

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond and Snaith, 1983) is a self-report scale consisting of two subscales, one measuring anxiety with seven items (HADS-A) and one measuring depression with seven items

(HADS-D). The subject gives answers to each question on a 4-point (0–3) Likert scale and answering how he/she has been feeling in the past week. Items 1, 3, 5, 7, 9, 11, 13 belong to the anxiety subscale, while items: 2, 4, 6, 8, 10, 12, 14 belong to the depression subscale. The total score is obtained by summing the scores within each subscale. According to Pais-Ribeiro et al. (2018) interpretation, the score 0–7 represents “normal,” 8–10 “mild,” 11–14 “moderate,” and 15–21 “severe.” In the present study, the cut-off score of ≥ 8 and of ≥ 11 was used for HADS subscales (Botega et al., 1995; Bjelland et al., 2002; Honarmand and Feinstein, 2009; Brennan et al., 2010; Watson et al., 2014; Litster et al., 2016).

Multiple Sclerosis Impact Scale-29

The MSIS-29 is a self-report scale capturing MS disease's impact from a patient's physical and psychological perspective (Hobart et al., 2001; Rogić Vidaković et al., 2021). The MSIS-29 is a self-report scale capturing MS disease's impact from a patient's physical and psychological perspective. The scale is structured into two subscales, a 20-item scale for measuring physical impact and a 9-item scale for measuring the psychological impact of the disease. The “physical impact” subscale consists of items from 1 to 20. The subscale of “psychological impact” consists of items from 21 to 29. The patient is instructed to read each statement about the disease's impact on his/her everyday life in the past 2 weeks. For each statement, the patient's task is to circle the

TABLE 2 | Score classification percentages of HADS anxiety and depression subscales for pwMS and control subjects.

| | Control subjects | | pwMS | |
|------------------|------------------|------------|------------|------------|
| | HADS-A (%) | HADS-D (%) | HADS-A (%) | HADS-D (%) |
| (0–7) normal | 65.7 | 79.7 | 41.4 | 50.3 |
| (8–10) mild | 21.3 | 12.9 | 22.9 | 21.8 |
| (11–14) moderate | 9.6 | 7.2 | 26.8 | 24.0 |
| (15–21) severe | 3.4 | 0.2 | 8.9 | 3.9 |
| ≥ 8 | 34.3% | 20.3% | 58.6% | 49.8% |
| ≥ 11 | 13% | 7.4% | 35.7% | 27.9% |

HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

number that best describes his/her condition and answering on a 5-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely. The patient's scores on two subscales generated by summing individual items can be transformed to a scale of 0–100, with higher scores indicating a more severe disease burden.

Translation and Cultural Adaptation

Croatian translation of the HADS questionnaire was used in the evaluation of anxiety and depression in patients suffering from oncological (Miljanović et al., 2017) and neurological (Vuletić et al., 2011; Ostojić et al., 2014) diseases or other conditions (Filipovic-Grcic et al., 2010). Recently, HADS was used in the general Croatian population during the COVID-19 infection (Galić et al., 2020). Among the mentioned studies that used the Croatian translation of HADS, two studies stated the origin of the translated version of the HADS questionnaire. Miljanović et al. (2017) used the purchased Croatian translation of HADS from Mapi Research Trust, and Galić et al. (2020) used the translated Croatian version of HADS from Pokrajac-Bulian et al. (2015).

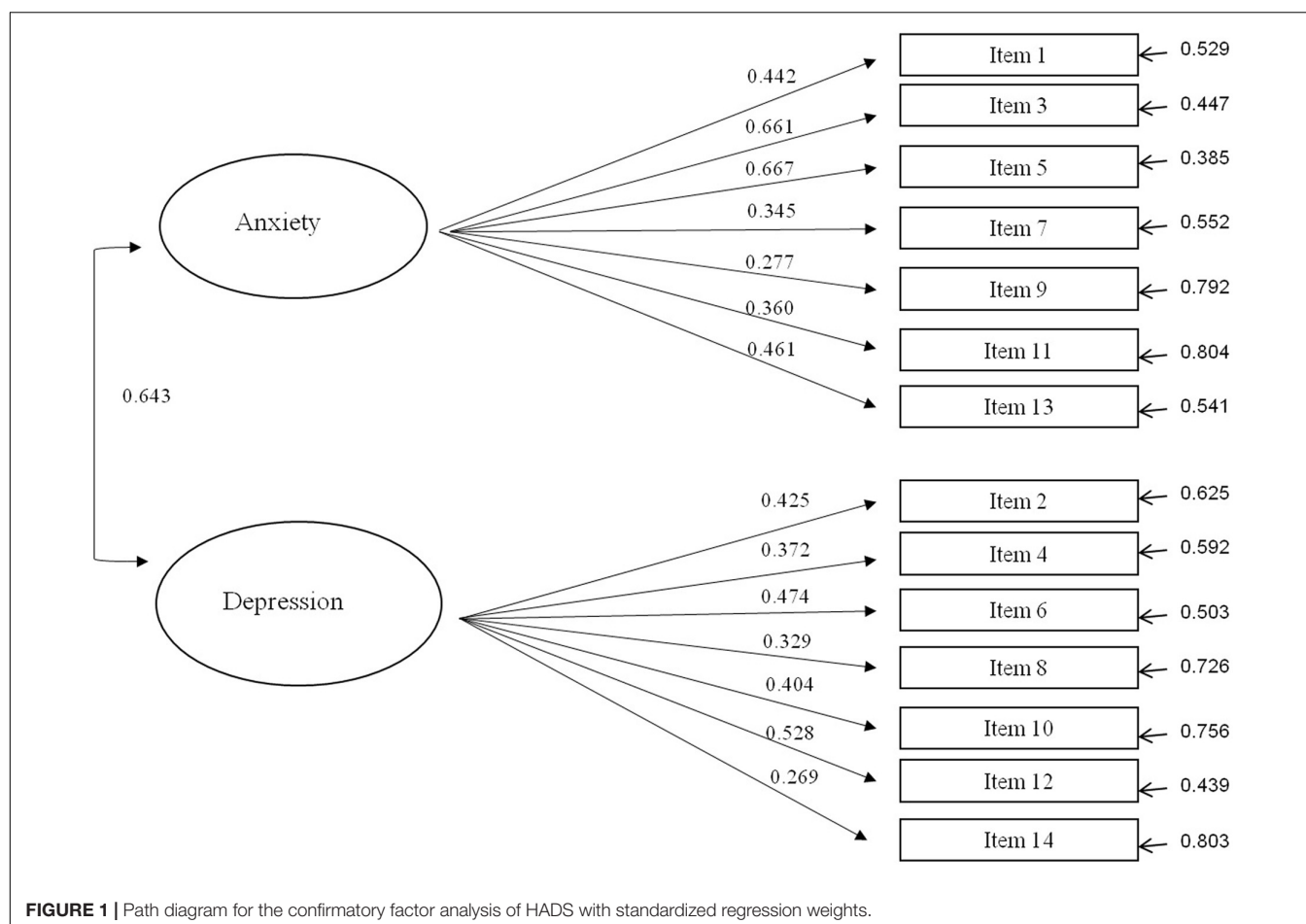
The reason why our group initiated the HADS translation procedure is the fact that the translation of HADS from Mapi Research Trust is not entirely in the spirit of the Croatian language according to the authors' opinion, and all authors of this study agreed not to use it in the present study. Also, the Croatian version of HADS from Mapi Research Trust is not publicly free of charge to the research community. Further, since Pokrajac-Bulian et al. (2015) did not detail the process of translating HADS into Croatian, having a relatively small sample size of obese people, and the main aim of the study was not the validation of HADS in the Croatian population, we did not consider it appropriate.

Therefore, our group translated HADS following current recommendations, methodological approaches, and guidelines in the process of translating, adapting, and cross-validating instruments (Sousa and Rojjanasirrat, 2011). One author of this study (MRV) and Professor of English language (Professor Dalibora Behmen – DB, from the University of Split School of Medicine), both natives in the Croatian language, translated the HADS from English to Croatian. Next, the English language professor (DB) compared both translated versions of HADS in the Croatian language and produced the final version of the questionnaires. Another independent English language professor (University of Split) who had no insight into the original English

TABLE 1 | Characteristics of study participants.

| | Control subjects (N = 999) | pwMS (N = 179) |
|--|-------------------------------|--------------------|
| Age in years (mean \pm SD) | 39.9 \pm 10.2 | 41.6 \pm 11.3 |
| Age (range) | 20–74 | 19–75 |
| Sex | | |
| Female | 81% | 84% |
| Male | 19% | 16% |
| MS type | | |
| RRMS | | 70.4% |
| SPMS | | 7.8% |
| PPMS | | 10.6% |
| Not known | | 11.2% |
| Years of MS disease (mean \pm SD) | | 8.7 \pm 7.2 |
| EDSS (median \pm IQR, range) | | 3.5 \pm 3.5, 0–9 |
| EDSS* | | 2.5 \pm 2.5 |
| EDSS** | | 6 \pm 2 |
| Self-report scales (mean \pm SD) | | |
| HADS-A | 6.5 \pm 3.6 | 8.8 \pm 4.1 |
| HADS-D | 5.1 \pm 3.1 | 7.8 \pm 3.9 |
| MSIS-29 PHYS | | 46.6 \pm 17.2 |
| MSIS-29 PSY | | 24.3 \pm 8.8 |

SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; EDSS*, fully preserved mobility 0–4.5; EDSS**, partially or fully impaired mobility 5–9.5; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PHYS, MSIS-29 Physical subscale; MSIS-29 PSY, MSIS-29 Psychological subscale.



version translated the last Croatian version of the questionnaires back into the English language, completing the final adaptation of the Croatian version of HADS used in this study (**Supplementary Material**).

Validation Procedure

Internal consistency of HADS was estimated by Cronbach's alpha coefficients and inter-item correlations. CFA was carried out to test the validity of the two-factor and one-factor models. Data were analyzed by using the generalized least square (GLS) method and the maximum likelihood (ML) estimator. Several criteria [ML Chi-square, root mean square (RMS) standardized residual, Steiger Lind RMSEA, and McDonald non-centrality index] are reported with an emphasis on the root mean square error of approximation (RMSEA), the most commonly used fit index. Convergent validity was demonstrated by the correlation between HADS and MSIS-29 subscales. Concurrent validity was assessed by comparisons between a group of pwMS and control subjects. A receiver operating characteristic (ROC) curve was used to determine the optimum cut-off score for each HADS subscales – the score that yielded the best balance between sensitivity and specificity. Furthermore, comparisons were also provided between published data on psychometric properties of the HADS (Watson et al., 2014; Pais-Ribeiro et al., 2018). Pais-Ribeiro et al.

(2018) offered psychometric properties of HADS, analyzing a sample of 380 pwMS (63.9% female; mean age 40.0 ± 10.9 years; range: 16–71 years) from the outpatient Neuroimmunology Clinic at a Central Hospital in Porto, Portugal, while Watson et al. (2014) included 34 pwMS (71% female and (29%) male; mean age 48.5 (11.1) from England.

The incremental validity of HADS was assessed by the hierarchical regression model using the MSIS-29 and relevant demographic and disease-related factors as criterion variables. Age, sex, EDSS, type of MS, duration of the disease were entered into the first step, while the scores on HADS subscales were added in the second step.

Statistical Analyses

Parameters of skewness and kurtosis were tested for HADS and MSIS-29 scales. Results indicated acceptable values for the parametric statistic. Mean value comparisons between our study and published studies using HADS (Watson et al., 2014; Pais-Ribeiro et al., 2018) in pwMS and differences between relevant disease-related variables were carried using *t*-tests, Chi-square test, Mann-Whitney *U* test, Kruskal-Wallis test, and variance analysis (ANOVA). The *post hoc* Bonferroni test was calculated when using multiple comparisons. Levene's test was used to assess the equality of variances between

groups. Correlation analyses were conducted using Pearson's r coefficient and Spearman rank-order correlation (ρ). Descriptive statistics of relevant participants' characteristics and applied scales were summarized by N , percentage, mean and standard deviations, median, and interquartile range. Psychometric properties were examined by estimating internal consistency, factor structure, convergent, concurrent, and incremental validity of the HADS. In all calculations, a p -value of <0.05 was considered statistically significant. Data analysis was performed using the software Statistica 12.

RESULTS

Overview Results

The demographic characteristics, disease-related variables, and mean results on self-rating scales (HADS and MSIS-29) of pwMS and healthy subjects are shown in **Table 1**. No significant sex ($\chi^2 = 0.05$, $p = 0.82$, $p > 0.05$) and age ($t = -4.84$, $df = 1390$, $p > 0.05$) differences were found between pwMS and control subjects. The scores on HADS depression ($t = -2.34$, $df = 177$, $p < 0.05$) and MSIS-29 physical ($t = -2.94$, $df = 177$, $p < 0.01$) subscales varied significantly by MS type in pwMS. People with RRMS type (Mean_{HADS-D} = 7.4; Mean_{MSIS-PHYS} = 43.9) were less depressed and had better physical health than people with SPMS (Mean_{HADS-D} = 10.0; Mean_{MSIS-PHYS} = 55.9) and PPMS (Mean_{HADS-D} = 10.1; Mean_{MSIS-PHYS} = 56.4). For women, HADS scores on depression subscale varied significantly with MS type. The women with RRMS were less depressed [$\chi^2(df=3) = 8.81$; $p < 0.05$] than women with SPMS and PPMS. However, the sex differences were found in pwMS in achievement on the HADS depression subscale, indicating that the male participants have a higher depression score than females with MS ($t = -2.10$, $df = 177$, $p < 0.05$). Further, in pwMS, significant differences were found between different age groups (19–34; 35–39; and 40–75 years) for HADS depression subscales ($F = 12.34$; $p < 0.001$) and MSIS-29 physical impact subscale ($F = 12.16$; $p < 0.001$). *Post hoc* results suggest an increase in depression and poorer physical health in older pwMS than younger pwMS ($p_{\text{younger vs. older}} < 0.001$; $p_{\text{middle age vs. older}} = 0.04$; $p < 0.05$; $p_{\text{middle age vs. younger}} = 0.04$; $p < 0.05$).

Further, the participants who suffer from MS for a more extended period (more than 11 years) have poorer physical health on the MSIS-29 than those who are younger and suffer from MS for a shorter period, less than 5 years ($F = 3.29$, $p < 0.05$). Furthermore, when levels of physical health and depression were compared for types of MS (1-participants with RRMS; 2-participants with other types of MS/SPMS, PPMS, MS type not provided), a significant difference was also found ($t_{\text{depression}} = 2.34$, $df = 177$, $p < 0.05$; $t_{\text{physical}} = -2.54$, $df = 177$, $p < 0.001$). Participants with RRMS had better physical health and were less depressed than people with SPMS, PPMS, and those who did not provide information on MS type.

Table 2 presents the score classification percentages of HADS anxiety and depression subscales for pwMS and control subjects. According to score classification for the HADS depression subscale, 49.8% of the pwMS exhibited a score of ≥ 8 compared

to 20.3% of control subjects. For HADS anxiety score, 58.6% of pwMS presented a score ≥ 8 , compared to 34.3% of control subjects. Moreover, based on the score of ≥ 11 , for the HADS depression subscale, 27.9% of pwMS exhibited moderate or severe depression compared to 7.4% of control subjects. For the HADS anxiety subscale, 35.7% of pwMS presented a score ≥ 11 compared to 13% of control subjects. The prevalence of depression in pwMS seems to be higher in comparison to anxiety.

Psychometric Properties of the Hospital Anxiety and Depression Scale (HADS)

Internal Consistency

Expressed by Cronbach's α coefficients, both HADS subscales ($\alpha_{\text{HADS-A}} = 0.82$ to $\alpha_{\text{HADS-D}} = 0.83$) and MSIS-29 subscales ($\alpha_{\text{MSIS-PHYS}} = 0.82$ to $\alpha_{\text{MSIS-PSY}} = 0.81$) had excellent internal consistency. Values for both HADS and MSIS-29 scales are considered indicative of good reliability. Inter-item correlations for HADS and MSIS-29 scales were > 0.3 , meaning that all items on each subscale correlate very well with the scale overall.

Factor Analysis of the Hospital Anxiety and Depression Scale (HADS)

Indicated by almost all obtained fitting parameters except for a slightly higher ratio between Chi-square and corresponding df (Kenny, 2020), CFA confirmed the original structure of the HADS in general (**Figure 1** and **Table 3**). Namely, HADS, as expected, shows a primarily two-factor structure (separate dimensions of anxiety and depression) with mutually significantly correlated factors. HADS-A subscale explained 18.66% of factor variance and with HADS-D subscale 21.85% of the variance. The CFA for the one-factor solution was also reported (**Table 3**), but all fit indices support the retention of the two-factor solution. The Steiger Lind RMSEA index was used as the main and most commonly used criteria for accepting models. Cut-off RMSEA

TABLE 3 | Fit indices for one-factor and two-factor model of HADS (CFA).

| | One-factor solution | Two-factor solution |
|-------------------------------|----------------------|-----------------------|
| ML Chi-square | 752.03 ($df = 77$) | 128.315 ($df = 28$) |
| RMS standardized residual | 0.059 | 0.024 |
| Steiger Lind RMSEA | 0.107 | 0.051 |
| McDonald non-centrality index | 0.643 | 0.93 |

Rms, root mean square; *Rmse*, root mean square error of approximation; *ML*, maximum likelihood.

TABLE 4 | Pearson correlation coefficient for HADS and MSIS-29 scale ($N = 179$).

| | HADS-A | HADS-D | MSIS-29 PHYS | MSIS-29 PSY |
|--------------|--------|--------|--------------|-------------|
| HADS-A | – | 0.54** | 0.33** | 0.69** |
| HADS-D | | – | 0.54** | 0.61** |
| MSIS-29 PHYS | | | – | 0.57** |
| MSIS-29 PSY | | | | – |

** $p < 0.01$; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PSY-MSIS-29 Psychological subscale.

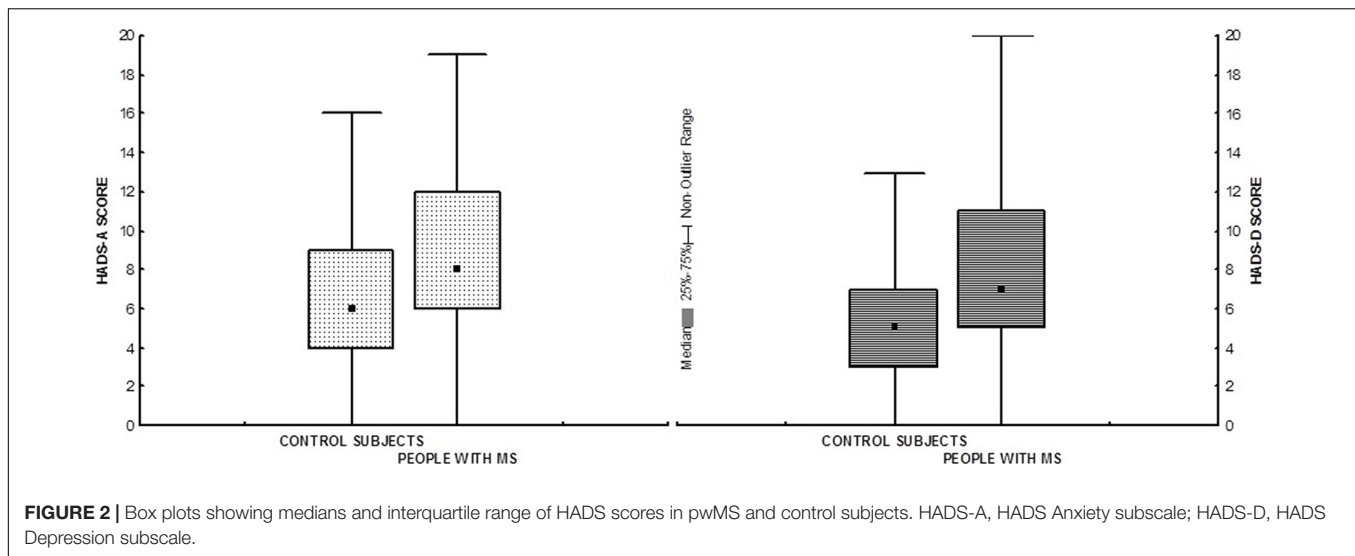


FIGURE 2 | Box plots showing medians and interquartile range of HADS scores in pwMS and control subjects. HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

value of <0.05 indicates a “close fit,” and that <0.08 suggests a reasonable model–data fit (e.g., Browne and Cudeck, 1993; Jöreskog and Sörbom, 1993).

Convergent Validity of the Hospital Anxiety and Depression Scale (HADS)

Convergent validity was demonstrated by the correlations of the HADS subscales and the MSIS-29 subscales (Table 4) for pwMS. HADS anxiety and depression subscales have a significant moderate correlation ($r = 0.54$; $p < 0.001$). Moreover, both HADS subscales are correlated with MSIS-29 subscales, noting that the correlations of HADS subscales are higher with the psychological MSIS-29 subscale ($r = 0.61$ – 0.69 ; $p < 0.01$) compared to the physical MSIS-29 subscale ($r = 0.33$ – 0.54 ; $p < 0.01$). Correlation coefficients between HADS subscales and MSIS-29 subscales indicate weak and moderate correlations.

Concurrent Validity

Concurrent validity was demonstrated by differences between MS and control subjects. HADS mean values for pwMS were significantly higher (Mann–Whitney U test; $z_{\text{anxiety}} = 6.98$, $p < 0.01$; $z_{\text{depression}} = 8.588$, $p < 0.01$) than those reported in control subjects (Figure 2). A non-parametric test was done because Levene’s test for homogeneity of variances was significant (both HADS-A and HADS-D). Further, compared to the results of the current study with Watson et al. (2014) and Pais-Ribeiro et al. (2018), depression and anxiety were not equally represented (Table 5). The results on both subscales were significantly higher in our sample than those presented by Pais-Ribeiro et al. (2018), and the difference is significantly more pronounced when it comes to HADS-D. Compared to Watson et al. (2014), there were no significant differences in depression levels, while the difference in anxiety exists (small effect size).

Receiver operating characteristic analysis (Table 6) indicated that for the HADS-A, the highest value of the Youden Index ($J = 0.245$) was obtained for a cut-off point of >7 and the HADS-D at the cut-off point of >6 ($J = 0.328$). For the HADS-A, the

statistically significant AUC was 0.664 ($p < 0.001$) with a 95% confidence interval of 0.635–0.692. For the HADS-D, AUC was 0.702 ($p < 0.001$) with 95% confidence interval 0.675–0.728. Both parameters (J and AUC) indicate that the HADS-A and the HADS-D have a significant diagnostic validity for group differentiation.

Incremental Validity

Table 7 represents the results of multiple hierarchical regression analyses and the incremental validity of the HADS. Results indicate whether HADS-A and HADS-D contribute to the explanation of MSIS-29 variance (incremental validity) in relation to some examined sociodemographic variables, MS type, and EDDS.

For the physical impact on the MSIS-29, the first set of predictor variables (age, sex, EDSS, MS type, and disease duration) only sex had a significant β coefficient. Step 2, which included HADS subscales, revealed that these variables

TABLE 5 | The HADS results from the present study and comparisons between published studies.

| | | HADS-A | HADS-D |
|--|-----------|------------------|-------------------|
| Present study $N = 179$ | Mean (SD) | 8.82 (4.11) | 7.80 (3.99) |
| Watson et al. (2014) $N = 34$ | Mean (SD) | 7.2 (5.4) | 8.1 (5.9) |
| | t | 1.99 | 0.37 |
| | df | 211 | 211 |
| | p | 0.04; $p < 0.05$ | 0.71; $p > 0.05$ |
| Pais-Ribeiro et al. (2018) $N = 380$ | Mean (SD) | 7.94 (4.31) | 5.63 (4.01) |
| | t | 2.29 | 5.98 |
| | df | 557 | 557 |
| | p | 0.02; $p < 0.5$ | 0.00; $p < 0.001$ |

HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale.

TABLE 6 | Psychometric properties of HADS-A and HADS-D at different cut-off scores (ROC analysis).

| | Sensitivity (95% CI) | Specificity (95% CI) | +LR | −LR |
|----------------------|----------------------|----------------------|------|------|
| HADS-A scores | | | | |
| ≤6 | 65.92 (58.5–72.8) | 54.44 (51.1–57.7) | 1.45 | 0.63 |
| ≤7 | 58.66 (51.1–66.0) | 65.39 (62.2–68.5) | 1.69 | 0.63 |
| ≤8 | 48.04 (40.5–55.6) | 73.38 (70.4–76.2) | 1.81 | 0.71 |
| ≤9 | 43.02 (35.7–50.6) | 80.94 (78.2–83.4) | 2.26 | 0.70 |
| ≤10 | 35.75 (28.7–43.2) | 87.19 (84.8–89.3) | 2.79 | 0.74 |
| ≤11 | 27.37 (21.0–34.5) | 90.25 (88.1–92.1) | 2.81 | 0.80 |
| ≤12 | 20.11 (14.5–26.7) | 93.32 (91.5–94.9) | 3.01 | 0.86 |
| HADS-D scores | | | | |
| ≤6 | 61.45 (53.9–68.6) | 71.37 (68.5–74.2) | 2.15 | 0.54 |
| ≤7 | 49.72 (42.2–57.3) | 79.58 (76.9–82.0) | 2.43 | 0.63 |
| ≤8 | 43.58 (36.2–51.2) | 85.39 (83.0–87.5) | 2.98 | 0.66 |
| ≤9 | 35.20 (28.2–42.7) | 89.19 (87.1–91.0) | 3.26 | 0.73 |
| ≤10 | 27.93 (21.5–35.1) | 92.49 (90.7–94.0) | 3.72 | 0.78 |
| ≤11 | 21.23 (15.5–28.0) | 96.30 (94.9–97.4) | 5.73 | 0.82 |
| ≤12 | 12.85 (8.3–18.7) | 98.70 (97.8–99.3) | 9.87 | 0.88 |

+, LR likelihood ratio for a positive result; −, LR likelihood ratio for a negative result; CI, confidence interval.

contribute to the explanation of an additional 18% of physical impact variance. Among these predictors, only HADS depression had significant β , which is positive, meaning that the greater depression is accompanied by greater physical impact (Table 7). For the psychological impact on the MSIS-29, age, among predictors included in the first step, significantly predicted psychological impact, accounting for 13% of the variance. Simultaneously, HADS depression and anxiety subscales entered in the second step explained 40% of the psychological impact variance. Anxiety and depression subscale significantly

contributed to the explanation of the criterion variable. For both criterion variables (MSIS-29 physical and psychological impact) HADS has been shown to have significant incremental validity in the explanation of MSIS-29, especially when it comes to the second criterion, MSIS-29 psychological impact. The additional contribution of physical impact is 13%, and for psychological impact, even 40%.

DISCUSSION

Anxiety and depressive disorders are among the most common psychiatric illnesses highly comorbid with each other and considered to belong to the broader category of internalizing disorders (Kalin, 2020). More than 50% of the patients with major depression have significant anxiety and were considered to have anxious depression (Fava et al., 2004; Beijers et al., 2019). When looking into a healthy population compared to pwMS in terms of developing mood disorders, the risk of depression, anxiety, and stress are higher in MS patients than in healthy subjects (Pham et al., 2018). The etiology of MS disease is not yet known and factors such as immune system deficiency, genetic predisposition, lack of vitamin D, Epstein-Barr virus, family background, geographical region, stress, and lifestyle play a role in this disease (Dehghani and Kazemi Moghaddam, 2015). Besides mood disorders, relevant clinical symptoms of MS include disturbances in motor functions (e.g., tremor, weakness, and spasticity), sensory deficits (e.g., pain), visual impairments (e.g., diplopia and optic neuritis), vascular dysfunctions, obesity, and cognitive impairments (e.g., attention deficits, working memory impairments, information processing). Karimi et al. (2020) investigated 87 MS patients in Iran and showed that 47.1% had moderate depression, 39.1% had moderate anxiety, and 44.8% had moderate stress. A study in Canada (Pham et al., 2018)

TABLE 7 | Multiple hierarchical regression analyses for the incremental validity of HADS and relevant variables on MSIS-29 subscales.

| Predictors | | MSIS-29 PHYS | | MSIS-29 PSY | |
|------------|-------------------------|---|---------|-------------|---------|
| | | Step 1 | Step 2 | Step 1 | Step 2 |
| | | β | β | β | β |
| Step 1 | Age | 0.07 | 0.05 | −0.37** | −0.40* |
| | Sex | 0.32** | 0.22* | 0.16 | 0.01 |
| | Duration of the disease | 0.17 | 0.10 | 0.11 | 0.01 |
| | Type MS | 0.11 | 0.14 | 0.01 | 0.04 |
| | EDSS | 0.05 | 0.08 | 0.05 | 0.09 |
| | R^2 | 0.19 | | 0.13 | |
| Step 2 | | $F(5,80) = 3.71 p < 0.001 F(5,80) = 2.50 p < 0.04$ | | | |
| | HADS-A | | 0.14 | | 0.20* |
| | HADS-D | | 0.36** | | 0.54** |
| | R^2 | | 0.37 | | 0.54 |
| | | $F(7,79) = 6.52 p < 0.001 F(7,78) = 13.00 p < 0.001$ | | | |
| | ΔR^2 | | 0.18 | | 0.40 |
| | | $F(7,79) = 11.18 p < 0.001 F(7,78) = 34.36 p < 0.001$ | | | |

HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; MSIS-29 PHYS, MSIS-29 Physical subscale; MSIS-29 PSY, MSIS-29 Psychological subscale; β , standardized regression coefficient; R^2 , coefficient of determination; ΔR^2 , change in the coefficient of determination; * $p < 0.05$, CI = 95%; ** $p < 0.01$, CI = 98%.

showed 30% of MS patients suffered from anxiety, and 16.3% were affected with depression. The results of a study in the United States (Boeschoten et al., 2017) revealed 20.6% of MS patients suffered from depression. A significant factor responsible for MS relapses is stressful life events (Brown et al., 2005; Stamoula et al., 2021). From a clinical point of view, it is therefore recommended to monitor psychological constructs such as depression, anxiety, and stress in pwMS (Glaser et al., 2019). According to a literature search, it is evident that scales such as DASS-21 (Lovibond P.F. and Lovibond S.H., 1995; Lovibond S.H. and Lovibond P.F., 1995) and HADS (Zigmond and Snaith, 1983) were mainly used for detecting depression, anxiety, and stress in pwMS. Recently psychometric properties for DASS-21 were published in pwMS (Rogić Vidaković et al., 2021), while psychometric properties for HADS in pwMS have been available on different languages from earlier years (Honarmand and Feinstein, 2009; Atkins et al., 2012; Watson et al., 2014; Marrie et al., 2018; Pais-Ribeiro et al., 2018). What it has to bear in mind is that HADS was not initially developed in pwMS. Instead, it is created as a self-report rating scale for evaluating depression and anxiety in patients with a general medical condition, but can be regarded as a useful screening instrument to detect potential psychological disturbances in pwMS (Honarmand and Feinstein, 2009; Watson et al., 2014).

By exploring the factor structure of the HADS, the present study confirmed a two-dimensionality of the HADS in a large community and patient samples (Mykletun et al., 2001; Norton et al., 2013), as well as in samples of pwMS (Pais-Ribeiro et al., 2018). Internal consistency, using Cronbach's alpha, for the two dimensions was good, 0.80 for anxiety and 0.81 for depression in the study of Pais-Ribeiro et al. (2018), while in the present study, the Cronbach's alpha, for the two dimensions was also good, 0.82 for anxiety and 0.83 for depression. A systematic review study conducted by Cosco et al. (2012) pointed out that previous findings on the latent structure of the HADS have been somewhat inconsistent factor structure with 25 of the 50 reviewed studies revealing a two-factor structure, 5 studies revealing unidimensional, 17 studies revealing three-factor, and 2 studies revealing four-factor structures. According to the findings of Cosco et al. (2012), different latent variable analysis methods gained correspondingly different structures: exploratory factor analysis studies revealed primarily two-factor structures, CFA studies revealed primarily three-factor structures, and item response theory studies revealed primarily unidimensional structures. Regarding factor structure of HADS in MS research, Pais-Ribeiro et al. (2018) conducted CFA and exploratory factor analysis and provided support for the bifactor model. The present study confirmed a two-factor structure, and several fit indices that were used support the retention of the two-factor solution.

Parameters of ROC analysis indicate that the HADS-A and the HADS-D have a significant diagnostic validity for group differentiation. Although the HADS depression scale shows slightly better concurrent validity than HADS anxiety, the accuracy of both measures to distinguish emotional disorder is not very high. Therefore, the present study provided data for the optimum cut-off score of >7 for HADS-A and a cut-off score of >6 for HADS-D. The cut-off score of >7 for

HADS-A is similar to findings of Nicholl et al. (2001) and Honarmand and Feinstein (2009), while the cut-off score of >6 for HADS-D was slightly lower compared to other studies using HADS in pwMS (Honarmand and Feinstein, 2009; Watson et al., 2014). When looking into studies using HADS in different samples of patients (not including pwMS) like cancer patients or psychiatric illnesses, the sensitivity and specificity of HADS-A and HADS-D with a threshold of 8+ were most often found to be in the range of 0.70–0.90. The variation in optimal cut-off values and sensitivity and specificity might be due to differences in HADS translations used, samples and procedures in administration, and method analysis of HADS (Bjelland et al., 2002; Cosco et al., 2012).

Both HADS subscales had excellent internal consistencies and good convergent validity expressed by inter-correlations between the HADS and the MSIS-29 subscales. Results of regression analysis suggest that the HADS showed incremental validity in relation to age, sex, MS type, and EDSS.

Further, we have to acknowledge several limitations of the study. The possible limitation of the study would be the time of conducting the survey. Namely, the study was conducted during the COVID-19 pandemic (1 year after the first lockdown in Croatia) and a series of earthquakes that hit Croatia, causing specific problems regarding the governmental social distancing measures and collective trauma effects. Although the study was conducted during COVID-19 disease and strong earthquakes in the eastern part of Croatia (Perinja and Zagreb region), we assume that COVID-19 and earthquakes did not significantly affect the HADS results in pwMS and control subjects. Galić et al. (2020) assessed depression and anxiety in the general population with HADS 3 weeks after the first registered cases of COVID-19 in Croatia. In line with the study of Galić et al. (2020), observed values of depression were similar to the results of control subjects in the present study, with less pronounced anxiety in the present study. Further, a comparison with the previous studies shows a higher prevalence of depression and anxiety in pwMS independently of specific external factors not related to the MS disease (Dahl et al., 2004; Karimi et al., 2020). Another possible limitation is that HADS was not used as a paper-pencil assessment but rather as an online survey. The advantage of the online survey was the possibility to reach a higher number of MS patients. The paper-pencil assessment of HADS would last longer since we could access the MS patients once a week at the University Hospital of Split during the regular control examinations at the Department of Neurology. An approximate number of MS patients that we could reach weekly would be approximately three to five. The second problem was that during regular control visits at the Department of Neurology, the MS patients are not registered at specific hours but are intermingled with other patients having other neurological diseases. Therefore, we believe by conducting an online survey, we reached a satisfactory number of MS patients in a shorter period and got a more appropriate sample size avoiding possible erroneous findings which might occur in the process of determining psychometric properties of the HADS, in particular the identification of the correct structure of the questionnaire (e.g., number of dimensions and items in each dimension).

CONCLUSION

The HADS is shown to be a reliable and valid patient-self report scale that captures meaningful psychological and physical clinical correlates of MS disease.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the School of Medicine, University of Split. The patients/participants provided their written informed consent to participate in this study.

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AJ: conceptualization, data curation, formal analysis, methodology, project administration, resources, and writing – original draft. APr: supervision, methodology, and writing – original draft. MM, KD, and ZĐ: supervision and writing – original draft. JV, AM, AĆ, VK, and LK: methodology, project administration, and resources. APo: methodology and project administration. MRV: conceptualization, data curation, formal analysis, methodology, project administration, resources, supervision, and writing – original draft. 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/fpsyg.2021.794353/full#supplementary-material>

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Life Design Counseling: Theory, Methodology, Challenges, and Future Trends

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With the rapid development of society and the dramatic change of environment, previous career counseling focusing on personal choice has been difficult to meet individuals' needs. It is very meaningful and valuable to introduce the ideology of Life Design Counseling (LDC). In this mini review, we introduce and analyze the theory and methodology of LDC. This review puts forward challenges in the field of LDC, including the lack of attention to clients from multiple backgrounds and professional counselors, the lack of diversified methods in the intervention process, and the lack of diversified research. The theoretical research, practical research, and the integration of theory and practice of LDC still need to be further concerned by researchers.

Keywords: life design counseling, theory, methodology, challenges, trends

INTRODUCTION

The current living environment changes faster than ever before, resulting in the trend of personal career development from static and linear to dynamic and nonlinear. Personal future work and employment are becoming more and more unstable in this world dominated by Volatility, Uncertainty, Complexity, and Ambiguity (VUCA) (Canzittu, 2020). Savickas et al. (2009) proposed the third paradigm of career intervention, which is called the "Life Design Paradigm," to deal with the drastic changes in the current social environment (Savickas et al., 2009). Based on this paradigm, Life Design Counseling (LDC) refers to a kind of counseling that helps clients define their career as a story, narrate their personal working life with continuity and coherence, discover life themes, create life meaning, construct identity, formulate adaptive actions, and pursue the life expected by individuals (Savickas and Pouyaud, 2016; Venter and Maree, 2020; Wong, 2021). LDC aims to help clients explore possible careers, reshape personal narrative identity through meaning construction, clarify self-concept, establish a life purpose and create a meaningful life (Savickas, 2012; Wehmeyer et al., 2018; Wen et al., 2020a). Compared with other career counseling methods, LDC provides a new perspective for individual or group counseling to formulate long-term career planning and has the potential for cross-cultural research (Savickas et al., 2018). Therefore, this mini review aims to introduce the theory, methodology, challenges, and future trends of LDC, so that researchers

engaged in this specific field can more effectively understand and master the research trends and future development trends in this field, and expand the application scope of LDC. In order to ensure the quality of the literature, LDC was used as the search term to conduct a full search on the Web of Science in this study. The search scope is limited to English articles. Specifically, the literature search was conducted from January 2000 to November 2021. In addition, this study only included standard research papers, excluding news, conferences and other types of documents.

WHAT IS LIFE DESIGN COUNSELING?

Life Design Counseling is a kind of career intervention, which originates from Guichard's self-construction theory and Savickas's career construction theory (Guichard, 2009; Maree, 2019). After entering the 21st century, individuals need to face more complex social relationships and work environments, especially to design their own lives. The premise of designing life is self-construction. In response to the above changes, Guichard put forward self-construction theory, which mainly points out that self-construction is a subjective identity system of past, present, and future (Guichard, 2009; Guichard et al., 2012). With the development of career theory, in order to explore career from a more integrated perspective, Savickas et al. proposed Career Construction Theory. Career Construction Theory attempts to look at individual career from an overall perspective, aiming to answer three core questions, namely "What kind of career will be established?" "How to construct a career?" and "Why build a career?" (Savickas, 2008; Savickas and Pouyaud, 2016). Specifically, "What kind of career will be established?" reflects the relationship between personal interests, abilities, values and career development from the perspective of social division of labor (Rudolph et al., 2019). "How to construct a career?" is manifested as the interaction between individuals and the environment in the current mobile society and flexible work organization, emphasizing that individuals reshape themselves in reflection and cope with external challenges based on their career adaptability. "Why build a career?" is the fundamental issue of Career Construction Theory, which truly reflects that individuals regard their own careers as creating their own life stories and strung the stories into a line around the theme of life. In general, career is a macro narrative about the role of work in one's life which was defined in career construction theory. Both those two theories involve social constructivism, emphasize the significance of understanding and intervening narrative thinking in the process of construction, and highlight the value of reflexivity based on individual in-depth thinking of past and present experience for individual behavior (Guichard, 2016b; Savickas, 2016). In short, whether it is the theory of Self-Construction Theory or Career Construction Theory, reflexivity emphasizes the formation of the individual based on current problems to guide the next step in life. However, there are also some differences between the two theories: self-construction theory focuses on the survival direction of individuals, emphasizes the dynamic development of individuals based on subjective

identity formal system (SIFS), and constructs self-concept in the social environment (Guichard, 2016a). LDC based on Self-Construction Theory adopts a relatively open interview form, pays attention to the role of clients' self-construction in meaning, identity, and future planning, focuses on helping clients reshape their narrative identity, and projects the new possibility of self-construction into their career role. Therefore, it is more suitable for teenagers or emerging adults (Di Fabio, 2014; Guichard, 2016a). While Career Construction Theory points out that career can be a dynamic construction process, and subjective self and external world can adapt to each other. LDC based on Career Construction Theory helps clients to focus on their own career through highly structured interviews and narration around personal interests and models, increase their control over their future career positioning, stimulate their curiosity to explore possible self and possible future scenes, and build their confidence in career development (Maree, 2014). Counselors help clients reconstruct the meaning, identity, and intention of life, as well as find the life theme and answer the meaning of life, which is more applicable for mature adults (Guichard, 2016a; Hartung and Santilli, 2018).

In summary, LDC means that counselors help clients give meaning to their lives and social relationships through various stories and find their understanding of life themes as well throughout this process (Cardoso et al., 2016b; Wong, 2021). LDC can be regarded as an intervention method combining Self-Construction and Career Construction, which reflects the integration of personal personality characteristics, development process and life story (Di Fabio and Maree, 2012; Wong, 2021). LDC emphasizes that individuals reflect on themselves and construct meaning based on continuous narration by considering the overall impact of the surrounding system, so as to generate expectations and motivation for the future (Cardoso et al., 2016a; Venter and Maree, 2020). Specifically, LDC focuses on people's interaction between themselves and the environment, establishes life trajectory through narration, and considers educational investment, work and life roles and meaning in life, so as to deal with the uncertainty of the future (Nota et al., 2016; Cardoso et al., 2019). In short, life-long, holistic, contextual and preventive are important characteristics of LDC (Savickas et al., 2009; Venter and Maree, 2020). LDC aims to help clients reshape their lives through narration based on personal needs, interests, abilities and experiences (Maree, 2020b). Clients can rewrite their narrative identity, clarify their self-concept, establish life goals and explore possible life tracks (Savickas et al., 2009; Cardoso et al., 2019; Maree, 2020a).

HOW TO USE LIFE DESIGN COUNSELING?

Life Design Counseling is an emerging method of career intervention. The research on LDC is mainly divided into three categories: process intervention, process evaluation, and results evaluation. According to these three categories, some pioneer scholars have made a comprehensive evaluation system of LDC.

Process Intervention

The process intervention on LDC mainly includes Guichard's Life and Career Design Dialogues (LCDD) and Career Construction Interview (CCI) (Pouyaud et al., 2016; Barclay et al., 2019; Wong, 2021). My Career Story (MCS) is a written expression tool developed based on CCI (Hartung and Santilli, 2018). In addition, Interpersonal process recall (IPR) is an important auxiliary method of LDC that is usually used to explore the experience of clients in the process of counseling dialogue (Cardoso et al., 2016a). Written exercises, career collages, and career portfolios are often combined with CCI creatively (Barclay, 2019).

Specifically, LCDD is a psychological counseling and intervention method which focuses on the dialogue between client and counselors to help the client understand the self-construction of subjective identity (Guichard, 2016b; Pouyaud et al., 2016). The dialogue took place in one-on-one interviews between clients and counselors lasting several weeks (Pouyaud et al., 2016). CCI designed by Savickas (2011) is widely used which is usually divided into three sessions (Cardoso et al., 2018). The first session is Career Construction Interview (Cardoso et al., 2018). After the client and counselor discussed their expectations for intervention, LDC focused on five aspects: role models; favorite magazines, TV programs, etc.; current favorite story; Motto to oneself; early recollections (Taylor et al., 2016; Taylor and Savickas, 2016). For example, clients are required to tell real or fictional role models. Counselors can discuss the similarities and differences of role models with clients, so as to reflect the clients' self-concept, including how to treat their own identity and values. Interested magazines and TV programs reflect the relationship between clients' interests and working environment. During the second session, counselors assist the client in constructing a story, which aims to provide continuity for the fragments of the client's life in the previous stage. In the third session, the focus of the intervention is to assist the client to connect life themes with career planning (Cardoso et al., 2018). As an auxiliary means, IPR aims to explore the experience of clients in the interview process. Clients are required to watch the video replay of the interview. Counselors need to ask clients how to experience the important moment in the video, help clients analyze the emotional experience of the important moment, and promote the reflection of clients in the process of interpersonal interaction with counselors. In addition, in the process of CCI, clients can create career collages based on paper pasting. The counselor assists the client in creating "a collage" and takes the collage as a tool for meaning construction. The client describes what the client attaches importance to and desires in his life by pasting images representing personal models, pictures of his favorite magazines and TV programs, so as to help the client imagine and design the future and obtain the power to realize the future.

Process Evaluation

The purpose of the process evaluation of LDC is to find out what changes have taken place in the counseling process. The process evaluation of LDC can be divided into the qualitative evaluation and quantitative evaluation. The focus of qualitative assessment is whether the clients have changed and what

changes have taken place in the LDC process. To analyze the changes of clients, researchers also used quantitative methods to process evaluation.

Specifically, Innovative moments (IMs) are usually used as a sign of changes in clients (Cardoso et al., 2020). At present, for the qualitative evaluation of IMs in LDC, the representative is the innovative moments coding system (IMCS) developed by Cardoso et al. IMCS is a tool for tracking IMs. IMs in the counseling process reflects the non-linear change of the clients, which is often accompanied by the circular ambivalence reflecting the self motivation of the clients. Researchers often use IMCS together with qualitative tools to evaluate the changes in clients' ambivalence during the counseling process. Representative tools include Return to the Problem Coding System (RPCS) and Ambivalence Coding System (ACS) (Da Silva et al., 2020). The former refers to that the client immediately returns after generating the innovation moment and re-emphasizes the problematic self narration, which weakens the significance of IM. The latter is often used to identify clients who immediately turn to problematic self narration after describing the moment of innovation.

Many researchers have conducted comprehensive research on LDC combined both qualitative evaluation and quantitative evaluation. Giving full play to the advantages of qualitative evaluation and quantitative evaluation, some scholars also try to develop a comprehensive evaluation of LDC. For instance, Maree Career Matrix (MCM) is used to measure the clients' interest and confidence in the successful pursuit of a variety of careers (Maree and Taylor, 2016). MCM with 19 categories showed good psychometric characteristics during the standardization process. In terms of the comprehensive evaluation, MCM shows good psychometric characteristics in the standardization process (Morgan and Ferreira, 2019). In addition, Maree (2007) developed the South African version of the qualitative questionnaire of Career Interest Profile (CIP) (Di Fabio and Maree, 2013), trying to construct narrative information from individual career stories.

Results' Evaluation

Results' evaluation is to compare the status of clients after counseling with those before counseling to find out the differences. From the aspect of the quantitative evaluation, researchers found that the clients' career uncertainty and career pending decreased, while their preparation for academic specialty and career decision-making, professional self-efficacy, career planning, professional identity, and professional control trajectory, life satisfaction increased (Barclay and Stoltz, 2016a,b; Nota et al., 2016; Cardoso et al., 2018; Di Maggio et al., 2021b). The above research shows that through the intervention of LDC, individuals can more accurately evaluate themselves, gather occupational information, select goals, make plans for the future, have more certainty about their career development, and improve their evaluation of their own quality of life. Still, there exist some discrepancies among different research. Some scholars found that career adaptability improved, and others assert that this variable did not change (Cardoso et al., 2018; Rudolph et al., 2019). These studies suggest that the impact of LDC on an individual's career

TABLE 1 | How the LDC is operated.

| Number | Category | | Illustration |
|--------|----------------------|---------------------|---|
| 1 | Process Intervention | Main methods | 1. Career Construction Interview (CCI) 2. My Career Story (MCS) 3. Life and Career Design Dialogues (LCDD) 4. Interpersonal process recall (IPR) |
| | | Additional ways | 1. Written Exercises 2. Career Collages 3. Career Portfolios |
| 2 | Evaluation | Process Evaluation | 1. Innovative Moments Coding System (IMCS) 2. Return to the Problem Coding System (RPCS) 3. Ambivalence coding system (ACS) 4. Career Interest Profile (CIP) 5. Maree Career Matrix (MCM) |
| | | Results' Evaluation | 1. Vocational Certainty Scale (VCS) 2. The Career Maturity Inventory–Form C (CMI-FC) 3. Career Decision Self-Efficacy Scale–Short Form (CDSE-SF) 4. The Career Adapt-abilities Scale(CAAS) |

adaptability is a complex issue, and more studies are still needed to examine the effects of interventions in more detail. In general, how the LDC is operated can be shown in **Table 1**.

WHAT ARE THE CHALLENGES OF LIFE DESIGN COUNSELING?

Lack of Attention to Clients From Multiple Backgrounds and Professional Counselors

On the one hand, LDC needs to pay attention to the psychological needs of more diverse cultural background groups, because the counseling needs of different types of clients are unique and different (Sampaio et al., 2021). Scholars have accumulated some group LDC research in the early stage, such as the research on college students (Pordelan et al., 2018), middle and high school students (Nota et al., 2016), Italian entrepreneurs (Di Fabio and Maree, 2012), etc. However, these groups are still limited, and the research group based on LDC needs to be further expanded. For example, LDC may become an effective way to help vulnerable groups develop their career. On the other hand, the effective implementation of LDC is inseparable from professional counselors. The lack of professional LDC counselors may bring the following negative effects: it is difficult for clients and counselors to establish a working alliance and sort out ambivalence through coherent narration and re conceptualization, then it is hard for clients to draw a life portrait and formulate a plan for moving forward (Cardoso et al., 2016a,b;

Barclay, 2019). In addition, long-term intervention is an important guarantee for the effectiveness of LDC (Di Fabio and Maree, 2012; Nota et al., 2016). If there is no professional LDC counselors, the continuous participation of clients may be reduced (Barclay and Stoltz, 2016a). Therefore, in the practice of LDC, it is particularly necessary to cultivate a large number of professional counselors who are familiar with the operation mode of LDC.

Lack of Diversified Methods in the Intervention Process

The intervention methods for LDC are still not diversified enough. The typical intervention methods for LDC only include CCI, MCS, LCDD, etc. The combination of LDC and other practical methods can give better play to the function of career counseling. For example, in view of the close relationship between career and psychosocial issues, how to combine LDC and psychotherapy to solve more complex life problems of clients is a topic worthy of attention (Cardoso, 2016). In addition, the creative use of LDC is still a problem that needs the attention of career practitioners. Specifically, how to combine intervention methods of methods with art (e.g., painting) to help clients better narrate, reconstruct their own life themes, and find the power for change is a issue that needs to be solved urgently (Barclay, 2019). LDC practitioners need to creatively develop intervention methods, so that they can be applied to a wider range of clients, help them express themselves through narration, generate motivation for substantial change, discover life themes, find life goals and plan their own future. In general, counselors need to creatively and flexibly use CCI and other major intervention methods to help clients build their future careers.

Lack of Diversified Evaluation Methods

Scholars lack research on the diversification of LDC in the existing research, especially in its evaluation method. First, the evaluation object is not comprehensive enough. Current research mainly focuses on the counseling effect on clients in LDC, while neglecting the different influence from counselors who plays the same important roles as well. Although clients are an important part of the counseling subject, the evaluation of counselors has a specific value, and researchers lack attention to the growth of counselors' counseling ability (Storlie et al., 2017). The second is the evaluation method: the current research mainly includes qualitative evaluation, quantitative evaluation, and comprehensive evaluation (McMahon et al., 2003; Di Fabio and Maree, 2013). However, these evaluation methods are limited and the evaluation content is not rich. It seems that the evaluation of LDC can be further improved by referring to other counseling and evaluation methods as well as other evaluation contents.

FUTURE RESEARCH TRENDS

Although LDC is a relatively new way of career counseling and opens up new ideas for counselors, the theoretical research, practical research, and the integration of theory and practice of LDC still need to be further concerned and promoted by

TABLE 2 | Future research trends of LDC.

| Number | Item |
|--|---|
| 1. Strengthen the in-depth study of clients and counselors | <ol style="list-style-type: none"> 1. More vulnerable groups 2. The general population with finer classification 3. Improve the quality of counselors 4. Increase the number of counselors 5. Create a standardized process for counselor training 6. Establishment a working alliance between client and counselor |
| 2. Extended intervention Methods | <ol style="list-style-type: none"> 1. Pay attention to the cutting-edge trends in the field of counseling methods 2. Combine the methods in LDC with art therapy methods 3. Online and offline intervention |
| 3. Improve intervention evaluation methods | <ol style="list-style-type: none"> 1. Learn from other disciplines and develop more process assessment tools, such as big data, NVivo, etc. 2. From the perspective of personality characteristics, such as career optimism, mindfulness, gratitude, benevolence, etc. 3. From the perspective of organizational contexts, such as decent work, job satisfaction, job burnout, thriving at work, reemployment, etc 4. Clarify the relationship between counselors and researchers in the evaluation process and focus on the evaluation of counselors |

researchers. The main trends of future development of LDC are shown in **Table 2**.

Strengthen the Needs Analysis of Clients and the Professional Training of Counselors of Life Design Counseling

Scholars need to create diversified counseling methods to broaden the application scope of LDC. On one hand, scholars especially need to pay more attention to the following groups: (a) vulnerable groups, such as the unemployed, people with disabilities, people who have experienced breakups or divorces, cancer patients, aging Chinese parents who lose their only child, patients with depression, survivors of family violence, refugees, ex-offenders, solitary person, the bereaved and the low-income people in remote areas (Nota et al., 2014; Li, 2018; Bergeron et al., 2021; Di Maggio et al., 2021a; Maree, 2021) and (b) the general population with finer classification, such as public or private primary school students in different countries or regions, middle school students from different regions and nationalities, high school students with different school characteristics, college students of different majors, workers of different occupations (Cardoso et al., 2016a; Maree, 2020a). Researchers may help these people achieve better career development by designing diversified LDC studies. On the other hand, more professional LDC counselors need to be trained, including improving the quality of counselors, increasing the number of counselors, and forming a complete and standardized process for training counselors, to serve more people who need LDC help (Di Fabio and Maree, 2012; Venter and Maree, 2020; Wen et al., 2020a). Researchers and practitioners need to pay particular attention to

the formation and maintenance of a good relationship between counselors and clients, because the establishment of a working alliance between them is an important guarantee for effective LDC (Cardoso et al., 2016a, 2021; Tian et al., 2020).

Increase Multi-Dimensional and Diversified Intervention Process Methods of Life Design Counseling

In order to solve the lack of diversified LDC intervention methods, career counseling practitioners can try the following paths. First, LDC counselors can integrate other counselor theories with LDC and find the coincidence points between some cutting-edge psychology and pedagogy theories and LDC, so as to create a diversified counseling model and serve more clients with different needs. For example, future researchers can try to combine PERMA (Positive Emotions, Engagement, Relationships, Meaning, Achievements) theory in positive psychology with LDC, so as to jointly promote the positive change of clients (Carreno et al., 2021). Second, the existing LDC methods can be presented in a diversified and creative way in order to promote the self-expression and reflexivity of clients. Future career researchers and practitioners can try to combine the methods in LDC with art therapy methods such as painting, music, dance, and writing, so as to serve a more diverse group of individual or group clients. Last but not least, scholars may be able to conduct online and offline LDC through computers, mobile phones, telephones, and e-mails (Savarese et al., 2020; Carbone et al., 2021), and other flexible forms and combined with other emerging psychological counseling methods. In general, career practitioners need to create diversified LDC intervention methods in the future to help clients through narrative construction, deconstruction and joint construction of their personal career stories, find the core life theme, and carry out a meaningful life.

Strengthen the Research on the Evaluation Objects and Methods of Life Design Counseling

Future research on LDC needs to enhance the research on the evaluation objects and methods of LDC. Strengthening the research on the evaluation is mainly reflected in the following three points: Firstly, researchers need to further broaden the application scope of the above evaluation methods and also create more process evaluation methods suitable for LDC because of big data, Nvivo to serve a wider group (Alam, 2020; Wen et al., 2020a). Secondly, in terms of personality characteristics, it should be paid more attention to such things as the meaning of life, mindfulness, and optimism (Ginevra et al., 2018; Wen et al., 2020b). From the perspective of the organizational situation, it should focus on exploring the influence mechanisms caused by self and the outside world, such as professional identity, job satisfaction, social support, and job burnout (Chen et al., 2020; Shen et al., 2021). Finally, strengthen the research on counselors in the evaluation of LDC. Scholars need to further enrich the evaluation objects of LDC and pay attention to the evaluation of counselors. Previous studies usually focused

on the evaluation of clients. However, it needs to pay more attention to the uniqueness of counselors and the important value of counselors' personal growth to the counseling effect, such as counselors' cultural background, personality, value, and helping counselor trainees' personal growth and professional development through supervision (Prosek and Michel, 2016). At the same time, since researchers and counselors may be the same group in some studies, future researchers need to further clarify the responsibilities and authorities of counselors and researchers in the LDC evaluation process (Tian et al., 2020).

CONCLUSION

Life Design Counseling is a new form of career counseling in the VUCA era. The emergence and development of LDC are based on Self-Construction Theory and Career Construction Theory. At present, the use of LDC mainly includes process intervention, process evaluation, and results evaluation. To sum up, this study found some challenges of LDC, including lack of attention to clients from multiple backgrounds and professional counselors, lack of diversified methods in the intervention process, and lack of diversified evaluation methods. Therefore, this study came up with some suggestions about how to deal with those challenges as follows: Firstly, facing the changeable environment, future

research should focus on strengthen the needs analysis of clients and the professional training of counselors of LDC. Secondly, for more individuals or groups to obtain career development through LDC, it is necessary to increase the research on the multi-dimensional and diversified intervention methods of LDC in future research. Finally, future researchers need to pay attention to strengthening the research on the evaluation objects and methods of LDC to ensure further prove the effect of LDC on individuals or groups.

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All authors participated in the study design. YW and HC wrote the first draft. KL and FL modified the manuscript.

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Open Science Within Pediatric Medical and Mental Health Systems: Practical Considerations for Behavioral Health Researchers

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Keywords: research methods, open science, reproducibility, preregistration, pediatric psychology

INTRODUCTION

The open science movement is an epistemological movement toward increasing accessibility of data and research processes in order to improve the quality and reproducibility of science (Hesse, 2018). A number of practices have been proposed in association with open science, including journal clubs, systems for project workflow, sharing code, sharing data, use of preprints, pre-registering studies, open-access publishing, an increased focus on statistical power, and greater transparency in data analysis documentation (Allen and Mehler, 2019; Kathawalla et al., 2021). In particular, researchers promoting open science practices focus on the benefits to scientific inquiry by improving reproducibility, improving public access to scientific findings, and allowing for more active collaboration and building on previous work, among other benefits (Hesse, 2018).

As technology increasingly improves connection between researchers, the pressure to engage in specific open-science practices, such as sharing raw data with other researchers, has increased. Still, data sharing in psychological research remains relatively rare due to a range of potential barriers (Houtkoop et al., 2018). Researchers identify practical concerns about the process of data-sharing, concerns about anonymity of participants, and concerns about being credited on subsequent research projects as specific concerns related to data-sharing (Cheah et al., 2015).

Further, implementation of open science practices has been uneven across settings, with pediatric medical and mental health system-based research lagging behind other psychology research contexts. Fewer than 10% of studies from these hospital-based settings engage in even low-stakes open science practices such as publishing supplemental code or promptly publishing results in clinical trials registries (Sixto-Costoya et al., 2020; Kadakia et al., 2021), let alone high-stakes or potentially difficult-to-implement practices. This problem is compounded by low standards for adherence to best practices by journals in these fields (Gardener et al., 2022). Despite clear potential for clinical benefit to pediatric populations when open science practices are utilized (Rubinstein et al., 2020), there has been little exploration or published discussion about how barriers are perceived by researchers in these systems or discussion about how previously established solutions to barriers might apply to these researchers.

Children and families within systemic pediatric medical or mental health systems are considered sensitive populations, deserving of particular ethical consideration in research and clinical processes (American Psychological Association, 2017), and their behavioral health data is often sensitive and/or identifiable. Goodie et al. (2013) advise that, for sensitive populations, researchers and other stakeholders should consider the balance between providing high quality, patient-centered services while collecting sound scientific data and decreasing the likelihood of adverse outcomes. Further, grant-funded research in pediatric medical and mental health systems is often costly and high-stakes, leading to particularly robust discussion of risk-management for

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participants in these settings (Wendler, 2006). These concerns about open science practices by behavioral health researchers are legitimate and worthy of serious consideration. Considerations for engaging in open science practices in these settings may be different than in other psychological research. Due to the potential need for additional protections, consideration of open science methods in the context of these populations is warranted.

FACTORS

Consideration: Protection of Participant Privacy

Concerns about participant welfare rightfully concern behavioral health researchers in pediatric settings who are considering open science practices. Sharing research data may increase the risk of compromising confidential information about participants. While many of these risks are preventable, adequate protection requires both preventative planning and clear informed consent by participants (Alter and Gonzalez, 2018). Some research, such as longitudinal studies or research that includes geographic tracking, may be particularly difficult to de-identify without compromising the research value of the dataset. Medical and mental health data has long been known to be at particular risk of re-identifying participants when combined with basic demographic data (Sweeney, 2000). In pediatric settings, where demographic information may include both children and their parents or guardians, the potential to re-identify participants is additionally heightened.

Data collected in medical or mental health settings also likely falls under other legislation, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States, the General Data Protection Regulation (GDPR) in the European Union, or the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada, and any data-sharing plan must consider this explicitly.

Actions for Researchers

Of course, researchers should ensure that sufficient processes are in place to ensure participant safety and appropriately document this with their Institutional Review Board. Researchers should engage in robust risk-management strategies regardless of whether or not they intend to share their data (e.g., data encryption for personal health data, splitting datasets to separate identifiable information from ID variables, etc.). Depending on the types of information gathered by researchers, partial datasets may be realistic for some projects, with only non-sensitive data available for data sharing. Example repositories include Open Science Framework (OSF), Mendeley Data, Figshare, and Zenodo.

However, in the context of sensitive personal health data that makes data sharing infeasible, researchers may also benefit from a selective use of open science practices. For example, in situations where data sharing is not feasible (e.g., due to patient confidentiality concerns), researchers may still choose to engage with other open science practices such as preregistration, reproducible code, and preprints. Additionally, publishing adequate summary statistics provides readers greater opportunity

to evaluate a research paper, particularly in contexts where original datasets have not been shared. For example, in addition to means and standard deviations, a researcher might choose to publish variance-covariance matrices of all variables in their work. Researchers may also choose to publish their statistical script alongside research papers to improve reader confidence in their results and facilitate researcher learning (Mair, 2016).

Kathawalla et al. (2021) identify the least difficult to most difficult open science practices as: (1) Starting an open science journal club, (2) Developing an open science-friendly project workflow, (3) Posting pre-prints, (4) Using reproducible code, (5) Sharing data, (6) Transparent manuscript writing, (7) Preregistering research, and (8) Publishing registered reports. Given that this list was not designed with protected health data in mind, research in pediatric medical and mental health systems, this difficulty order may be somewhat different, with data sharing likely causing the most significant concern, due to the potentially sensitive nature of these datasets. Even in cases where no data sharing is feasible, researchers can likely engage in some of the other open science practices endorsed by Kathawalla et al. (2021).

Consideration: Propriety of Information

Data collected in pediatric medical and mental health settings are often collected at great monetary and temporal expense. Researchers in these settings may intend to produce a large number of publications with a single dataset and worry that procedures such as data sharing may result in reduced ability to maximize their collected materials for their own research output. Concerns about the ability to adequately utilize one's own dataset, procedure, or planned analyses before opening it up to other researchers are valid.

Actions for Researchers

In addition to choosing some of the other open science practices discussed above, researchers may consider using project management tools that enable timelocks (e.g., preregistering a hypothesis and not publicly releasing it until there has been sufficient time to complete all relevant work) to avoid the possibility of getting "scooped," a colloquial term referring to instances where one researcher publishes a novel project in advance of another researcher, who was already working on this idea. If data sharing is possible, it may be reasonable to require that researchers request access in order to access the full dataset. In these cases, sharing variables or codebook material may be more feasible. Notably, there are likely advantages of data sharing, when feasible to do so, for overall research impact. For example, linking data in a repository increases researchers' citation count by 25% (Colavizza et al., 2020). Researchers may also wish to license their data, code, and materials to ensure that it is used appropriately (e.g., a Creative Commons license).

Consideration: Data Ownership and Permissions

Ownership and legal issues may disrupt the possibility of data sharing even among willing participants. In many cases, the grantee for ownership of research data is the university or research hospital, not the individual researcher (Alter and

Gonzalez, 2018). Other times, research may be published that is clearly not within the purview of the project leader. For example, a secondary data analysis by a graduate student, completed with permission from the data steward, is almost certain to be derived from a dataset that is not the intellectual property of the student. In these cases, a researcher may be unsure of their ability to share their data, or simply unable to do so due to restrictions imposed by the data owner.

Previously-collected data in pediatric settings may also lack adequate informed consent procedures to facilitate data-sharing, or complications may arise in creating pathways for sharing sensitive or protected information in these settings. These concerns may be more likely to come up for large scale studies operating out of medical centers within major pediatric health systems.

Actions for Researchers

Researchers in leadership roles may find value in drafting guidelines for open science practices within their organization in collaboration with their research ethics team to improve access to data sharing options. For example, if researchers have historically used consents that prohibit data sharing, a relatively common practice in large healthcare facilities, choosing a more flexible option with informed consent of participants may allow for more open science-related workability in future projects.

Importantly, Campbell et al. (2019) highlight the complications of setting up adequate informed consent procedures for highly sensitive information or for populations that have historically been wronged by psychological or medical researchers. They recommend a tiered consent approach to allow parents or guardians to choose the level of data sharing that feel comfortable with. Notably, children in pediatric settings are not able to offer informed consent to participation in research. Based on developmental stage, children may be able to provide assent in conjunction with parental consent. Thus, child health and mental health data deserves additional considerations related to consent when children reach the age of majority, such as policies around re-contacting to establish consent for data-sharing when children become adults

(Brothers et al., 2014). Despite these potential complications, setting up standard procedures to facilitate the conversations around open science practices can improve the reproducibility of future research.

DISCUSSION

Generally, the benefits of open science practices have the potential to be robust. However, legitimate concerns may limit the ability of some researchers operating within healthcare settings to engage in certain practices such as data sharing. Although steps can be taken to encourage data sharing when feasible, importantly, there are a range of potential actions in addition to data-sharing that researchers can take to improve both the accessibility and reproducibility of science. This article aims to encourage interested but hesitant researchers in pediatric medical and mental health systems to consider manageable steps in the direction of open science.

In particular, researchers are encouraged to:

1. Explicitly consider which open science practices are feasible for their project and specific datasets with large health and mental health systems.
2. Proactively plan for large scale research trials to ensure rigorous data reporting standards while balancing the rights of children and families who participate in research.
3. Connect with peers to create a culture that encourages open science within pediatric-focused institutions including active supports for researchers.

Future research should examine setting-specific barriers or hesitations to engaging with open science practices as well as facilitators and the impacts of potential interventions (e.g., creating an open science journal club) on the reproducibility of research within institutions.

AUTHOR CONTRIBUTIONS

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

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Impact of a Remotely Supervised Motor Rehabilitation Program on Maternal Well-Being During the COVID-19 Italian Lockdown

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COVID-19 Lockdown was particularly challenging for most mothers of people with intellectual disabilities, including those with Rett syndrome (RTT), leading to feelings of abandonment from healthcare services of their children. Within those days, telerehabilitation has represented a valid alternative to support physical activity and treatment, supporting parents in structuring their children's daily routine at home. This article aims to describe the well-being level of two groups of mothers of girls and women with RTT who were involved in a home-based remotely supervised motor rehabilitation program, respectively, before and during the COVID-19 Italian lockdown. Forty participants with classic RTT were recruited before the lockdown and randomly assigned to two groups that performed the intervention immediately before (Group 1) and during (Group 2) the lockdown, respectively. The intervention included an individualized daily physical activity program carried out for 12 weeks by participants' parents and fortnightly supervised throughout Skype contacts to plan, monitor, and accommodate individual activities in the participant's life at home. The short form Caregivers Well-Being Scale was collected for the mothers in each group 12 weeks before intervention (T1), at intervention initiation (T2), immediately after intervention termination (T3), as well as at 12 weeks after intervention termination (T4). Mothers of participants in the Group 1 showed a stable level of well-being across all four evaluations with a slight improvement during the lockdown, without significant change. Similarly, the well-being level of mothers in the Group 2 showed a statistically significant increase in their well-being between T2 and T3 (during the lockdown) and its reduction to the pre-intervention level between T3 and T4 (after the lockdown). The results suggest that the lockdown did not negatively affect the participants' mothers' well-being, leading to its improvement. Moreover, the proposed intervention could have supported the mothers in managing the new daily routine at home, positively affecting maternal well-being.

Keywords: Rett Syndrome, telerehabilitation, parental well-being, exercise therapy, parents, COVID-19, home exercise program

INTRODUCTION

Rett Syndrome (RTT) is a rare neurological disorder observed mainly in females (Amir et al., 1999, 2000). RTT is characterized by normal birth and apparently normal psychomotor development during the first 6–18 months of life (Epstein, 1995). The disorder's trademark is the repetitive stereotypical hand movements appearing after the child has entered the typical regression phase of RTT. Additional characteristics at the breakthrough of the disease include autistic-like behavior, panic-like attacks, breathing disturbances, sleeping problems, gait ataxia and apraxia, and acquired microcephaly (Hagberg et al., 1983). After this period of rapid functional deterioration, the disorder progresses relatively stable, although the child with RTT could develop dystonia and musculoskeletal deformities (Sponseller, 2001) as she grows old. Seizures occur in 50–85% (Epstein, 1995; Glaze et al., 2010) of individuals with RTT. Females with RTT typically survive into adulthood, and their estimated life expectancy is 49 years, suggesting the need for life-long support. Due to the complexity of the disorder, RTT is a particularly challenging disorder even for highly trained rehabilitation therapists due to its severity and complexity (Perks et al., 1994).

The challenges presented by the individual with RTT and their expected longevity necessitate constant individual adaptations of intervention in all educational and therapeutic areas. The literature reported that brain development continues after the onset of RTT (Kaufmann et al., 2005). Moreover, the cognitive and communicative abilities of the individual with RTT do not deteriorate over the years. Therefore, setting proper and achievable rehabilitative, educational and communicational goals is vital for the individual with RTT (Cass et al., 2003).

Within the last decade, researchers published new therapeutic strategies for treating each aspect of the disability associated with RTT. These developments include technologically supported strategies for cognitive (Fabio et al., 2020, 2021; Dovigo et al., 2021), communicative (Fabio et al., 2013, 2018b; Stasolla et al., 2014; Vessoyan et al., 2018; Fabio, 2019), and motor (Romano et al., 2020, 2021; Lotan et al., 2021a,b) rehabilitative evaluations and interventions. Technology-supported strategies resulted in adequate support for skills acquisition and improvements in all these fields. The technology-supported strategies available for people with RTT mainly refer to telerehabilitation strategies. Telerehabilitation, also known as net therapy, virtual rehabilitation, mobile rehabilitation, or remote rehabilitation (RR), delivers services over distance *via* technologies addressing therapeutic issues by presenting remote services to individuals with DD (Capri et al., 2021). Clinically, the term 'telerehabilitation' encompasses a range of rehabilitation and habilitation services that include evaluation, assessment, monitoring, prevention, intervention, supervision, education, consultation, and coaching. Technologies used to deliver rehabilitation and habilitation services may incorporate but are not limited to video and audio conferencing, chat messaging, wearable technologies, sensor technologies, patient portals or platforms, mobile health applications, virtual reality, robotics, and therapeutic gaming technologies (Richmond et al., 2017). The benefits of telehealth

include improved access to rehabilitation services and specialists, preventing unnecessary delays in care and support (Cason and Cohn, 2014).

Life-long rehabilitation interventions should be performed to maintain individuals with RTT as functional as possible along with their life span, accompanying the person through the disease evolution (George et al., 1988; Lotan and Hanks, 2006; Lotan et al., 2010) and overcoming all the medical and functional impediments mentioned above. Yet, the complexity of the disorder necessitates treatment delivery to the individual with RTT and her family with utmost proficiency and intensity.

Previous findings suggest that an intensive intervention program can enhance the abilities of individuals with RTT in numerous areas, such as learning skills (Elefant, 2001; Koppenhaver et al., 2001a,b; Elefant and Wigram, 2005), new skills (Demeter, 2000; Jacobsen et al., 2001; Leonard et al., 2001), literacy (Koppenhaver et al., 2001a; Hetzroni et al., 2002; Fabio et al., 2013), communication abilities (Sigafoos et al., 2000; Elefant, 2001; Hetzroni et al., 2002; Lindberg, 2006; Wine, 2009; Fabio et al., 2018a), cognitive abilities (Fabio et al., 2011, 2016, 2019, 2020, 2021), manual abilities (Sullivan et al., 1995; Pizzamiglio et al., 2008), osteoporosis (Zysman et al., 2006), functional abilities (Lotan et al., 2004; Downs et al., 2008; Maciques Rodríguez and Lotan, 2011; Lotan et al., 2021a), orthopedic issues (Legrand et al., 1997; McClure et al., 1998; Elefant and Lotan, 2004; Lotan et al., 2004, 2005; Maciques Rodríguez and Lotan, 2011), and sensory issues (Pizzamiglio et al., 2008; Drobnyk et al., 2019). In addition, such programs have been found effective when suggested to individuals with RTT of all ages (Gillberg, 1997; Demeter, 2000; Lindberg, 2006).

As the primary caregivers, the parents and family play a vital role in ensuring the health and well-being of children. The focus of health and developmental services has evolved from a child-centered, traditional "medical" model to a family-centered "developmental" model. Bly suggests that as: "The more involved the family becomes, the more consistent therapeutic management becomes" (Bly, 1999). In this framework, those who coordinate services consider the essential contributions of the family unit and the ability of families to adapt to new challenges. The pediatric healthcare professional must involve family members in all areas of planning, delivery, and evaluation of health and developmental services. Communication between parents and pediatric healthcare professionals should be open, comprehensible, culturally sensitive, and sincere (Ramey and Ramey, 1996). Therefore, the family's involvement is a fundamental resource. However, in planning the involvement of parents in the therapeutic path of their child with disability, therapists cannot ignore the impact of that decision on the parents' stress level (Smith et al., 2001). Stressful experiences are considered as person-environment interactions, in which both external stressors and available psychological, socioeconomic, and cultural resources influence the person's appraisal of the stressor (Lazarus and Folkman, 1984). Stress was found as a multi-dimensional construct that can be operationalized in various ways, often related to having children with developmental disabilities (Crnic et al., 2009).

Furthermore, it is known that stress levels negatively influence the well-being of parents of children with developmental disabilities (Cramm and Nieboer, 2011). In general, it can be determined that exposure to prolonged or chronic psychological distress has resulted in adverse health outcomes, ranging from inadequate sleep to negative psychological and physiological well-being (Lee, 2013).

It is known that the process of caring for a child with RTT is, by itself, a difficult task for the family, requiring the activation of psychological, social, and economic resources, and may represent a source of stress for family members (Downs and Leonard, 2016). The risk of increased parental stress level arises from the beginning of the disorder when parents must face the onset of RTT in a child who has shown an initial normal development. Moreover, additional medical comorbidities can arise during childhood, requiring increased attention and constant adaptation of the parents' caring strategies, all within a framework of uncertainty regarding their daughter's life expectancy (Mori et al., 2019). Recent articles explored the stress levels of parents of girls with RTT. Authors reported an increased stress level in this population of parents, with mothers showing a higher stress level than fathers (Perry et al., 1992; Pari et al., 2020). Moreover, parental stress level and health-related quality of life were found to correlate with the degree of clinical severity (Sarajlija et al., 2013; Pari et al., 2020). Nevertheless, the stress level appears higher for those parents who had taken care of a girl with RTT for many years and were, on average older, showing a cumulative effect (Mori et al., 2019; Pari et al., 2020). Despite this regression in stress levels, several authors agree that many families with RTT have found functional strategies to cope with the strains of their particular parenting (Perry et al., 1992; Mori et al., 2019). The existing literature agrees in affirming the need for solid support for these parents, which should follow them across their whole parental experience (Perry et al., 1992; Pari et al., 2020). Considering the delicate balance of the need for an intense, long-lasting structured rehabilitative program while maintaining a healthy familial infrastructure, it is necessary to investigate the effects of parental involvement in their daughters' therapeutic activities on their well-being.

In February 2020, first COVID-19 patients were recognized in Italy. From that moment, the number of affected people started to increase all over the country and abroad and, on March 11th, 2020, the world health organization declared the COVID-19 global pandemic (World Health Organization, 2020). On the same date, the Italian government ordered the first national lockdown closing the majority of the working places, schools, and places of worship and prohibiting all recreational activities. During the lockdown, people have been confined to their houses with the possibility to go out for only a few specific reasons. According to the literature, many Italian parents experienced significant parenting-related exhaustion and well-being levels reduction with increased anxiety, with mothers more severely affected (Cusinato et al., 2020; Marchetti et al., 2020; Bentenuto et al., 2021). Coherent results were found related to mothers of people with disabilities.

An Italian study reported increased sleep difficulties and feelings of reduced external support for mothers of children with X-Fragile syndrome. However, their perceived self-efficacy as caregivers did not change during the lockdown (Di Giorgio et al., 2021).

Feelings of abandonment, powerlessness, and fear for their and their children's health have been reported in numerous studies that have explored the experiences of mothers of both children and adults with intellectual disabilities during the lockdown (Asbury et al., 2021; Embregts et al., 2021; Patel et al., 2021; Rogers et al., 2021). Moreover, in an online survey administered with 527 Italian parents of children with autism spectrum disorder, 93.9% of parents reported that the COVID-19 emergency was a challenging period with difficulties in free time management and structured activities development. The same study reported a low level of specialist support for medical and behavioral needs (Colizzi et al., 2020). Coherently, Bova et al. (2021) analyzed data from interviews conducted with parents of 514 Italian children with neurological disorders who reported that 67.7% of programmed specialist appointments were canceled during the lockdown and about half (49.5%) of children who usually received rehabilitation continued it remotely.

On the other hand, a study from the United Kingdom reported that well-being in families of children with intellectual disabilities measured before and during/immediately after the lockdown did not show any difference. The authors concluded that the general belief of the lockdown's negative impact on these families could be as straightforward as expected (Bailey et al., 2021). Sporadic similar results were available in other articles that reported benefits for parents due to changes in their daily routines. For these parents, the house confinement represents a possibility to spend more time with their family, strengthening the parent-child relationship and contributing to their well-being (Bentenuto et al., 2021; Embregts et al., 2021; Rogers et al., 2021).

Reports suggest the need for support by most parents of people with intellectual disabilities. Remote rehabilitation has represented a valuable strategy to continue the treatment and support the families in those difficult days (Assenza et al., 2020; Rabanifar and Abdi, 2021). However, patients who have received remote rehabilitation intervention perceived differences in the quality of service and preferred traditional in-person treatment to service delivery *via* remote rehabilitation (Milani et al., 2021). This article aims to describe the well-being level of two groups of mothers of girls and women with RTT who were involved in a home-based remotely supervised motor rehabilitation program, respectively, before and during the COVID-19 Italian lockdown.

MATERIALS AND METHOD

Ethical Approval

Declaration of Helsinki principles was followed while conducting this research. The research protocol was approved by Ariel University IRB (AU-HEA-ML-20190326-1) and explained to

all participants' parents, who signed an informed consent form after understanding the protocol and agreeing to participate.

Participants

Participants were recruited from the Italian Rett syndrome Association database (AIRett). To be included in the current investigation, participants must be genetically diagnosed with classic RTT and reside with their parents. Moreover, participants' parents must have approved their availability to follow a physical rehabilitation activity program with their daughter for one non-consecutive hour a day, 5 days a week, for 3 months. Candidates for participation were excluded if they presented a neurological or psychomotor developmental deficit comorbidity other than RTT. All candidates were approved to participate by a specialist doctor certified (due to unstable health conditions, e.g., ongoing or recurrent infections, severe gastrointestinal disorders, and drug-resistant epilepsy with multiple daily seizures).

Study Design

A randomized between-groups comparison design was applied. Participants were randomly divided into Group 1 and Group 2. Both groups followed the same A-A-B-A-A protocol. Group 2 started the intervention program 3 months after Group 1. Letter "A" represents the evaluation meetings that occurred 3 months apart. Letter "B" represents the intervention phase. Before the COVID-19 outbreak, when the study was planned, the authors intended to analyze the intervention effects on participants in Group 1 and Group 2 together. However, the Italian COVID-19 lockdown occurred before the beginning of the Group 2 intervention phase occasioning the opportunity to investigate the intervention impact on maternal well-being within the context of the lockdown limitations. Therefore, for the current article, the research protocol planned before the lockdown initiation was not changed due to the COVID-19 outbreak, but the collected data were analyzed for the two groups independently and compared. The research timetable is outlined in **Figure 1**.

The Participatory Action Research (PAR) method was used. Within the PAR model, participants (in this case, the family members, caregivers, and referral therapists of the person with RTT) are involved throughout the whole research process (Mackenzie et al., 2012). They are asked to participate with the researchers in planning their involvement in the research, identifying problems, and finding solutions to disentangle them

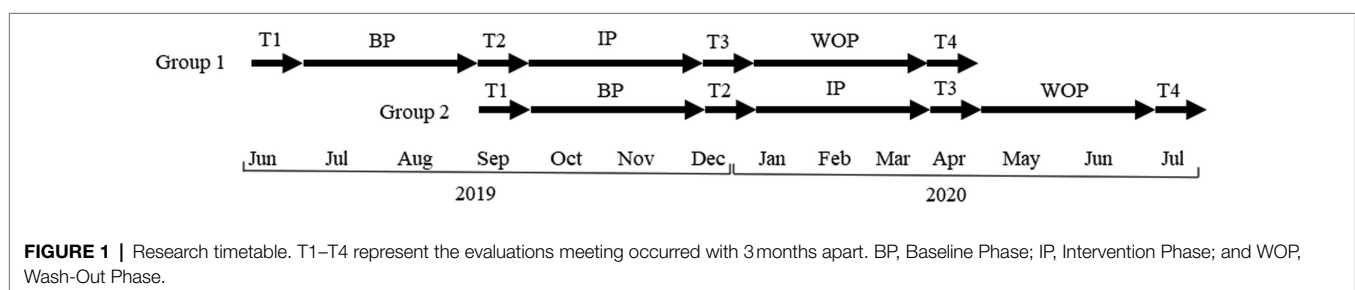
through the direct application of research findings in a practical context (Ison, 2014). PAR design is characterized by three recurring stages: inquiry, action, and reflection (Kemmis and McTaggart, 2005). In the current article, the PAR process was developed through the implementation of numerous and continuous cycles of:

- Assessment (of each participant's therapeutic needs);
- Mutual goal attainment (individualized therapeutic goals were set in mutual agreement with each participant's parents taking into consideration the participant need and her parents expectation, needs, and availability within the family's framework);
- Action (the family members implemented the program);
- Reflection (each program was discussed with participant's family members within the bi-weekly supervised Skype meetings between a trained supervisor and parents); and
- Evaluation (if necessary, the program was modified and re-implemented).

The theoretical framework of PAR allows the participants to actively participate in the research protocol construction they are involved in resulting in greater intervention effectiveness (Newig, 2007). Thus, PAR researchers collaborate with the participants to obtain changes and identify new solutions according to their family's needs and desires (Ozanne and Saatcioglu, 2008). Even considering the lower level of evidence of PAR design compared to the randomized controlled trial, it best-suited studies that provide a protocol requiring a high level of collaboration between researchers and participants, as is the present investigation (Mackenzie et al., 2012). Moreover, it is the researchers' intention that the participants' parents fully understand the process of planning positive physical activity for their daughter (similar to those proposed in the present research) becoming able to develop them even after the research concludes to maintain long-lasting well-being and functional status of the participants with RTT.

Procedure

All participants' parents signed an informed consent explaining the research protocol before the research initiation. Each participant was evaluated four times at their house. Evaluation meetings were conducted with 3 months apart from each other (± 1 month, T1–T4). Participants' mothers' well-being was assessed during each evaluation meeting.



During the first evaluation meeting (T1), anamnestic information related to participants' medical situation was collected (e.g., epilepsy, bone density condition, feeding problems, sleep disorders, and other comorbidities typically associated with RTT) together with the extent and type of ongoing physical therapeutic interventions (such as physiotherapy, hippotherapy, hydrotherapy, and others). At the end of this meeting, the researchers compiled a draft of the individualized rehabilitation goals in collaboration with participants' parents to be pursued in the intervention phase. The objectives set followed the SMART principles to best suit each participant's potential. Under SMART principles, goals should be specific, measurable, attainable, realistic, and timely (Bovend'Eerd et al., 2009). No change was made between the first and second evaluation meetings (baseline phase) to the participants' and their parents' daily routines.

In the second evaluation meeting (T2), identified treatment goals were re-discussed with participants' parents, and corrections were applied if needed. At the end of the second (T2) evaluation meeting, an individualized motor activity program was designed for each participant and discussed with the family. Each activity program was developed to pursue the identified intervention goals through easily constructed physical activities that did not require professional competencies to be carried out.

After the second evaluation meeting termination, participants' parents were asked to conduct the activities of their daughter's program within her daily routine, for one non-continuous hour a day, 5 days a week, for 3 months. Researchers helped the parents to plan the therapeutic activities development within their weekly routines and habits. After 2 weeks from the delivery of the program, necessary for familiarization with the activities, each family started to participate in remotely conducted supervision meetings with a researcher experienced in the rehabilitation of people with RTT. Supervision meetings occurred fortnightly and lasted for a maximum of 1 h. A videoconference platform (Skype) was used to conduct the supervision meetings. These meetings continued until the end of the intervention phase. The first supervision meeting was mainly dedicated to clarifying any doubts about the practical execution of the activity programs, guiding the parents in the activity development, and modifying them if necessary to meet the families' needs. The subsequent supervision meetings aimed at supporting the adherence to the program and their execution by answering parents' questions, adapting the program to emerging needs, solving problems, rearranging the timetable, adapting the proposed exercises, evaluating and sharing the achievement of objectives and, if necessary, setting new goals. Due to the experience of the researchers in RTT, the weekly meetings did not refer only to the program implementation but also to general issues related to RTT, raised by the parents.

After the 3 months of programs implementation, the third evaluation meeting (T3) was conducted. In this meeting, the level of achievement of identified goals was assessed, and the parents' considerations relating to the intervention phase were collected.

Between the third (T3) and fourth (T4) evaluation meeting (wash-out phase), the remote supervisions were suspended,

and parents were informed that they could, at their discretion, continue or interrupt the program. The researcher took this choice to support the continuation of the activities learned, promoting the participants' physical fitness.

Measures

RTT Severity Level

Rett Assessment Rating Scale (RARS; Fabio et al., 2005) was administered at T1 to assess the participants' level of RTT clinical severity. This is a 31-item scale aimed to score many specific RTT phenotypic characteristics. Each item is scored on a four-point scale from one to four. Intermediate scores (e.g., score of 2.5) can be attributed to the subject to make the scale more sensitive to the typical variability of RTT. In the theoretical framework of this scale, RTT severity is conceptualized as a continuum between mild deficit (lower score) to severe symptoms (higher score; Vignoli et al., 2010). RARS standardization procedure for the Italian population with RTT was conducted involving a sample of 220 individuals with RTT. Solid psychometric values were proved for this scale (Fabio et al., 2005, 2014; Vignoli et al., 2010; Romano et al., 2020). The results obtained at this scale will be only briefly discussed within the present article. The results obtained from this scale will be presented to provide the reader with a more precise description of the participants' disease severity.

Mothers' Well-Being

The change in the well-being level across the protocol was evaluated with the short form of the Caregiver Well-Being Scale (CWBS-SF; Tebb et al., 2013). This is a 16-items scale targeted to address areas relevant to caregivers that allow obtaining information related to their well-being. The scale covers basic needs (meeting the biopsychosocial needs to sustain life) and activities of daily living (regarding the implementation of the biopsychosocial needs). A daily need is presented for each item, and the parent is asked to assign a score based on the level he feels he has satisfied that need in the previous 3 months. The score is attributed on a five-point Likert scale from 1 (the need was never or almost never satisfied) to 5 (the need was almost always satisfied). The scores of each item were averaged together for the subsequent analysis. This scale showed an overall internal consistency of 0.83 (Tebb et al., 2013). The CWBS-SF was administered with participants' mothers only as few fathers participated in all the evaluation sessions.

Statistical Analyses

The Shapiro-Wilk normality test was used to assess the normality of the data distributions. As most analyzed data sets were not normally distributed, the non-parametric statistic was used to analyze the obtained results. Friedman's test was run to compare the CWBS-SF scores obtained from the mothers in each group and all together at the four evaluation points. *Post-hoc* analysis with Wilcoxon signed-rank tests was conducted for pairwise comparisons. Mann-Whitney U Test was used to compare the results obtained by Group 1

with those achieved by Group 2 at each time point for all the outcome measures. The Spearman rank correlation coefficient was used to explore the relations between participants' mothers' well-being (CWBS-SF score) and participants' and their mothers' age and level of participants' clinical severity at T1 (RARS score). The threshold for significance for the analyses above has been assumed as $\alpha=0.05$. No correction for multiple comparisons was applied to avoid missing significant results (Armstrong, 2014).

RESULTS

Main Descriptive Statistics

Forty-two families were involved in the first evaluation (T1). Two families (4.8%) did not complete the research protocol. One drop-out happened in Group 1 and was due to health problems of the participant's mother that arose during the baseline period. The other drop-out occurred in Group 2 and concerned a family living in a rural area with negative external involvement by local healthcare professionals who gave them contradicting advice about the proposed program for their child with RTT. Therefore, data of 40 participants with RTT were used for the subsequent analysis. Participants' and parents' ages and RTT severity levels measured with RARS were collected in **Table 1**.

At the first evaluation meeting (T1), 11 participants were younger than 10 years, 19 were aged between 10 and 20 years, and 10 were older than 20 years. Seven participants attended motor rehabilitative intervention for at least 4 h a week. Twenty-six subjects attended such interventions between 1 and 3 h per week. Five participants were not involved in any motor rehabilitative treatment. All the rehabilitative interventions were suspended during the lockdown. All participants resided at home with their parents. All the participants and their parents were born in Italy. The participants' and parents' daily routines and the amount of parents' working hours varied widely within our sample. In three families, the parents were divorced, and the participants lived with their mother. A weak correlation was found between maternal well-being and both participants' and mothers' ages

at T1 ($p=0.001$, $\rho=0.491$ and $p=0.006$, $\rho=0.429$, respectively), T2 ($p=0.005$, $\rho=0.433$ and $p=0.032$, $\rho=0.339$, respectively), and T4 ($p<0.001$, $\rho=0.530$ and $p=0.011$, $\rho=0.398$, respectively). No correlation emerged between the maternal well-being level and participants' RTT severity level.

Differences Regarding Mothers' Well-Being

CWBS-SF was assessed to investigate the impact of program implementation on participants' mothers' well-being. Descriptive statistics of CWBS-SF are collected in **Table 1**. The variation of maternal well-being within the current project differed consistently between Group 1 and Group 2 (see **Figure 2**).

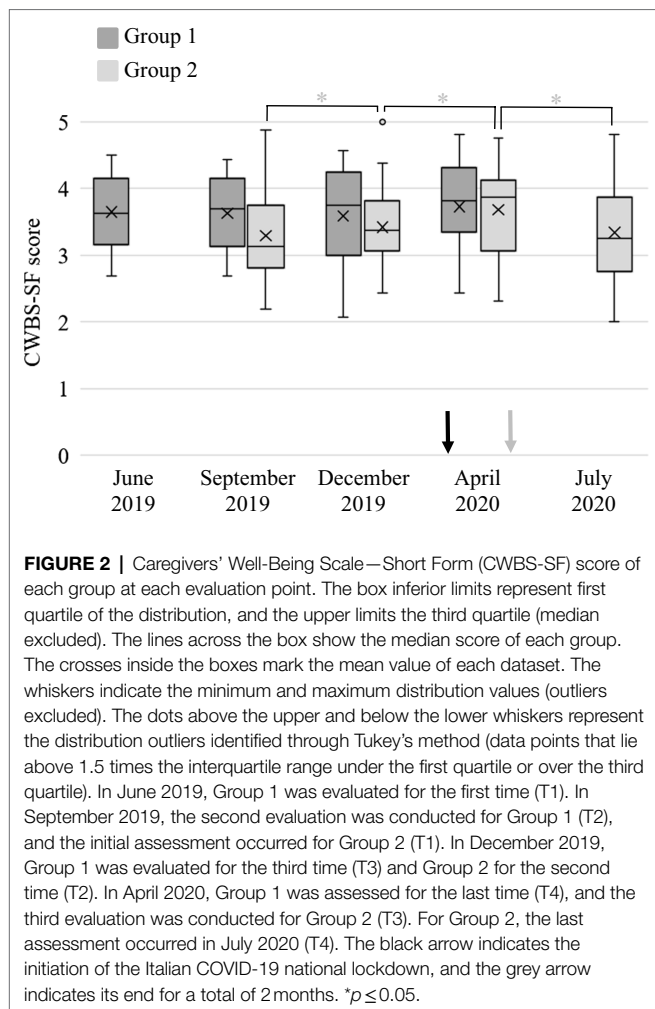
However, when analyzed with the Mann-Whitney U Test, no statistical difference emerged between mothers in Group 1 and Group 2. Mothers in the Group 1 showed a stable level of well-being across all four evaluations with a slight improvement of median well-being level between T1 and T4. These changes were not statistically significant at any conducted analysis. Conversely, the well-being level of mothers in the Group 2 showed a significant change across the four evaluations at the Friedman test ($p=0.012$). Significant increases in mothers' well-being were found between T1 and T2 and between T2 and T3 ($p=0.002$; $p=0.013$, respectively), but a statistically significant reduction between T3 and T4 ($p=0.031$) was found. Looking at participants' mothers altogether (see **Figure 3**), the Friedman test identified no significant score change among the four evaluation meeting. However, the maternal well-being showed a significant increment between T1 and T2 ($p=0.018$) and between T2 and T3 ($p=0.050$) and then slightly reduced at T4, but without reaching the statistical significance with any of the other evaluations.

Moreover, on average, the CWBS-SF score in our group remained within the range described as acceptable for families without children with disabilities (average: 3.6—range: 2.7–4.9; Tebb et al., 2013). No correlation emerged between the mothers' well-being level and the other outcome measures.

TABLE 1 | Descriptive statistics of participants' and parents' age, RTT severity level (RARS), and CWBS-SF score.

| | | Participants' age | Mothers' age | RARS score | CWBS-SF | | | |
|------------------------------|-----------|-------------------|--------------|------------|----------|----------|----------|----------|
| | | | | | T1 | T2 | T3 | T4 |
| All participants (No. 40) | Mean (SD) | 15.7(9.7) | 50.0(9.8) | 67.3(9.8) | 3.4(0.6) | 3.5(0.6) | 3.6(0.7) | 3.5(0.8) |
| | Median | 13.3 | 48.4 | 67.8 | 3.3 | 3.5 | 3.8 | 3.5 |
| | Max–Min | 40.3–2.8 | 75.1–29.1 | 82.5–45.5 | 4.9–2.2 | 5–2.4 | 4.8–2.1 | 4.8–2 |
| Group 1 (No. 17) | Mean (SD) | 16.4(7.9) | 53.4(7.1) | 66.5(10.7) | 3.6(0.6) | 3.6(0.6) | 3.6(0.7) | 3.7(0.7) |
| | Median | 13.3 | 51.4 | 68.0 | 3.6 | 3.7 | 3.8 | 3.8 |
| | Max–Min | 38.2–5.4 | 67.5–39.5 | 82.5–45.5 | 3.6(0.6) | 3.6(0.6) | 3.6(0.7) | 3.7(0.7) |
| Group 2 (No. 23) | Mean (SD) | 15.1(11.0) | 48.8(10.8) | 67.8(9.2) | 3.3(0.7) | 3.4(0.6) | 3.7(0.7) | 3.3(0.8) |
| | Median | 13.3 | 46.7 | 67.0 | 3.1 | 3.4 | 3.9 | 3.3 |
| | Max–Min | 40.3–2.8 | 75.1–29.1 | 82.5–51.5 | 3.3(0.7) | 3.4(0.6) | 3.7(0.7) | 3.3(0.8) |

SD, Standard deviation; RTT, Rett syndrome; RARS, Rett assessment rating scale; and CWBS-SF, Caregiver well-being scale—short form.



DISCUSSION

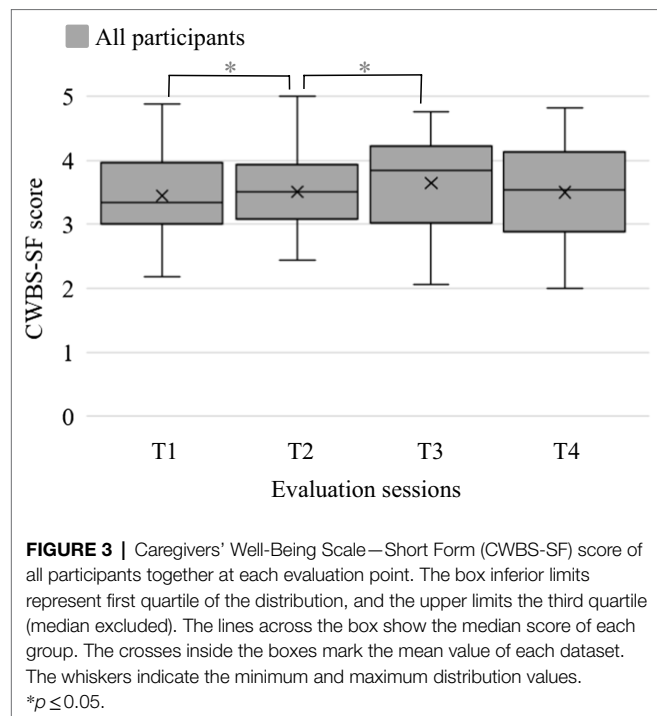
This article described the well-being of mothers of girls with RTT and how it was affected by their enrollment in their daughter's rehabilitation program during the COVID-19 lockdown in Italy. A motor activity program was given to each involved family to be carried out at home and was fortnightly remotely supervised through video calls. Parental well-being was assessed before and after treatment. However, on March 9th, the Italian government established the first national lockdown to face the COVID-19 outbreak. This has led to the interruption of most working and recreational activities and to the obligation for all Italian citizens to stay at home and go out only if strictly necessary. In this phase, rehabilitation and assistance facilities for people with disabilities and schools were also closed. The lockdown and the related restrictions continued until May 4th, when most work activities were resumed, but without the reopening of shops, restaurants, cafes, and places of worship that occurred on May 18th. On the same day, some, but not all, rehabilitation activities for people with disabilities were also resumed. However, the limitations

to some recreational activities, such as cinemas and theaters, and the attendance of summer camps for children continued until June 11th, and school attendance did not start again until September 2020. The restriction progression caused the parents to spend 2 months at home with their families without working activities. Subsequently, after the recovery of the working activity (May 4th), the parents' situation has changed. They were asked to go back to work within a context of social distancing, reduced availability of recreational activity, fear of contagion, and with their child at home from school and rehabilitation facilities.

In this study, two groups of people with RTT and their families followed the same research protocol starting with 3 months apart. For this reason, the lockdown occurred in a different phase of the protocol for the two groups. For Group 1, the restrictions began within the wash-out phase while, for Group 2, the lockdown started during the intervention phase (see Figure 1). The mothers' well-being scores across the four evaluation meetings differed for the two groups. The mothers in Group 1, after stable well-being scores in the first three evaluation meetings, showed a slight increase at T4 (during the lockdown). Similarly, the well-being of mothers in the Group 2 increased at baseline and, more markedly, during the intervention phase, before going back to the pre-intervention level at T4. These results suggested that the lockdown did not negatively affect the mothers' well-being level but increased it. This effect can be explained by the fact that the lockdown situation allowed the mothers to spend more time with their families in the absence of working activities. These results are correlated to the findings of Bailey et al. (2021) and with sporadic results from other studies (Bentenuto et al., 2021; Embregts et al., 2021; Rogers et al., 2021).

Nevertheless, within the lockdown, mothers in Group 2 showed a more markedly improved well-being than those in Group 1. These can be explained by the presence of the remote supervision meeting that occurred during the lockdown for Group 2 but before it for Group 1. The literature reports that parents of children with intellectual disabilities suffered the reduction in healthcare professional support they received through the lockdown (Asbury et al., 2021; Embregts et al., 2021; Patel et al., 2021; Rogers et al., 2021). This did not happen in the case of mothers in group 2 who received an organized program to implement and constant follow-up talks where they could unload their fears and concerns.

Furthermore, the positive correlation between mothers' and participants' age and maternal well-being suggests that older mothers have higher well-being levels than younger ones contrasting with published literature (Perry et al., 1992; Pari et al., 2020). The fact that both articles investigated parental stress while our study focused on maternal well-being could explain this difference. However, both Perry et al. (1992) and Pari et al. (2020) suggested that families with RTT frequently find suitable strategies to cope with the strains related to their parental role. In this light, our findings agree with the researches mentioned above, as shown by the average well-being level of parents in our groups that remained in the range reported for parents without children with disabilities (Tebb et al., 2013).



However, these results may also relate to the fact that all participating families remained protected from the COVID-19 contagion and were financially well established, thereby reducing the burden associated with the pandemic.

The current investigation presents some limitations. First, only one measure of maternal well-being was used. For more solid results, more evaluation tools should be used to investigate more dimensions of maternal well-being and stress level in the future. Moreover, the amount of time each parent spent in their daughter's program was not collected, but we asked them never to exceed 1 h of treatment per day for 5 days a week. Furthermore, a relatively small sample was enrolled in this study, challenging the external validity of the obtained results. Additionally, each group's participants' data were analyzed together, preventing further fine-grained analyses. As a correlation between the participants' ages and their mothers' well-being level was identified, the age effect may have affected the whole group's well-being outcome. Therefore, future studies are needed to evaluate the impact of the participants' and parents' ages on the well-being of parents involved in activity programs, such as the one presented. Plus, the maternal working status changes due to the lockdown were not assessed within the present study limiting the validity of the discussion of the results. However, most workplaces were closed, and people were forbidden to leave their houses (except for a few reasons) within those months in Italy. Therefore, the authors reasonably assumed that, on average, the participants' mothers' working hours were reduced during the lockdown. Similarly, it would have been interesting to analyze the amount of social support the mother received in the different phases of the present study and their impact on maternal well-being. Finally, only mothers' well-being was analyzed due to fathers' missing data. Future research should investigate these variables

individually for each parent to understand the differences between the impact of the treatment on both mothers and fathers.

CONCLUSION

The results obtained at the CWBS-SF hint that the availability of an activity program and the conducted remote supervision calls positively affected maternal well-being in a challenging period, such as the COVID-19 lockdown. Moreover, as the researchers were highly familiarized with RTT, their bi-weekly calls enabled the parents to consult on other issues which were not directly connected with the motor elements of the program. It is the authors' opinion that the strategies and suggestions given to parents within the current project supported the daily caring of their daughters, supporting the maternal well-being in accordance with existing literature, not specifically related to RTT (Singer et al., 2007; Todd et al., 2010).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ariel University Institutional Review Boards, Ariel University, Ari'el, Israel. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ML obtained the funds. MZ and ML coordinated the project. ML and AR conducted participants' evaluations. AR organized the participants' evaluations and carried out all remote supervision meetings. EI and MF collected the data that MZ and AR analyzed. MZ, ML, and AR wrote the article. All authors have read the article and suggested improvements and changes until agreement was reached.

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Clinical Guidelines of the Egyptian Psychiatric Association for the Management of Treatment-Resistant Unipolar Depression in Egypt

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Background: Major depressive disorder (MDD) is a public health burden that creates a strain not only on individuals, but also on the economy. Treatment-resistant depression in the course of major depressive disorder represents a clinically challenging condition that is defined as insufficient response to two or more antidepressant trials with antidepressants of the same or different classes that were administered at adequate daily doses for at least 4 weeks.

Objective/Hypothesis: To develop a treatment guideline for Treatment Resistant Depression (TRD).

Methodology: Experts in the field gathered and reviewed the available evidence about the subject. Then, a series of meetings were held to create recommendations that can be utilized by Egyptian psychiatrists.

Results: The guidelines provide recommendations in various clinical settings. It evaluates different situations, such as patients at risk of resistance, those with resistance and recommends strategies to resolve the clinical case.

Conclusion: The consensus guidelines will improve the outcomes of patients, as they provide recommendations across various domains that are of concern for the practicing psychiatrist.

Keywords: depression, treatment resistance, guidelines, clinical psychiatry, neuropharmacology

INTRODUCTION

MDD is defined as a disorder of having one or more major depressive episodes in a person's life with the absence of manic or hypomanic symptoms; to meet the criteria of MDD five out of nine symptoms, two of which must be low mood and anhedonia (loss of pleasure) persisting for a 2-week period. The nine symptoms include low mood, loss of interest or pleasure, disturbed sleep, change of eating pattern or weight, agitation or psychomotor slowness, unexplained fatigue, feeling worthless or guilty, inability to concentrate and thoughts of death or suicide (1).

Major depressive disorder (MDD) is a major public health concern. It is projected to be the first cause of disease burden worldwide by 2030 (2). According to the World Health Organization (WHO), depression affects over 260 million individuals worldwide (3). Results of a recent systematic review by Odejimi et al. reported that the prevalence of depression in Egypt ranges between 23.7 and 74.5% (4).

This mental disorder results from the interaction of several factors, including psychological, social and biological factors (5).

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), a person is diagnosed with MDD when he or she consistently depressed mood or anhedonia, along with five of the following symptoms; difficulty in concentration, appetite changes, decreased energy, sleep disturbance, suicidal thoughts and tendencies, concentration difficulties, or psychomotor agitation or depression (6).

In medicine, the term “resistance” is used to describe the failure of standard treatment; although there is no distinct definition for TRD as clinical practice is ever evolving and because treatment “failure” is sometimes judged by physicians themselves when their patients do not respond as much as they expected them to. In short, TRD is described as depression that is unresponsive to antidepressant drug treatment at adequate dosing for an adequate amount of time (5).

Response to traditional treatment has been assessed by several studies (6). One major trial highlighted that the remission rate after step 1 of treatment was 36.8%, with the remission rate decreasing after each step of treatment, reaching only 13% at the fourth step (7, 8). In other words, the more advancement in treatment lines, the more likely is the patient to relapse. The same study concluded that the overall remission rate was 67%, highlighting that about 1 in every 3 patients fails treatment (9).

Several psycho-pharmacotherapeutic strategies have been suggested to overcome TRD, whereby augmentation treatment represents the currently recommended first-choice in case of insufficient response to the initial antidepressant treatment. In accordance with available international evidence, second-generation antipsychotics or lithium should be preferably employed (6).

Many patients are labeled as treatment resistant mistakenly when they are actually pseudo-resistant cases of depression; most common causes of this case are due to sub-therapeutic dosing or non-adherence to medication. According to APA guidelines it is important for physicians to assess any patient comorbidities, modifying doses of first line treatment if it failed after 4 weeks, considering patient history when adding second line treatment to ensure that the patient will positively respond to the medication and only initiating second line treatment after unsatisfactory response at 4 weeks (9).

“According to available international evidence, this publication will cover treatment options and recommendations from the Egyptian Psychiatric Association for the management of TRD in the course of MDD in Egypt.”

METHODS

Expert recommendations were determined after a thorough examination of available literature to identify and assess the recent global updates about the subject. Prior to the meeting, two senior members of the committee performed a comprehensive search on the PubMed database to identify the available literature relevant to the topic using keyword, such as “treatment-resistant depression”, “major depressive disorders” and their derivatives. Then, those senior members prepared a questionnaire using the Delphi technique and invited committee members to assess the literature and respond to the questionnaire.

Afterwards, responses of clinicians to the questionnaire were captured, analyzed and ranked. Then, another round of questions was dispensed in a second meeting based on the outcomes of the first committee gathering and questionnaire responses. The second round was when a consensus was reached by all committee members, therefore there was no need for further meetings (10).

RESULTS

Panel Description

An expert panel of 8 professors of psychiatry from different universities and the ministry of health representing the Egyptian Psychiatric Association drafted the following guidelines. Information about panel members can be found in the **Appendix**.

Definition of Resistant Depression

According to a meta-analysis by Gaynes et al. 2019, there is no clear-cut definition for TRD, however, most experts unanimously agree that lack of response to initial treatment is deemed as TRD. The APA (American Psychological Association) and NICE (National Institute for Health and Care Excellence) guidelines also state that the next step of handling TRD also differs between experts which makes it more challenging to develop universal treatment guidelines. The classes of medications should be among the following: (11).

- Tricyclic antidepressants (TCAs) (equivalent to 300 mg imipramine) (12)
- Selective serotonin reuptake inhibitors (SSRIs) (equivalent to 50 mg fluoxetine) (13)
- Serotonin norepinephrine reuptake inhibitors (SNRIs) (equivalent to 225 mg venlafaxine) (14)

Antidepressant treatment has been the mainstay treatment of depression for years; the first class of such drugs were tricyclic antidepressants followed by more novel agents namely SSRIs and SNRIs. Both classes of TCA and SSRIs are equally affective in ameliorating depressive symptoms and decreasing depression scores as proved by a meta-analysis to compare the two classes. However, SSRIs are preferred by patients as well as physicians as they do not produce bothersome side effects as TCAs (15).

SNRIs are a group of antidepressants with a dual mechanism of action of both serotonin and adrenergic reuptake inhibition; research has suggested that SNRIs are superior to SSRIs in more severe depression; which insinuates their possible effectiveness in TRD. Moreover, SNRIs have established efficacy in treating depression with somatic manifestations as pain and other physical symptoms (16). The Danish guidelines; which incorporates the APA and NICE guidelines states that most patients first diagnosed with MDD are treated with SSRIs then switched to SNRIs. The ten most prescribed treatments for TRD mainly constitute of both SSRI's and SNRI's as first, second- and third-line treatments (17). Other antidepressants as trazodone, vilazodone and tranylcypromine are also available options however, are not easily accessible in the Egyptian market.

The advisory committee recommended of TRD be as follows:

Treatment-resistant depression shall be defined as the failure of 2 different classes of antidepressant medications, given that the medications have been used for a period of 6–8 weeks at the desired dose.

N.B. (Nota bene) to the above definition and in order to account for the definition of TRD in Egypt, the committee added 6–12 monitored sessions of BST (Brain Synchronization Therapy)/ECT (Electroconvulsive Therapy).

The panel recognized the importance of identifying the term “pseudo-resistance”, which was defined by the panel as a patient not responding to medication because of a problem in the diagnosis or the type of depression or the presence of depression secondary to another psychiatric, personality or medical disorder.

In addition to pseudo-resistance, the clinical experts highlighted additional predictors for TRD, as follows:

- Other forms of depression such as bipolar depression.
- Other comorbid conditions, including concurrent anxiety, drug abuse, chronic organic medical conditions, and personality-related disorders (e.g., mood swings in borderline personality disorder).

Assessment of Treatment-Resistant Depression

Clinical panel experts recommended using the following set of clinical tools and tests to identify and diagnose TRD.

- Depression severity scales such as Montgomery-Asberg Depression Rating Scale (MADRS) and psychiatrist-rated scales. Montgomery-Asberg Depression Rating Scale has long been used by physicians for assessing depression, the advantage of MADRS is that avoids the drawbacks of the HAM-D score and is more robust. It is used mainly to detect any patients' response changes to antidepressant therapy with high sensitivity and is positively correlated to change in degree of depression (18).
- Hypomania check list: The hypomania checklist has long been used in many countries and in different languages to differentiate bipolar depression from MDD. This is important as manic/psychotic symptoms in depression should not be confused with TRD (19).

- Suicide scale [e.g., Beck's Scale for Suicide Ideation or Columbia Suicide Severity Rating Scale (C-SSRS)]. Suicide ideation scales are mainly used to monitor patient's health and to predict the risk of actual suicide for timely intervention (20). The BSS is one of the most reliable tools to predict a patient's risk and plan for suicide. The C-SSRS is also a sensitive scale to use especially that it is sensitive to change of suicidal ideation over treatment time and with the use of medication (21).
- Complete blood count (CBC), liver and kidney function tests, lipid and glycemic profiles: Complete blood count (CBC), liver and kidney function test and lipid and glycemic profiles; all these tests can be used and are done to eliminate any disease that could precipitate symptoms of depression (22).
- Thyroid function test: Regarding thyroid profiling; it is established through a wide volume of research that hypothyroidism presents with some depressive symptoms, in a study conducted by Bathla et al. 56% of males and 64% of females with hypothyroidism presented with some symptoms of depression and anxiety (23).
- Electrocardiogram: An electrocardiogram could be beneficial since stress (a component of MDD) is linked to heart disease. Not only that; depression onset is often seen in up to 40% of patients after a major cardiac event. Therefore, an ECG could be of use to determine heart health of patients and to stratify patients who could be at risk of developing MDD or TRD (24).
- Brain imaging techniques like magnetic resonance imaging (MRI): Recently, brain imaging using MRIs or CT scans have been utilized in the diagnosis of MDD especially in the elderly. This is because some cases of depression indicate an underlying mental disease as Parkinson's, Alzheimer's and Pick's disease; moreover, geriatric depression has been associated with leukoencephalopathy that can be detected using brain imaging techniques (25).

The panel highlighted the importance of periodic performance of most of the above tests upon prescribing ADs. In addition to the aforementioned tests, the panel also recommends performing the following tests based on clinician's discretion and the patient profile, as follows:

- Assessing vitamin D plasma levels
- Assessing sex hormones plasma levels
- Toxicological analysis of blood and urine samples

Principles of Management

Hospitalization: Indications

Upon careful assessment of the condition, the expert panel agreed that psychiatric hospitalization is warranted in severe cases that fall under the umbrella of one of the following:

- Catatonic cases
- Patients with high suicidal tendency
- Severe psychotic symptoms
- Advanced cases of MDD
- The presence of severe uncontrolled comorbid medical conditions
- Insufficient familial support to the patient

Therapeutic Options for Treatment-Resistant Depression and Comorbid Conditions

Pharmacotherapeutic Options of Comorbid Conditions

For patients suffering from comorbid conditions, the expert panel recommends the following:

Patients suffering from anxiety and its features are recommended to receive benzodiazepines. Buspirone and pregabalin are also available options. Anxiety and depression often go hand in hand; therefore, a multi-modal treatment approach for handling both illnesses are often recommended. The evidence in the treatment of anxiety disorders greatly points to SSRIs, SNRIs and benzodiazepines. Benzodiazepines have long been used as anxiolytics as they demonstrate a relatively high safety and tolerability profile, they also have a rapid onset of action and manage acute anxiety symptoms and somatic complaints according to the NICE guidelines. The common issue physicians and patients face with benzodiazepines is dependence and abuse; thus, benzodiazepines should be preferentially used for a short amount of time (26).

The NICE guidelines usually recommend pregabalin in patients with anxiety if they do not tolerate SSRIs and SNRIs; pregabalin is an anti-convulsant and is also used for neuropathic pain; the advantage of pregabalin over benzodiazepines is that it does not cause dependence; however, sudden discontinuation may cause confusion. Buspirone, a non-benzodiazepine alternative is also prescribed for anxiety symptoms; the evidence regarding its efficacy in comparison to benzodiazepines is conflicting; however, it does not cause sedation, withdrawal symptoms or addiction as benzodiazepines (27).

Patients with depression or TRD frequently suffer from sleep disturbances; therefore, a sleep-aid can be used to overcome this symptom. Benzodiazepines; although excellent sleep-aids; often cause residual daytime sleepiness or “hangover”, high doses of benzodiazepines also cause cognitive impairment and respiratory depression therefore, pose a risk; in contrast to hypnotic agent zolpidem that lacks effect of residual day-time sedation or psycho-motor impairment. Zopiclone, another hypnotic agent; is also free of any day-time sleepiness side effect but slightly impairs psychomotor function especially at high doses. Both agents are reported to be tolerated, efficacious, safe and have low rates of dependence or abuse (28).

Other non-benzodiazepines that also act as sedatives are trazodone (an antidepressant from a class of serotonin modulators) and low dose quetiapine (an atypical antipsychotic). Quetiapine has a wide array of indications; it has the advantage of ameliorating anxiety symptoms so can be used in TRD comorbid with anxiety, chronic pain and PTSD. In depression; 27 patients in a MDD episode were administered low dose quetiapine along with venlafaxine or escitalopram, by the end of the 4 weeks test time; sleep parameters had definitely improved in all patients (29). A head-to-head comparative study between trazodone and low dose quetiapine in hospitalized psychiatric patients at St. Helena's Hospital suffering from insomnia revealed that trazodone is a superior agent in patients

with depressive symptoms and offers higher improvement in sleep parameters than quetiapine (30).

Patients at high risk of self-inflicted injury are recommended to receive lithium, benzodiazepine, or second-generation antipsychotic medication. This is because second benzodiazepines generation anti-psychotics as clonazepam have a mood stabilizing effect and reduce impulsivity and mood swings (31).

Treatment Duration

The clinical committee members recommended that patients should be maintained on their ongoing antidepressant medication for a period of 9–12 months following the achievement of clinical remission.

Patients suffering from the following conditions are recommended to receive a longer course of treatment:

- Long period to reach remission
- History of 2 prior depression episodes
- History of early relapse after treatment discontinuation
- Presence of suicidal tendency, symptoms of psychosis, family history of suicide or mood disorders or comorbid psychiatric condition.
- Resistance to an antidepressant medication when given at proper dose and adequate duration.

Therapeutic Options of Patients Suffering From TRD

The panel experts highlighted the available treatment options for patients suffering from TRD. The available therapeutic options are captured in **Figure 1**.

Pharmacological Strategies in Treatment-Resistant Depression

Switching Strategies

Switching involves shifting to another antidepressant medication, either within the same class or from a different class. Switching to a medication within the same class is undertaken to obtain a different pharmacological property, while switching to another class usually yields a different neurochemical effect. This strategy is tailored to suit individual patient needs and preferences (5).

According to evidence gathered about switching treatment in TRD; switching has certain pros over augmentation therapy; first it carries lower risk of drug-drug interactions, has higher patient adherence, moreover, it is preferred for patients who suffered severe side effects from first line medication and displayed partial or no response.

Only two major trials have been conducted to observe switching of medications in TRD, the first was about patients who had previously failed two antidepressants (mostly SSRIs) and were switched to either SSRI paroxetine or SNRI venlafaxine; response rates were 33 and 52%, respectively while remission rates were 20 and 42%. Other studies involved switching from SSRI to extended-release venlafaxine and switching from an SSRI to mirtazapine or sertraline, both studies showed no significant difference in depressive symptoms.

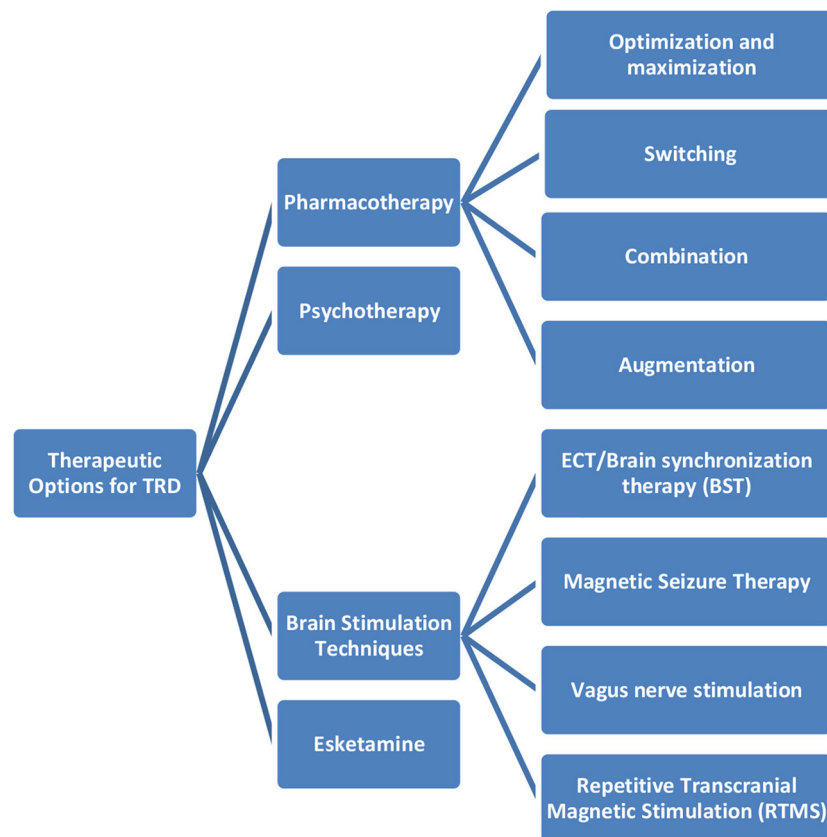


FIGURE 1 | The available therapeutic options for TRD.

The panel experts recommend switching to be carried out in the following situations:

- Lack of response or poor tolerance to initial treatment
- Prior response to the introduced medication

The clinical experts highlighted 3 different types of switching strategies, with concurrent switching being the most recommended, except for medications belonging to monoamine oxidase inhibitor (MAOIs) class. These strategies are captured in **Figure 2** (32).

Recommendations for switching antidepressant medications are captured in **Figure 3**.

Combination Strategies

Combination strategies usually involve using 2 different antidepressant medications belonging to different classes and having different pharmacodynamic profiles (33).

The panel recommends the use of combination strategy in patients with partial response after adequate treatment with a medication for a period of 2–4 weeks (4–6 weeks if with TCAs).

The recommended first-line combination strategy involves mirtazapine plus one of the following:

- Selective serotonin reuptake inhibitor.
- Serotonin–norepinephrine reuptake inhibitor.
- Tricyclic antidepressant.

Augmentation Strategies

Augmentation strategies refers to the addition of non-standard antidepressant medications, like lithium and quetiapine, to enhance the outcome of classical antidepressants (34). The panel summarized the medications and lines of choice in **Table 1**.

The panel recommends this strategy in patients who demonstrate partial response after 2–4 weeks of treatment (4–6 weeks with TCA as they have a delayed effect than newer agents).

The panel recommends adding lithium or quetiapine to improve efficacy of the antidepressant medication.

The panel recommends a second choice of thyroid hormone supplementation in addition to serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants, and with selective serotonin reuptake inhibitors or mirtazapine at a later stage.

The recommended dose of thyroid hormone supplementation is between 25 and 60 ug/day of liothyronine (L-T3) and is required to achieve TSH levels ranging between 0.1 and 1 ug/L. Prior to initiating treatment, the panel recommends performing the following assessments:

- Physical examination
- Electrocardiogram (ECG)
- Thyroid-stimulating hormone (TSH) levels.

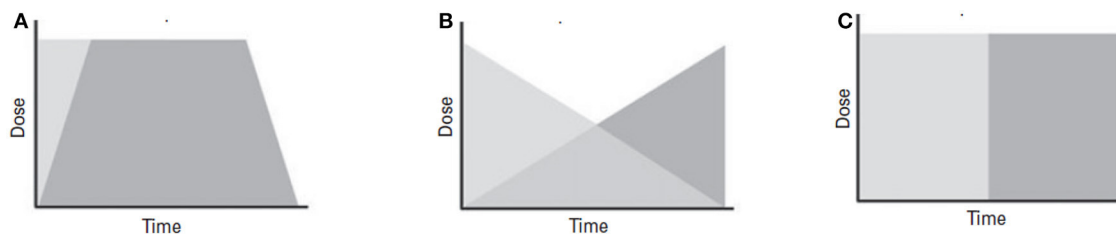


FIGURE 2 | Schematic diagrams of switching strategies. **(A)** Concurrent switch is best suited for patients demonstrating partial response, where simultaneous change in the dose of both medications is implemented. **(B)** Overlapping switch is suitable for patients who demonstrate partial response, where the dose of the original medication is maintained until the second medication reaches its optimal dose. **(C)** Sequential switch is considered to be the safest switching technique, as it is the least likely to cause any interaction. In this strategy, one medication is substituted with another. This technique is used in patients who do not respond to initial treatment.

Treatment Sequence for Depression Dimensions

Major depressive disorder is a multidimensional disorder that originates from multiple etiologies. The symptom dimension may act as predictor of antidepressant treatment response (35).

The panel recommendations for the first and second lines of treatment of several depression dimensions are illustrated in Table 2.

Brain Stimulation Techniques

The panel selected ECT/BST, and repetitive transcranial magnetic stimulation (rTMS) as the preferred brain stimulation techniques that are either used alone or in combination with antidepressants. The panel agreed that ECT/BST represent effective approaches to prevent relapse, either alone or in combination. Recommendations of brain stimulation techniques are as follows:

BST is recommended for resistant cases after failure of 3 adequately used antidepressants.

Novel Therapeutic Agents

Esketamine

Esketamine, the S enantiomer of ketamine, is a N-methyl-D-aspartate (NMDA) receptor antagonist that has higher affinity to the receptor compared to the R enantiomer and the racemic mixture of ketamine (36). In the form of a nasal spray, this molecule has recently gained approval in the United States for the indication of TRD as well as by the EMA in Europe for the indication of TRD, bringing hope to patients who suffer from the condition (37).

Esketamine, in combination with SSRIs or SNRIs, is indicated for the treatment of TRD in patients who did not respond to least 2 different classes of antidepressant medications (38).

Strategies to Prevent Relapse

A relapse is the return of depressive symptoms to patients. Relapse could be early or delayed. In the former, symptoms return is expected to be within the first 3–12 months, while the latter refers to the emergence of new depressive episodes following remission or initial short-term improvement in symptoms (39).

It is of importance to have measures to prevent relapse from the first relapse episode. With regard to preventive strategies, the following has been highlighted:

The panel recommends the use of ECT and lithium as effective first-line options to prevent relapse.

The panel recommends the use of lamotrigine or quetiapine as second-line options to prevent relapse.

The panel recommends the following strategies when patients achieve full remission:

- Continuous assessment of patients' adherence to treatment.
- Continuous assessment of social functioning of patients.
- Continuous assessment of quality of life (QoL) of patients.

The panel recommends the following complementary approaches for relapse and recurrence prevention:

- Undertaking regular physical exercises and activities.
- Eating healthy food
- Control physical illness (e.g., hypertension, diabetes, etc....)

DISCUSSION

Treatment resistant depression is regarded as patients failing 2 subsequent antidepressant treatments (38); in Egypt TRD's definition is slightly altered to the latter by the addition of failure of 6–12 sessions of ECT or BST (Brain Stimulation Techniques). Approximately 60–70% of depressed patients do not respond to first line treatment and more than a third become treatment resistant. However, TRD should not be confused with “pseudo-resistance”. This means that patient-related factors that might contribute treatment failure should be taken into account before deeming their depression as “resistant”. These factors are numerous, however inadequate dosing, compliance, follow-up and primary mis-diagnosis are prime examples (38). Another review also added other patient traits; the presence of comorbid psychiatric illnesses as OCD (Obsessive Compulsive Disorder), bipolarity, anxiety and eating disorders as well as the presence of psycho-somatic disorders as Fibromyalgia and IBS (Irritable Bowel Syndrome), all of which must be assessed carefully (with several available diagnostic tools) as they may lead to high rates of depression recurrence and severity; higher severity of depressive

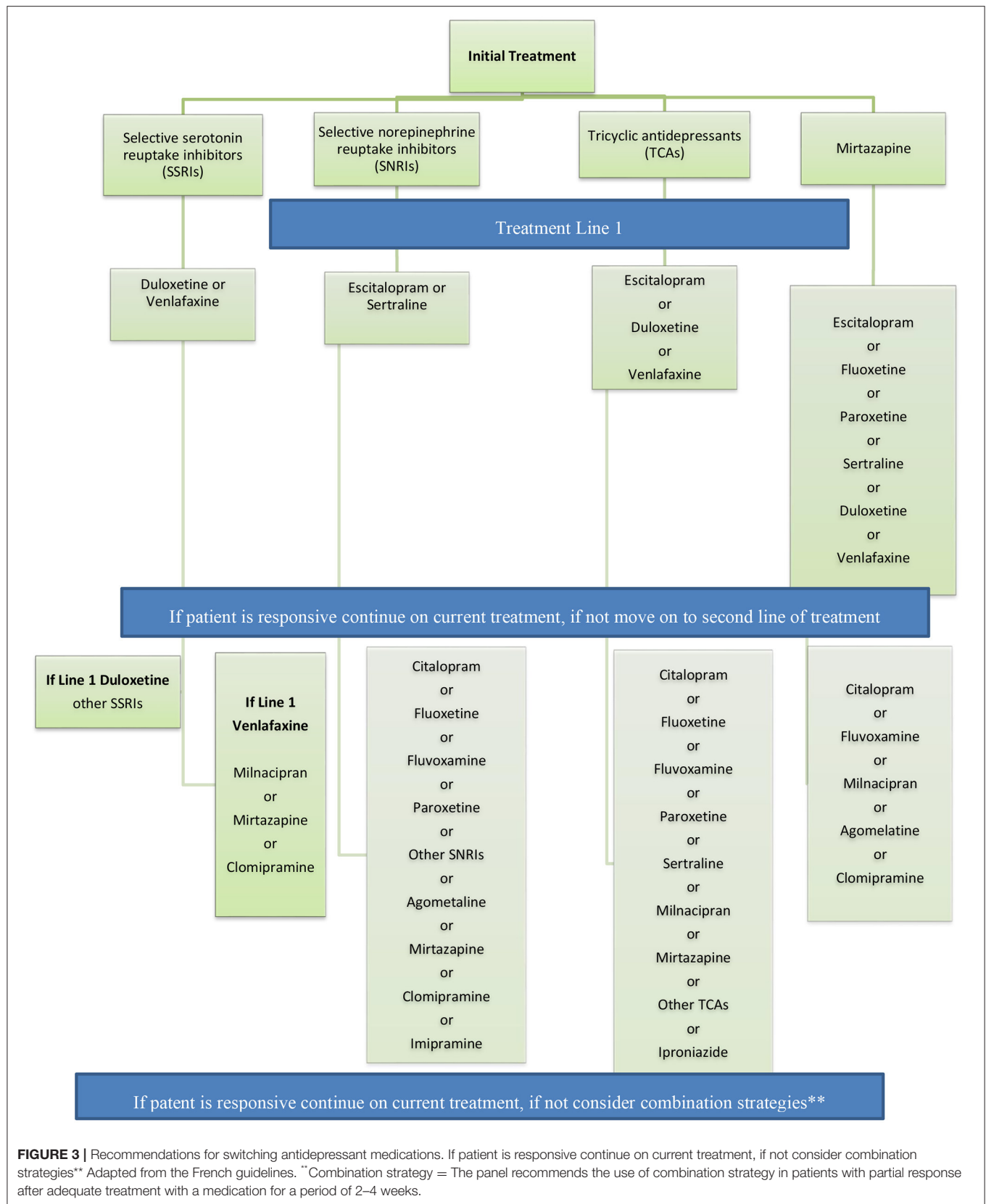


FIGURE 3 | Recommendations for switching antidepressant medications. If patient is responsive continue on current treatment, if not consider combination strategies** Adapted from the French guidelines. ** Combination strategy = The panel recommends the use of combination strategy in patients with partial response after adequate treatment with a medication for a period of 2–4 weeks.

TABLE 1 | Therapeutic lines in augmentation strategy in non-psychotic patients.**Potential treatment****First choice**

- Lithium with serum level must be at least 0.8 mmol/L
- Second generation anti-psychotic with antidepressant action (Quetiapine, Asenapine, loperidone, Brexpiprazole, Lurasidone, Cariprazine)

Second choice

- Aripiprazole
- Tri-iodothyronine
- Lamotrigine

TABLE 2 | Treatment lines recommendations for clinical dimensions in MDD.

| Dimension | First choice |
|--|--|
| With marked anhedonia | NDRI or SNRI |
| With marked psychomotor retardation | SNRI or NDRI |
| With marked sleep disturbances | SSRI or SNRI or Mirtazapine or agomelatine |
| With atypical features (hyperphagia, hypersomnia) | SSRI or SNRI |
| With psychotic features | SNRI in monotherapy or SSRI in combination with an atypical 2nd generation antipsychotic with an antidepressant action |
| With anxious features | SSRI or SNRI or Mirtazapine or Lithium |
| With high suicidal risk | SSRI or SNRI or Mirtazapine or Lithium or 2nd generation antipsychotic with an antidepressant action |
| Positive family history of bipolar disorder or suicide | Mood stabilizer (Lithium) |

illness and the higher rates of relapses in between remission periods is definitely a precipitating factor for TRD (39).

The panel urges that patients are monitored for both psychiatric and somatic diseases; this is reinforced by Kornstein's data who reported that patients with hypothyroidism and depression had higher remission rates when properly treated for under-active thyroid, this agrees with the panel's recommendation in augmenting therapy with T3 hormone supplementation. Patient history and concurrent medications must be known as some drugs such as gluco-corticosteroids and anti-inflammatories are associated with causing depressive symptoms (39). Ergo, the panel suggests using a list of tools and tests as MRIs, blood work, organ function tests etc. to monitor for certain patient conditions that may cause depression treatment failure or increase severity of the illness.

The panel agrees with the international guidelines for hospitalization indications in patients with TRD, this is because hospitalization prevents further complications that may be caused if TRD and/or its comorbidities are not under continuous medical supervision (8). A study conducted in Finland on a population of hospitalized patients as a result of depression followed-up patients up to 24 years after discharge to evaluate their outcomes. Of about 15,000 patients followed-up; only 2,567 died by suicide with an overall cumulative risk of suicide of 6.13%; which is considerably lower than depressed patients who remain unhospitalized (40).

Regarding comorbid mental illnesses with depression the panel recommends using several drugs in addition to antidepressants; the anxiolytics used is in line with the Canadian clinical practice guidelines; generally, benzodiazepines are fit for all anxiety disorders; Buspirone is indicated for a wide range of anxiety diseases as panic disorder, social anxiety, OCD (Obsessive Compulsive Disorder), GAD (Generalized Anxiety Disorder) and PTSD (Post-traumatic Stress Disorder), Pregabalin however, is used as second line treatment if first line drugs are not tolerated. For sleep disorders and self-harm comorbid with TRD, the panel's recommendations are based on clinical experience; which of course at times conflicts with published research. A Cochrane meta-analysis had similar documented patients who were prescribed drugs similar to the panel's recommendations as atypical anti-psychotics and benzodiazepines for both self-harm and sleep disorders (41).

Physicians however, must be aware of which drug to add to the patient's treatment plan and patient monitoring and continuous follow-up is crucial to their wellbeing. In **Table 3**, the panel has several recommendations of which medications to prescribe if TRD were associated with any other clinical issue such as sleep disturbances, suicide ideation, anxious features etc. Mirtazapine is an excellent antidepressant with a wide array of indications (and off-label uses) and has demonstrated superiority to tricyclic antidepressants due to its lack of any anti-cholinergic, adrenergic and serotonin-mediated side effects; clinical evidence has proved that it has transferred the treatment of depression. In comparison to tricyclic antidepressants as amitriptyline, clomipramine, doxepin and serotonin modulator trazodone, the clinical effect of mirtazapine was similar and at times superior, not only that, but it is also strongly advocated in cases of depression with poor sleep scores in which mirtazapine improved drastically in comparison to placebo. According to these findings, mirtazapine's adverse effects as dry mouth, increased appetite and weight gain should be weighed together with its high safety and effective treatment profile, when exploring other drugs to prescribe/augment/combine with the current treatment profile (42).

Another interesting agent that can be used and is recommended by Egyptian psychiatrists is agomelatine, one of the first melatonergic agents and a 5-hydroxytryptamine receptor (5-HT_{2C}) antagonist both of which act harmoniously to adjust disrupted circadian rhythms (sleep cycles) typically found in depressive illness. As mentioned above, depressed patients must be closely monitored to avoid any consequences unintentionally caused by treatment; agomelatine should not be used in patients with a compromised liver and in healthy patients, liver function tests must be routinely done at the beginning of treatment and subsequently at 6 weeks, 12 weeks and 6 months as recommended by the EMA (European Medicines Agency) (43).

Moving forward, a pharmacological treatment algorithm was devised as mentioned above in **Figure 3**; there are several strategies that physicians can adhere to when approaching TRD, these include switching, combination or augmentation strategies. A study in 2001 evaluated patients with low response to Fluoxetine 20 mg/day who were switched to mianserin 60 mg/day. The results were intermediate but were still sound with depression scores lower by 1.8 in the mianserin group than those

TABLE 3 | The main findings of this study.

| Area of interest | Recommendation |
|--|--|
| Hospitalization: indications | The panel members recommended the consideration of psychiatric hospitalization for the following cases. <ul style="list-style-type: none"> - Catatonia - Patients with high suicidal tendency - Severe psychotic symptoms - Advanced cases of MDD - The presence of severe uncontrolled comorbid medical conditions - Insufficient familial support to the patient |
| Therapeutic options for treatment-resistant depression and comorbid conditions pharmacotherapeutic options of comorbid conditions | For patients suffering from comorbid conditions, the expert panel recommends the following: Patients suffering from anxiety and its features are recommended to receive benzodiazepines. Buspirone and pregabalin are also available options. Patients suffering from sleep disorders are recommended to receive adjunctive hypnotic medications, such as zolpidem or zopiclone. Patients at high risk of self-inflicted injury are recommended to receive lithium, benzodiazepine, or second-generation antipsychotic medication. |
| Treatment duration | The clinical committee members recommended that patients are maintained on their ongoing antidepressant medication for a period of 9–12 months following the achievement of clinical remission. Patients suffering from the following conditions are recommended to receive a longer course of treatment: <ul style="list-style-type: none"> - Long period to reach remission - History of 2 prior depression episodes - History of early relapse after treatment discontinuation - Presence of suicidal tendency, symptoms of psychosis, family history of suicide or mood disorders or comorbid psychiatric condition. - Resistance to an antidepressant medication when given at proper dose and adequate duration. |
| Therapeutic options of patients suffering from TRD | The panel experts highlighted the available treatment options for patients suffering from TRD. The available therapeutic options are captured in Figure 1 . |
| Pharmacological strategies in treatment-resistant depression | |
| Switching strategies | The panel experts recommend switching to be carried out in the following situations: <ul style="list-style-type: none"> - Lack of response or poor tolerance to initial treatment - Prior response to the introduced medication The clinical experts highlighted 3 different types of switching strategies, with concurrent switching being the most recommended, except for medications belonging to monoamine oxidase inhibitor (MAOIs) class. These strategies are captured in Figure 2 (32). Recommendations for switching antidepressant medications are captured in Figure 3 . |
| **Combination strategies | The panel recommends the use of combination strategy in patients with partial response after adequate treatment with a medication for a period of 2–4 weeks (4–6 weeks with TCAs). The recommended first-line combination strategy involves Mirtazapine plus one of the following: <ul style="list-style-type: none"> - Selective serotonin reuptake inhibitor. - Serotonin–norepinephrine reuptake inhibitor. - Tricyclic antidepressant. |
| Augmentation strategies | The panel recommends this strategy in patients who demonstrate partial response after 2–4 weeks of treatment (4–6 weeks if on TCAs). The panel recommends adding lithium or quetiapine to improve efficacy of the antidepressant medication. The panel recommends a second choice of thyroid hormone supplementation in addition to serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants, and with selective serotonin reuptake inhibitors or mirtazapine at a later stage. The recommended dose of thyroid hormone supplementation is between 25–60 ug/day of liothyronine (L-T3) and is required to achieve TSH levels ranging between 0.1 and 1 ug/L. Prior to initiating treatment, the panel recommends performing the following assessments: <ul style="list-style-type: none"> - Physical examination - Electrocardiogram (ECG) - Thyroid-stimulating hormone (TSH) levels (Table 1). |
| Treatment sequence for depression dimensions | The panel recommendations for the first and second lines of treatment of several depression dimensions are illustrated in Table 2 . |
| Brain stimulation techniques (BST) | The panel selected ECT/BST, and repetitive transcranial magnetic stimulation (rTMS) as the preferred brain stimulation techniques that are either used alone or in combination with antidepressants. The panel agreed that ECT/BST represent effective approaches to prevent relapse, either alone or in combination. Recommendations of Brain Stimulation Techniques are as follows: BST is recommended for resistant cases after failure of 3 adequately used antidepressants. |
| Novel therapeutic agents | Esketamine, in combination with SSRIs or SNRIs, is indicated for the treatment of TRD in patients who did not respond to least 2 different classes of antidepressant medications (38). |
| Strategies to prevent relapse | It is of importance to have measures to prevent relapse from the first relapse episode. With regard to preventive strategies, the following has been highlighted: |

(Continued)

TABLE 3 | Continued

| Area of interest | Recommendation |
|------------------|---|
| | <p>The panel recommends the use of ECT and lithium as effective first-line options to prevent relapse. The panel recommends the use of lamotrigine or quetiapine as second-line options to prevent relapse. The panel recommends the following strategies when patients achieve full remission:</p> <ul style="list-style-type: none">- Continuous assessment of patients' adherence to treatment.- Continuous assessment of social functioning of patients.- Continuous assessment of quality of life (QoL) of patients. <p>The panel recommends the following complementary approaches for relapse recurrence prevention:</p> <ul style="list-style-type: none">- Undertaking regular physical exercises and activities.- Eating healthy food- Control physical illness (e.g., hypertension, diabetes, etc....) |

who continued on Fluoxetine. The same study also had a third treatment arm with patients on fluoxetine therapy combined with mianserin (=combination strategy) in which the depression score plummeted by 4.6 in the combined treatment group; this is a commonly observed phenomenon in combination strategies as both drugs synergistically act to create a larger overall effect in managing symptoms especially of a multi-modal disease as depression (44).

Furthermore, augmentation strategy is adding a different class of medication to a current antidepressant; this was done in a study where randomized depressed patients who remitted from ECT. They received placebo, lithium or lithium with nortriptyline; 84% relapsed on placebo, 60% on lithium monotherapy and 39.1% on the combination therapy which consolidates the fact that combination therapy with non-antidepressant agent proves useful in treatment of depression as well as preventing relapses (45). There is also evidence that suggests that Lithium decreases the risk of suicide in depressed patients (46).

There are other methods of treatment in TRD to resort to such as ECT (a brain stimulation technique) or the use of esketamine (a relatively novel therapeutic agent). ECT therapy has long been recommended by the British guidelines of 2000 for severe cases of depression especially those who have failed two or more drugs (TRD), rTMS is recommended second to ECT but must be done by a team of specialists. Ghasemi made a more interesting discovery when comparing patients who received three sessions of ECT vs. those who received low dose esketamine over 3 days; results supported that both treatments although comparable, esketamine had a more rapid and more pronounced resolution of symptoms (47). The use of esketamine is not yet approved in Egypt; although it has long been approved by the FDA in the United States and the EMA in Europe for its relative safety and efficacy; moreover, adverse effects of dissociation, vertigo and dizziness from esketamine usually resolved on the same day, shortly after administration; (48) future-wise; the use of esketamine (only as nasal spray) must be warranted in Egypt due to its pronounced effect with patients feeling better within hours of administration and lower relapse rates as maintenance treatment all of which is vital for a TRD patient.

Following achieving remission for depression; a major challenge is to prevent relapse of depressive episodes; the use of lithium is widely agreed upon in patients who were suicidal,

ECT is proposed for patients with frequent relapses. Physiological wellbeing is also an aspect to be considered; any emerging or residual mental or physical illness should be tended to in order to prevent relapse (46).

Like all studies, this study carries its own strengths and limitations. Surely the first strength of this study is that this is the first consensus of guidelines between Egyptian psychiatrists for the treatment of TRD; the panel's recommendations came from practicing them on TRD patients in an expert clinical setting. The limitation of this study is that the panel constituted of only eight doctors who only represent a small group of psychiatrists from a much larger number in Egypt; additionally, there is no scientifically exact or official definition of TRD or for its treatment of TRD in Egypt or world-wide (internationally) to base these recommendations on; they were merely observations collected by the panel experts.

CONCLUSION

The integration of clinical practice with the latest updates of clinical studies yields the best outcomes for patients. TRD puts a significant burden on the patient, therefore, it is always best to manage the condition with careful review and step-wise approach. The development of recent pharmaceutical options for patients with TRD ushers a new area to tackle this condition.

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.

AUTHOR CONTRIBUTIONS

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.797150/full#supplementary-material>

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Examining Motor Anticipation in Handwriting as an Indicator of Motor Dysfunction in Schizophrenia

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Dysfunction in motor skills can be linked to alterations in motor processing, such as the anticipation of forthcoming graphomotor sequences. We expected that the difficulties in motor processing in schizophrenia would be reflected in a decrease of motor anticipation. In handwriting, motor anticipation concerns the ability to write a letter while processing information on how to produce the following letters. It is essential for fast and smooth handwriting, that is, for the automation of graphomotor gestures. In this study, we examined motor anticipation by comparing the kinematic characteristics of the first *l* in the bigrams *ll* and *ln* written on a digitiser. Previous studies indicated that the downstroke duration of the first *l* is modulated by the anticipation of the local constraints of the following letter. Twenty-four adult individuals with diagnosis of schizophrenia and 24 healthy adults participated in the study. The classic measures of duration (sec), trajectory (cm), and dysfluency (velocity peaks) were used for the kinematic analysis of the upstroke (US) and downstroke (DS). In the control group, the duration of the downstroke of the *l* was longer in *ln* than *ll* (US: *ln* = *ll*; DS: *ln* > *ll*) whereas no differences were found for the group with schizophrenia. Likewise, the control group showed a longer DS trajectory for the *l* of *ln* than *ll* in downstrokes, while the group of patients failed to show this effect. These results suggest that the motor alterations in patients with schizophrenia could also affect their ability for motor anticipation.

Keywords: handwriting, schizophrenia, motor anticipation, motor alterations, kinematical measurement

INTRODUCTION

Experimental and neuropsychological models consider that word writing results from a series of central and peripheral processes that function according to a hierarchical manner (Van Galen, 1991; Bonin et al., 2001; Miceli and Capasso, 2006; Damian and Stadthagen-Gonzalez, 2009; Kandel et al., 2011, 2017; Ellis, 2014). The central processes refer to linguistic processing, such as gearing up the semantic system, syntactic construction, and orthographic retrieval. The peripheral processes point to the motor-related aspects of letter production, where graphomotor planning for handwriting takes place. They are involved in the selection of allographs, where motor program retrieval takes place, local parameter adjustments and muscular activation leading to the production of letters (Bertram et al., 2015). The present research focuses on

the latter, lower level peripheral aspects of writing. Of particular interest for the purpose of the study is the phenomenon of motor anticipation. Motor anticipation refers to the ability to predict future behaviors, related to the perception of trajectories and synchronization of movements (Oña et al., 1999). Motor anticipation can be considered as a relevant motor-perceptual process in most learned behaviors (Kandel et al., 2000), and its dysfunction can be linked to some motor disorders as the ones observed in schizophrenia (Finney, 2015).

Traditionally, research has employed diverse measures of handwriting in the study of motor symptoms in psychotic disorders (Caligiuri et al., 2015; Gawda, 2016). Motor symptoms were first studied in psychosis as side effects of the antipsychotic treatment (Chengappa et al., 1994; Simpson and Lindenmayer, 1997). However, recently, the role of motor symptoms in psychotic disorders has been revised (Jahn et al., 2002; Rogowska et al., 2003) and they have been considered as a core feature in the evaluation and the prognosis of the disorder. In this regard, they have been detected in antipsychotic naïve patients with a first psychotic episode (Peralta et al., 2010), and handwriting measures have revealed spontaneous motor abnormalities even in individuals at high risk of psychosis who have never been in pharmacological treatment (Dean et al., 2013, 2014). The present study examined a novel measure of handwriting, motor anticipation in handwriting, in order to gain insight on motor dysfunctions in schizophrenic patients.

Planning and execution of complex sequences of movements involve a significant amount of look-ahead. In fact, units of motor action being executed often carry the imprint of yet-to-be-executed units. More precisely, motor anticipation in fine motor skills, such as writing, concerns the ability to write a letter while processing information on how to produce the following letters. It is essential for fast and smooth handwriting, that is, for the automation of graphomotor gestures. In this study, schizophrenic patients and healthy adults had to write cursive letters on a digitizer. We compared the productions of the two groups on their ability to anticipate forthcoming motor sequences in cursive handwriting.

Previous studies carried out by Orliaguet and Boë (1990) with healthy adults indicated that the anticipation of the local production constraints of the following letter modulates the spatio-temporal course of the current movement. These authors compared the kinematic characteristics of the first *l* in bigrams *ll* and *ln* written on a digitizer (Figure 1).

They observed that the anticipatory processing of changes in size and rotation direction of the *n* increased the downstroke duration of the *l* with respect to the first *l* of *ll*, where the same motor program is reproduced (Orliaguet and Boë, 1990; Boë et al., 1991). Furthermore, Kandel and Perret (2015) studied motor anticipation in children at the period of writing automation. Children of ages 8, 9, and 10 years wrote bigrams *ll*, *le*, *ln* in cursive writing on a digitizer. They analyzed the duration, trajectory, and dysfluency of the first letter *l*, both on the upstroke and downstroke. They found that at all ages, the *l*'s downstroke duration was shorter for *ll* than *le* and the latter was in turn shorter than *ln*. This modulation of the *l* duration reflects that during this downstroke movement, the children

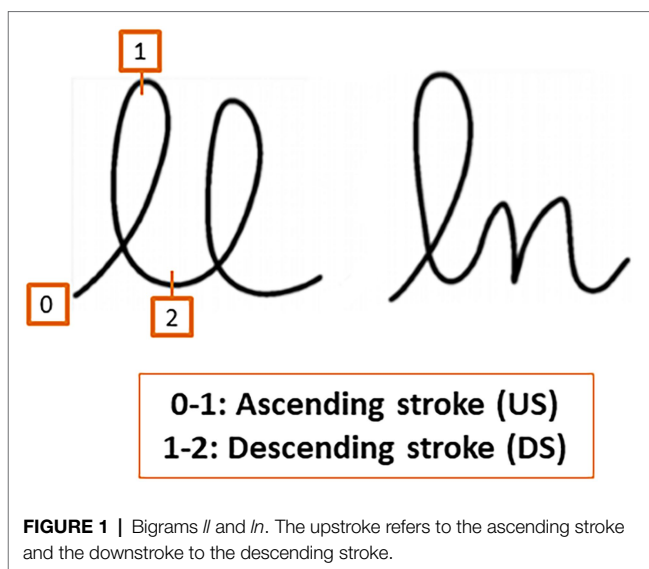


FIGURE 1 | Bigrams *ll* and *ln*. The upstroke refers to the ascending stroke and the downstroke to the descending stroke.

were processing in advance the following letter. The measures of the length of the paths of the children's productions further revealed that the trajectories of the *l* of *ll* were shorter than those of the *l* of bigrams *le* and *ln*. The dysfluency data—measured as the number of absolute velocity peaks in the velocity profile for each stroke—indicated that at age 8, dysfluency values were equivalent for upstrokes and downstrokes, whereas children of ages 9 and 10 years old showed more dysfluency on downstrokes than upstrokes. This experiment suggested that learning to anticipate in handwriting production requires: (a) rendering the movements to produce the upstroke constant; and (b) modulating the downstroke as a function of the spatial characteristics of the following letter. The pattern of movement time data suggested that motor anticipation would start to be adult-like at around age of 9. In other words, motor anticipation is already present at age 8 and is a core component of the automation process of handwriting production.

Motor anticipation has also been studied in Parkinson's patients (Bidet-Ildei et al., 2011). In this study, motor anticipation of the control group was compared with the clinical sample before and after a treatment phase of dopaminergic medication or bilateral deep brain stimulation. The results showed that the control group participants exhibited signs of anticipation whereas Parkinson's patients did not. More specifically, the downstroke duration of the first *l* of the healthy adults increased as the constraints of the following letter increased, such that ($ll < le < ln$). In the group of patients, there were no differences in the duration of the downstroke between different conditions. However, after treatment, the patients did exhibit a decrease of the *l* downstroke duration when it was followed by another *l*.

As mentioned above, motor anticipation is a key process for handwriting automation. The production of a movement while anticipating the requirements of the following motor sequence facilitates a smooth handwriting and, as motor demands are reduced, more cognitive resources can be devoted to higher order processes, such as linguistic or conceptual processes. Therefore, a poor motor anticipation would result in poor

execution of handwriting and other cognitive-motor tasks (Lozano and Acosta, 2009; Blanchard et al., 2011; Fett et al., 2011). This can be observed in some mental disorders, such as in schizophrenia, which is characterized by a wide variety of cognitive and motor deficits. Besides this, schizophrenia is associated with increased involuntary movements (Pappa and Dazzan, 2009) and with neurological abnormalities in sensory integration, motor coordination, sequencing complex motor acts, and primitive reflexes (Bombin et al., 2005). Therefore, motor-related deficits associated with schizophrenia could affect the processes involved in automation during handwriting. The main objective of the present research was to examine motor anticipation in handwriting in schizophrenia. We hypothesized that patients with schizophrenia would not be able to anticipate the production of forthcoming movements. This would result in an absence of modulation of the kinematic patterns of the downstroke of the first letter of the sequence.

As in previous experimental studies on motor anticipation, we followed the methodology presented by Orliaguet and Boë (1990). We measured motor anticipation by comparing the kinematic characteristics of the first *l* in the bigrams *ll* and *ln*. The classic measures of duration (movement time in seconds), trajectory (path in cm), and dysfluency (number of velocity peaks) were used for the kinematic analysis of the upstroke (US) and the downstroke (DS; see **Figure 1**). Motor anticipation would be reflected in a modulation of the kinematic parameters of the DS of the first letter, depending on the following letter (*l* vs. *n*). As in the studies with adults (Orliaguet and Boë, 1990; Bidet-Ildei et al., 2011) and children (Kandel and Perret, 2015), the bigram was written in cursive handwriting on a digitizing tablet. We predicted that the difficulties in the cognitive processes involved in fine motor production in schizophrenia would be reflected in a decrease or absence of this modulation.

MATERIALS AND METHODS

Participants

Twenty-four adult individuals attending the Mental Health Day Unit at the University St. Agustin Hospital (Spain) participated in the study. Inclusion criteria were ICD-10 diagnosis of schizophrenia (F20), and age between 20 and 55 years old ($M = 37.29$; $SD = 9.58$). Diagnosis of participants was made using a semi-structured interview (SCID-I) according to ICD-10 criteria by the psychiatrist or clinical psychologist in charge of the patient. Out of the 24 participants, 17 (70.8%) were male. Twenty-two participants were right-handed whereas 2 were left-handed. Their mean illness duration was 15.36 years ($SD = 10.11$). Due to the fact that in Spain there have been different education regulations in the last years, we transformed the academic degree reported by the participants in the number of years needed to obtain it. According to this criterion, the average number of years in the formal education system in this group was 10.79 ($SD = 4.48$ years). To try to better characterize the educational level of the participants, we categorized the number of years in the educational system into three other categories: low educational level (from 0 to 6 years in the formal

educational system), medium educational level (from 7 to 12 years), and high educational level (more than 13 years). According to these categories, the sample of patients included 12.5% with a low educational level, 62.5% with a medium level, and 25% with a high level. There were no patients who suffered from Tardive Dyskinesia: All patients had absent or minimal symptomatology (a score of 0 or 1 in the items of the AIMS). In order to compare doses of antipsychotic treatment, we used Chlorpromazine equivalence (CPZE). CPZE is defined as the dose of a drug which is equivalent to 100 mg of oral dose of chlorpromazine (779.37 , $SD = 419.28$).

The SAS rating scale was used for assessment of drug-induced parkinsonism (Simpson and Angus, 1970). This scale is used in both clinical practice and research settings, and it is composed of 10 items: one item measures gait (hypokinesia), six items measure rigidity, and three items measure glabella tap, tremor, and salivation. For each item, the severity of the symptoms was rated from 0 (none) to 4 (severe). A score of 1 in an item indicated the presence of motor symptoms in a mild form. A mean global score of 3 or more in the full test was used as a threshold to indicate the presence of the extrapyramidal symptoms in a mild form (Ayehu et al., 2014). The mean obtained in our sample was 3.21 ($SD = 5.09$).

To assess clinical symptoms of schizophrenia, we applied the Spanish version (Peralta and Cuesta, 1994) of the Positive and Negative Syndrome Scale (PANSS; Andreasen and Olsen, 1982; Kay et al., 1987). The PANSS is a 30-item rating instrument comprising three subscales: the seven-item Positive Symptoms subscale (PANSS-P), the seven-item Negative Symptoms subscale (PANSS-N), and the 16-item General Psychopathology subscale (PANSS-G). All 30 items are rated on a seven-point scale (1 = absent to 7 = extreme). Obtained results were $M = 16.04$, $SD = 5.39$ for PANSS-P, $M = 20.22$, $SD = 6.96$ for PANSS-N, and $M = 33.86$, $SD = 10.00$ for PANSS-G.

In order to exclude patients with gross motor dysfunctions, we measured finger and hand dexterity with the Purdue Pegboard test (Tiffin and Asher, 1948; Tiffin, 1968). This board consists of two parallel rows of 25 holes each. Pins (pegs) are located at the extreme right-hand and left-hand cups at the top of the board. Metal collars and washers occupy the two middle cups. In the first three subtests, the subject places as many pins as possible in the holes, first with the preferred hand (dominant), then with the non-preferred hand (non-dominant), and finally with both hands, within a 30-s time period. To test the right hand, the subject must insert as many pins as possible in the holes, starting at the top of the right-hand row ($M = 13.74$, $SD = 8.65$). The left-hand test uses the left row ($M = 10.73$, $SD = 2.95$). Both hands then are used together to fill both rows top to bottom ($M = 8.01$, $SD = 2.25$). In the fourth subtest, the subject uses both hands alternately to construct "assemblies," which consist of a pin, a washer, a collar, and another washer. The subject must complete as many assemblies as possible within 1 min ($M = 28.59$, $SD = 9.23$). We did not exclude any participants based on their scores on this test.

For the control group, 24 adults were recruited from the University of Jaén and an adult school of Jaén. The inclusion criterion was that age was between 20 and 60 years ($M = 36.83$ years

old; $SD=12.83$ years old). Out of the 24 participants, 14 were male. All of the participants were right-handed. Regarding educational level, 3 participants had low level, 8 medium and 19 participants had high education level ($M=13.25$, $SD=10$). Importantly, there were no significant differences between groups on age ($t=1.73$, $p=0.08$), sex ($\chi^2=0.82$, $p=0.36$) or educational level considered either as the number of years in the educational system ($t=1.159$; $p=0.12$) or categorized in low, medium or high level ($\chi^2=4.70$, $p=0.09$).

Exclusion criteria for both groups were: concurrent diagnosis of neurological disorder, concurrent diagnosis of substance abuse, history of developmental disability, inability to sign informed consent or vision disorders (those vision disorders which, although corrected by glasses or contact lenses, suppose a loss of visual acuity, e.g., cataracts). In addition, an exclusion criterion for the control group was the diagnosis of a mental disorder (according to verbal reports from participants).

All participants gave their written informed consent according to the Declaration of Helsinki and the Ethics Committee on Human Research of the Hospital approved the study.

Procedure and Data Analysis

Participants were asked to perform an easy and brief handwriting task. A A4 paper was affixed to the surface of a WACOM (Intuos pro small) digitizing tablet with dimensions of $269 \times 170 \times 8$ mm ($10.6 \times 6.7 \times 0.3$ in), with an active area of 160×100 mm (6.3×3.9 in) and a resolution of 5,080 lpi. The different bigrams (*ll*, *ln*) were presented randomly on a computer screen, and participants were required to write the bigrams using this paper, with a Wacom Pro Pen 2 (KP504E) digital pen with 8192 levels of pressure sensitivity. Handwriting tasks were carried out individually. The task had no time limit.

We measured three dependent variables: the time per stroke (Duration, seg.), the path of the pen for each stroke (Trajectory, cm), and the number of velocity peaks (Disfluency).

For each of these dependent variables, we run separate mixed models with Group, Direction and Bigram as independent variables. Random intercepts were included for subjects. Analyses were done in R [R Core Team (2020)] using the lmer() function of the lme4 package (Bates et al., 2015). We utilized the restricted maximum likelihood as the estimation procedure and the Welch–Satterthwaite (Luke, 2017) approximation of the degrees of freedom because of our relatively small sample size (Gumedze and Dunne, 2011).

RESULTS

Duration

Figure 2 presents mean movement time per stroke across trials, as a function of group (Schizophrenia-SCZ vs. Control-CTRL), stroke direction (downstroke-DS vs. upstroke-US), and type of bigram (*ll* vs. *ln*). The ANOVA on duration revealed a significant effect was found for Direction [$F(1, 138)=4.83$, $p=0.029$, $\eta_p^2=0.033$], indicating a longer duration for DS ($M=0.21$, $SD=0.01$) than US ($M=0.20$, $SD=0.01$). A significant effect was also found for Bigram [$F(1, 138)=11.69$,

$p<0.01$, $\eta_p^2=0.078$], indicating a longer duration for *ln* ($M=0.21$, $SD=0.11$) than for *ll* ($M=0.19$, $SD=0.09$). The interaction Group by Direction by Bigram was also significant [$F(1, 138)=4.39$, $p=0.037$, $\eta_p^2=0.031$]. No other effects were significant.

In order to analyze the Group by Direction by Bigram interaction, we conducted pairwise comparisons using emmeans function in R (Russell Lenth, 2020). In the control group, we found no significant differences in US between LL and LN ($t<1$), but we found significant longer duration for LN than for LL ($t=-3.32$, $p=0.24$) in DS. In the schizophrenia group, we found no significant differences were found between LL and LN ($t<1$) neither in US ($t=-2.18$, $p=0.36$) nor in DS ($t=-1.20$, $p=0.93$).

Trajectory

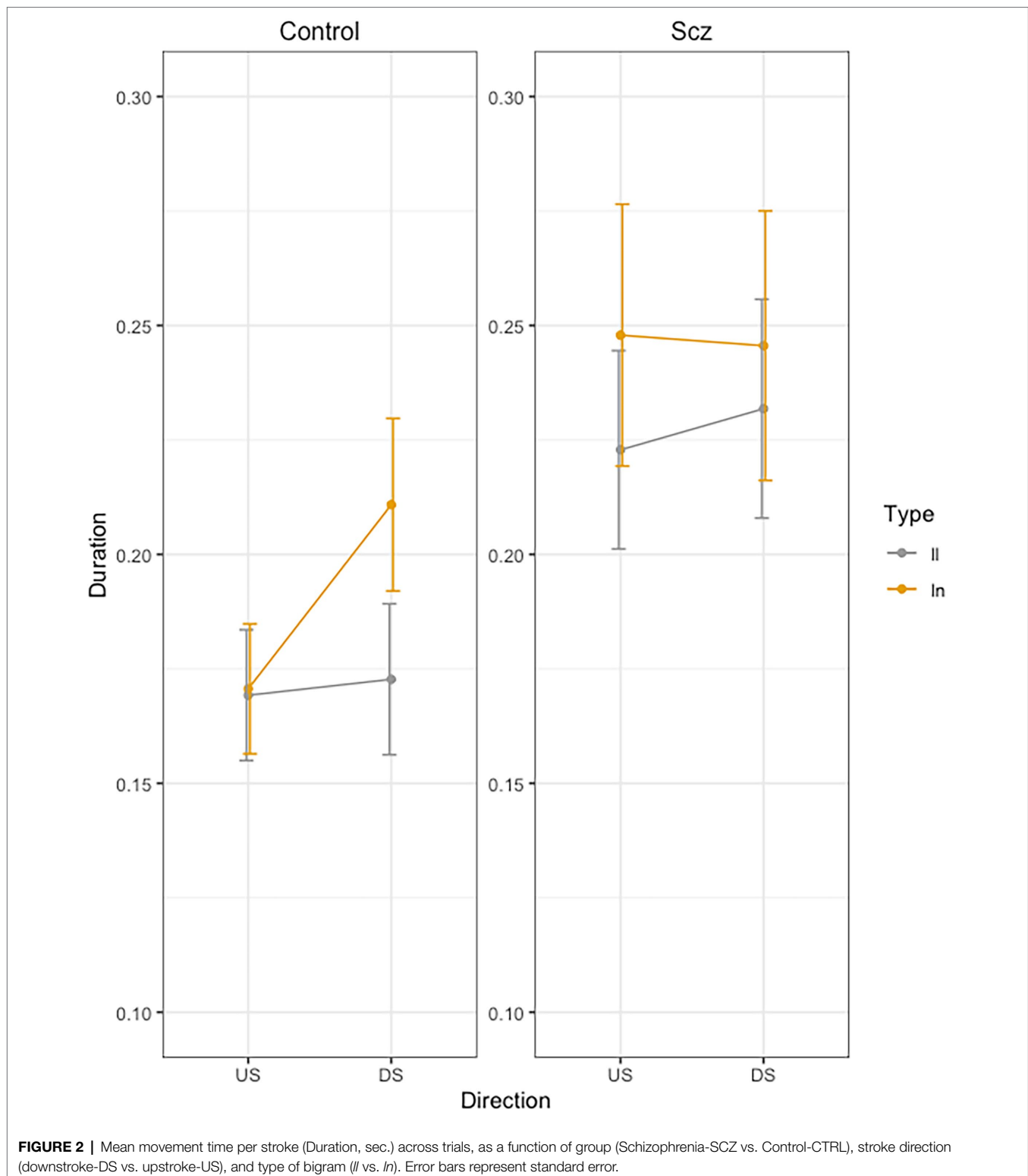
Figure 3 presents the mean Trajectory each stroke across trials, as a function of group (Schizophrenia-SCZ vs. Control-CTRL), stroke direction (downstroke-DS vs. upstroke-US), and type of bigram (*ll* vs. *ln*). Error bars represent standard error. The ANOVA showed a significant effect of Group [$F(1, 46)=12.68$, $p<0.01$, $\eta_p^2=0.216$] indicating longer trajectory in the SCZ group ($M=0.84$, $SD=0.23$) than the Control group ($M=0.65$, $SD=0.18$). A marginally effect was also found for Type of bigram [$F(1, 138)=3.64$, $p=0.058$], indicating a longer trajectory for *ln* ($M=0.76$, $SD=0.25$) than for *ll* ($M=0.73$, $SD=0.19$). The interaction Group by Direction was significant [$F(1, 138)=5.87$, $p<0.016$, $\eta_p^2=.040$]. The interaction Group by Direction by Bigram was also significant [$F(1, 138)=3.91$, $p<0.049$, $\eta_p^2=.027$]. No other effects were significant.

In order to analyze the Group by Direction by Bigram interaction, we conducted pairwise comparisons using emmeans function in R (Russell Lenth, 2020). In the control group, we found no significant differences in DS between LL and LN ($t=-1.98$, $p=0.49$), but we found significant longer duration for LN than for LL ($t=-3.32$, $p=0.24$) in US. In the schizophrenia group, we found no significant differences were found between LL and LN ($t<1$) neither in US ($t=-2.18$, $p=0.36$) nor in DS ($t=-1.20$, $p=0.93$).

Disfluency

Figure 4 presents mean Dysfluency values as a function of group (Schizophrenia-SCZ vs. Control-CTRL), stroke direction (downstroke-DS vs. upstroke-US), and type of bigram (*ll* vs. *ln*). The results yielded a significant Group effect [$F(1, 48)=4.34$, $p=0.042$, $\eta_p^2=.082$] indicating more dysfluency in the SCZ group ($M=1.47$, $SD=0.98$) than in the Control group ($M=1.09$, $SD=0.24$). A significant effect was also found for Direction [$F(1, 144)=6.31$, $p=0.013$, $\eta_p^2=.041$], indicating more velocity peaks for the DS ($M=1.33$, $SD=0.81$) than US ($M=1.22$, $SD=0.61$). No other effects were significant.

Finally, correlations were carried out between the different measures from motor evaluation scales, psychopathology scales, and other characteristic variables of the disorder (illness duration, educational level or pharmacological treatment doses), and the kinematic measures of handwriting (see **Figure 5**). We found



no significant relationships between kinematic measures of handwriting and the rest of variables, except for Trajectory, which correlated with motor functioning values from the Purdue test: patients with a worse motor function showed longer trajectories in handwriting.

DISCUSSION

Handwriting becomes automatic with practice. Motor automation is essential to free up cognitive and attentional resources for the rest of the components of handwriting: conceptual planning,

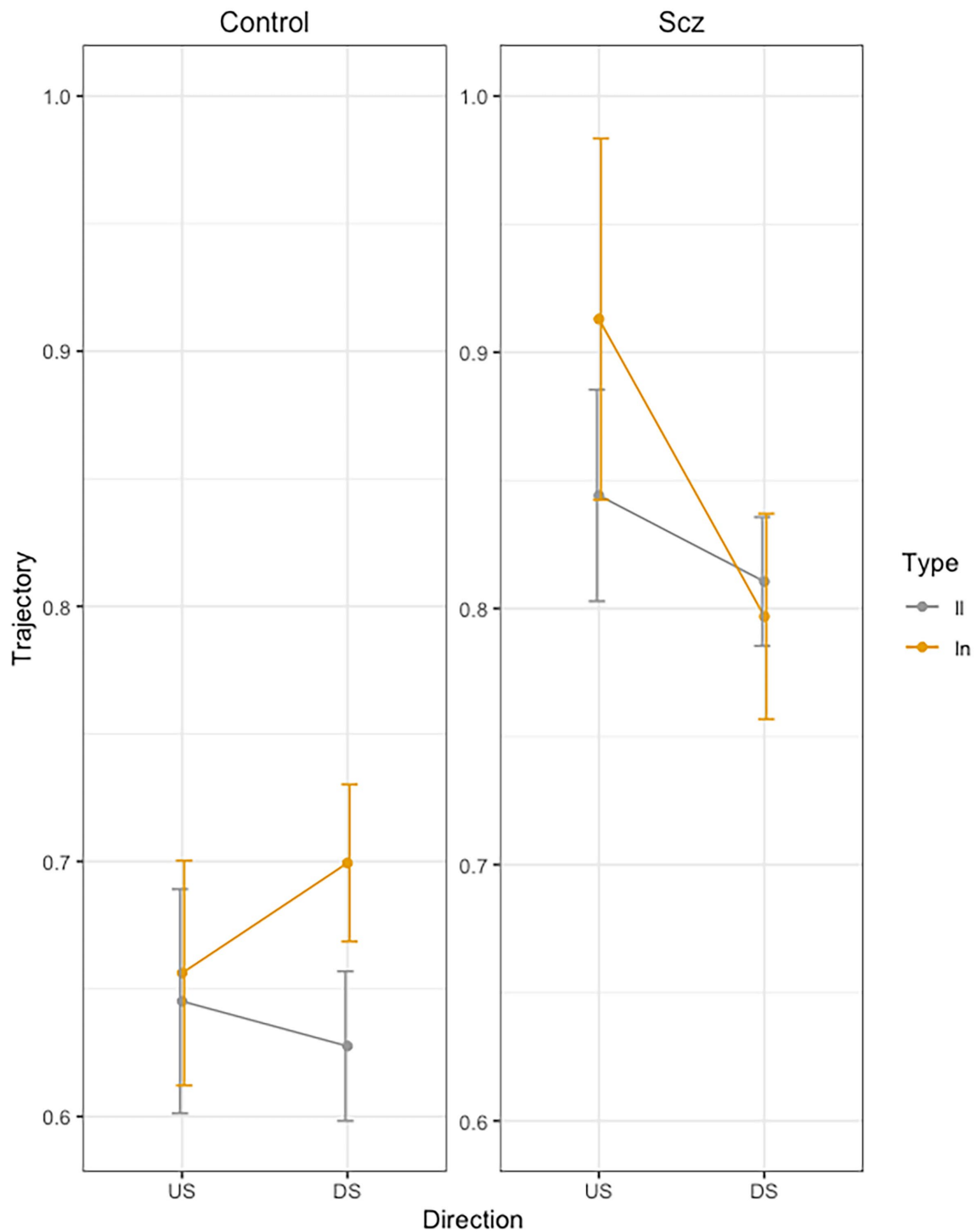


FIGURE 3 | Mean trajectory (path in cm of the pen) for each stroke across trials, as a function of group (Schizophrenia-SCZ vs. Control-CTRL), stroke direction (downstroke-DS vs. upstroke-US), and type of bigram (II vs. In). Error bars represent standard error.

syntactical construction, lexical selection, etc. In adult cursive handwriting, movements are smooth and continuous. Part of this continuity is due to motor anticipation. It allows for the programming of the graphomotor constraints of the following

stroke while executing the previous one. Since letters vary in size and direction of the stroke when they are written in lowercase, the anticipation of these variations requires a supplementary cognitive load while preparing the production of the following

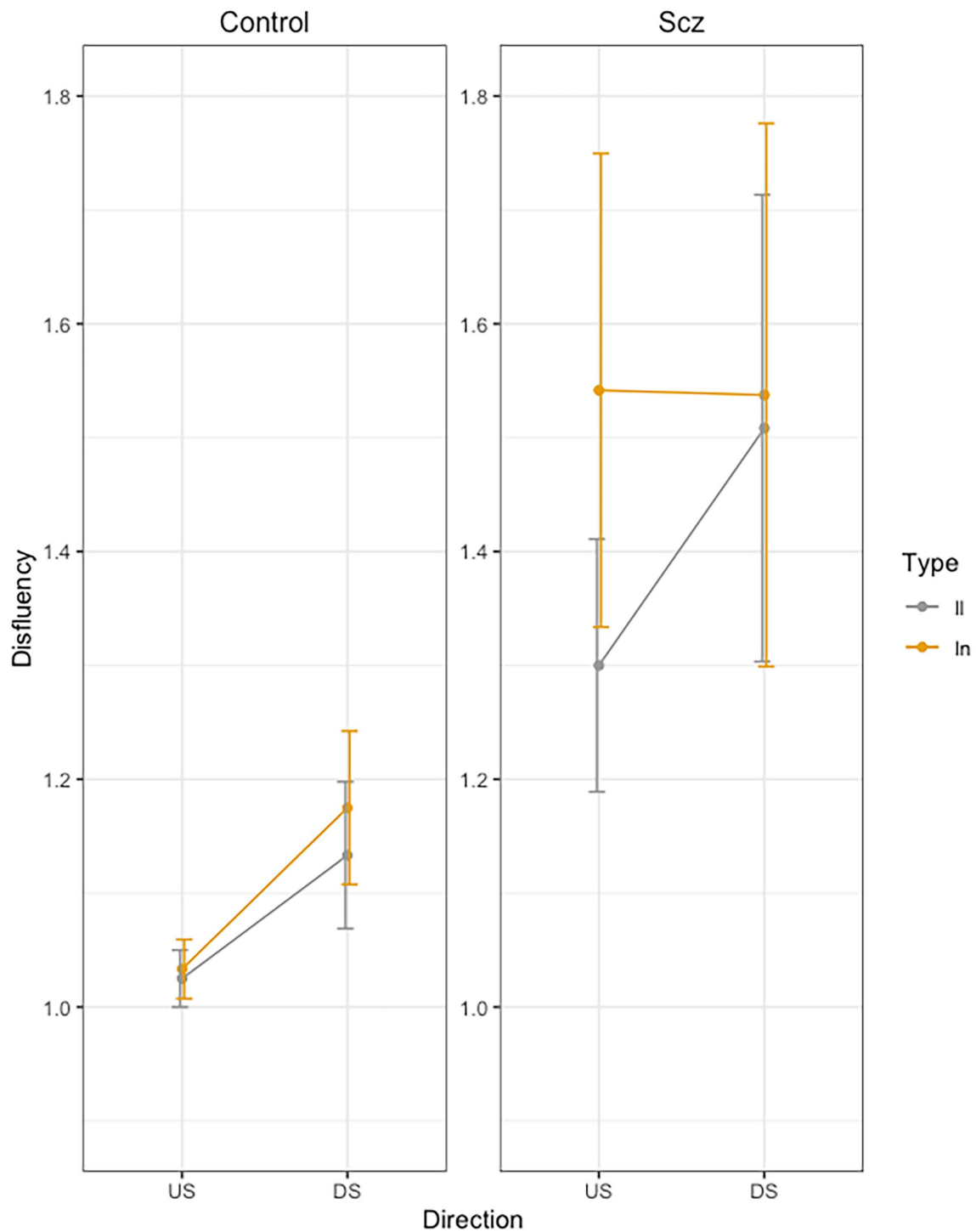


FIGURE 4 | Mean Dysfluency (number of velocity peaks) across trials, as a function of group (Schizophrenia-SCZ vs. Control-CTRL), stroke direction (downstroke-DS vs. upstroke-US), and type of bigram (ll vs. ln). Error bars represent standard error.

letter. This anticipation modulates the spatio-temporal course of the production movement, which can be observed in some kinematic parameters of handwriting. Based on this idea, and following the experimental paradigm presented by Orliaguet and

Boë (1990), the present research evaluated motor anticipation in patients with schizophrenia and controls. We measured the kinematic variations in the upstroke (US) and downstroke (DS) of the first letter *l* of a bigram, as a function of the graphomotor

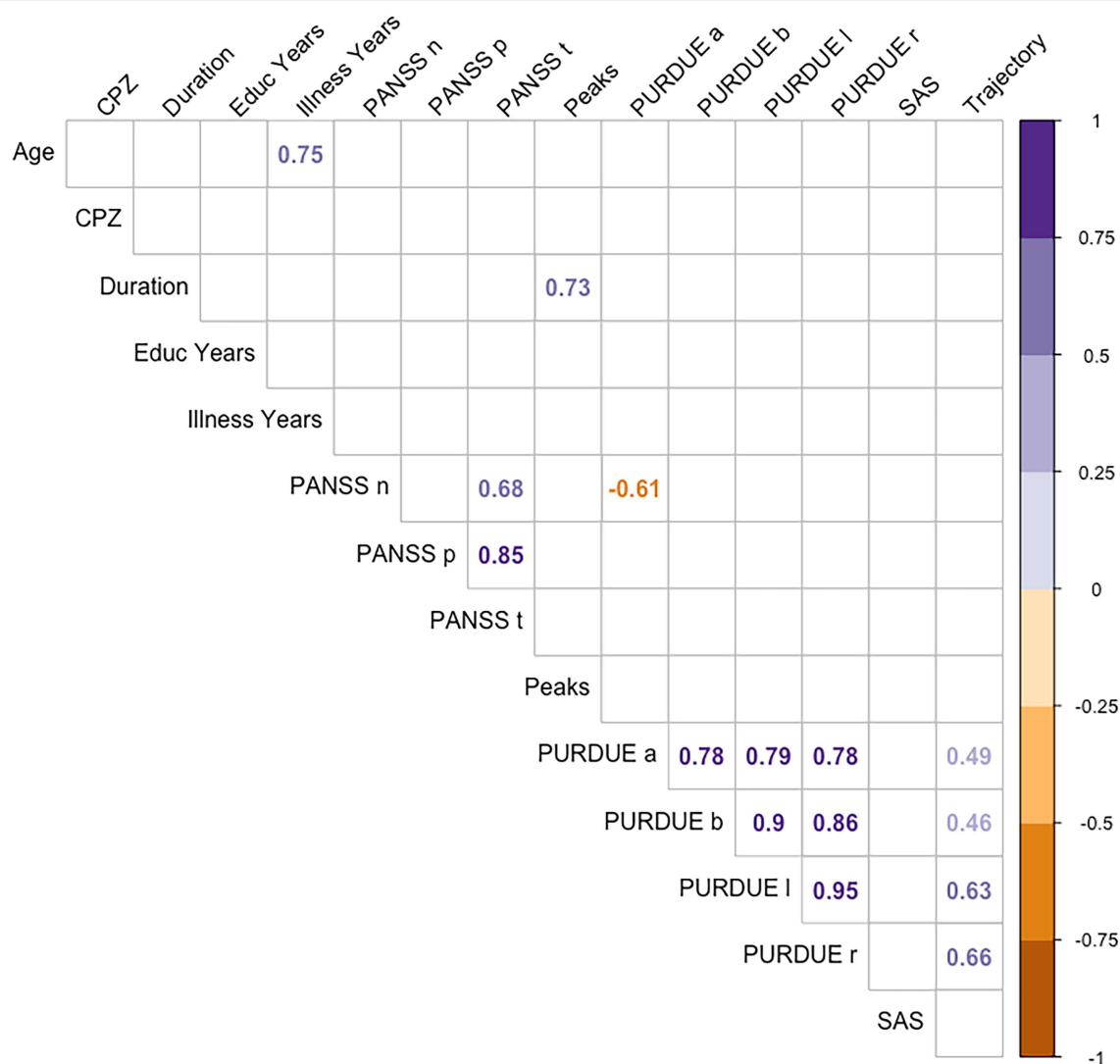


FIGURE 5 | Spearman coefficients for CPZ, educational level, illness years, PURDUE, SAS, PANSS, and the handwriting variables.

constraints of the following letter. Motor anticipation implies a modulation of the duration of the descending stroke as a function of size and rotation direction of the following letter (e.g., Kandel and Perret, 2015). If the forthcoming letter requires a change in size and direction from one letter to the other as in *ln*, the cognitive load is usually reflected in an increase in the duration of the descending stroke compared to a bigram in which the same motor program is repeated as in *ll*.

The results supported our main hypothesis: patients with schizophrenia did not exhibit any sign of motor anticipation. In the control group instead, changes in letter size and direction increased the downstroke duration of the first *l*, whereas for the upstrokes it remained unaffected (*l* US: $ln = ll$; *l* DS: $ln > ll$). The fact that the duration of the downstroke increases as the spatial parameters of the following letter change, is interpreted as a sign of motor anticipation. These results contrast with those of the schizophrenia group: no differences were found

in duration according to the type of bigram ($ll = ln$) or stroke direction (US=DS); interaction type of bigram and direction failed to reach significance (US: $ln = ll$; DS: $ln = ll$).

Stroke duration seems to be the most sensitive kinematic measure of motor anticipation according to previous research (Orliaguet and Boë, 1990; Bidet-Ildei et al., 2011; Kandel and Perret, 2015). There are several brain structures involved in handwriting that are disrupted in schizophrenia, but it is the basal ganglia that have been mostly related to the deautomatization of writing. This dysfunction of the basal ganglia can result in a general impairment in motor planning and coordination. This impairment, associated to a delay in corrective movements, could cause a segmentation of sequential movements and disrupt motor anticipation in handwriting (Pantelis et al., 1992; Lange et al., 2006; Smiley-Oyen et al., 2007; Bidet-Ildei et al., 2011).

The trajectory results also reflect this kind of impairment in motor anticipation in the patients. The control group produced

longer trajectories for the DS of the *l* of *ln* than *ll* and no differences in US, while the group of patients failed to show this effect. These results can be interpreted as another sign of motor anticipation in healthy people compared to patients with schizophrenia. Although previous studies have not found this trajectory modulation, our data clearly support that anticipation can also be reflected in the trajectory of the stroke. We also found that the strokes in the schizophrenia group were in general longer than the strokes in the control group. This result is consistent with previous studies that report the presence of macrography in schizophrenia (Gallucci et al., 1997; Caligiuri et al., 2015; Kömür et al., 2015). Of particular interest are those studies that relate a decrease in the size of handwriting with dopamine D2 receptor occupancy after risperidone treatment (Kuenstler et al., 1999; Regenthal et al., 2005). Future research could deepen these results.

Finally, the fluency measure (i.e., the number of velocity peaks) was not sensitive to motor anticipation, although the patients exhibited more dysfluency than controls. This is in line with previous studies revealing more dysfluent movements in handwriting in patients with schizophrenia and related disorders (Lohr and Caligiuri, 2006; Caligiuri et al., 2015; Crespo et al., 2019). In general, dysfluent movements occur when the muscles that coordinate the movements receive dysregulated signals from the basal ganglia (Caligiuri et al., 2009, 2010). Whether operationalized as absolute velocity peaks or acceleration changes over time, dysfluency in handwriting is always present in schizophrenia. The fact that in our study the schizophrenia group presented greater trajectory length and more dysfluency is a sign of a general motor impairment in this disorder.

It is also noteworthy that we did not observe any relation between psychotic symptoms, pharmacological treatment, and demographic variables and kinematic measurements. We can therefore discard that the groups differences in motor anticipation could be due to psychomotor slowing related to the evolution of the disorder. It is also noteworthy that we did not observe any relation between psychotic symptoms, pharmacological treatment, and demographic variables and kinematic measurements. We can therefore discard that the groups differences in motor anticipation could be due to psychomotor slowing related to the evolution of the disorder, but not to the pharmacological treatment or another demographic variables. However, we think that the absence of motor anticipation in patients is not caused by pharmacological treatment. First, drug induced parkinsonism consists of a number of motor symptoms, such as rigidity, bradykinesia, and tremor, but, to our knowledge, deficits in motor anticipation have never been considered as a symptoms of parkinsonism. Parkinsonism could be reflected in some characteristics of patients handwriting, for example, velocity, trajectory or fluency, but it would be reflected in a group effect, not in an interaction between these characteristics and bigram or direction. That is, parkinsonism could be reflected in patients handwriting being slower than controls handwriting, but, in our opinion, it has no sense that a difference between patients and controls only in upstrokes but not downstrokes would reflect parkinsonism. Thus, we interpreted that, in our study, results in fluency reflect parkinsonism (idiopathic or drug-induced), but results

in duration and trajectory (where we found an interaction between group, direction, and bigram) reflect a specific deficit in motor anticipation.

In summary, patients with schizophrenia fail to show the typical motor anticipation effect in handwriting, evidenced by a modulation of duration of the first letter of the bigram as a function of spatial constraints of the second letter. In a broader sense, this research constitutes further evidence in favor of the analysis of handwriting as a quantitative, objective, and reliable tool to detect motor alterations in schizophrenia. Traditionally, the assessment of motor alterations has been carried out by means of observation scales, such as the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movements Scale (AIMS). However, some studies have highlighted the insufficient predictive value of these scales, a low specificity (Blanchet et al., 2012) and an acceptable reliability only if the evaluation is performed by trained evaluators (Lane et al., 1985; Tonelli et al., 2003). The analysis of handwriting on digitizing tablets allows us to extract a number of handwriting measures that can reveal different cognitive and motor processes disrupted by the disorder.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de ética de la investigación de Jaén, Junta de Andalucía. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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

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The Effectiveness of the Moving to Emptiness Technique on Clients Who Need Help During the COVID-19 Pandemic: A Real-World Study

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With Western therapeutic techniques prevailing in Chinese therapies, some techniques that include Chinese traditional cultural features are required since some cultural factors are not considered in the Western method. Our study introduced a new technique, the moving to emptiness technique (MET), which combines Western structural progress and core factors of Chinese culture. Seventeen therapists treated 107 clients with the MET. Clients reported their target symptoms initially, and therapists helped them transfer invisible symptoms to perceivable stuff and remove their jarring stuff using the psychological emptiness area. At the end of the consultations, we found that MET could eliminate symptoms immediately. By grouping target symptoms according to their frequency, the results showed that clients in the high-frequency symptom group had higher rehabilitation rates than those in the low-frequency symptom group. Additionally, the results of the bereavement group were better than those of the non-bereavement group, indicating that the MET can significantly alleviate clients' target symptoms. In future studies, the replication and stability of the MET can be assessed by integrating questionnaires, experimental designs, and neurological equipment.

Keywords: moving to emptiness, COVID-19, psychological consultation, clients, Chinese traditional cultural

"There is no Bodhi tree, mirror, or stand. Originally, there was nothing around us. Therefore, no dust will fall." – Hui Neng, the founder of Zen Buddhism.

INTRODUCTION

There are many psychosomatic symptoms in the community as a result of the COVID-19 pandemic, such as panic, tension, melancholy, and helplessness. Therefore, China has paid increasing attention to providing psychological therapy for those with mental health problems. However, most therapists in China still use Western therapies, which leads to some cultural maladjustment. Because of this, some experts in China are now researching the application of Chinese traditional philosophy and culture in Western structural therapies. The moving to emptiness technique (MET) has become a choice for therapists in this context.

THE THEORETICAL FOUNDATION OF THE MET

In one branch of Chinese philosophy, nothing exists around us. Anything that disturbs us comes from our inner world. Therefore, if we put any of our problems into a more extensive context, the so-called emptiness state, our mental troubles will no longer exist. Clinical psychology is regarded as a valuable field for all human beings in China, even if the research method is still new. Moreover, China has a long history of psychological thinking, which can be traced back to various traditional philosophical and medical works (1, 2). Confucianism, Taoism, and Buddhism are three philosophical branches that impact Chinese civilization on a large scale. As mentioned earlier, poems are common in modern China, in which principles lay a solid foundation for Chinese people's faith and actions. Additionally, these philosophical ideas have influenced the Chinese medical system since ancient times, especially in treating mental disorders and illnesses and cultivating a healthy life. The MET is one therapeutic skill that applies the essence of traditional Chinese philosophical thinking and cultivates medical systems in clinical therapies (3).

Structural therapeutic techniques, such as cognitive behavioral therapy, [CBT, (4)] and non-structural therapeutic techniques, such as psychoanalysis, are two main methods that are popular among therapists. CBT is a type of therapy in which therapists focus on how clients' dysfunctional beliefs affect their current behaviors and functions (5). CBT helps clients explore, challenge, and modify their dysfunctional beliefs, which is called cognitive restructuring, and can transfer the distorted way they interpret reality into a more adaptive direction. CBT offers an operational structure for therapists to lead clients in identifying their beliefs and core values and then better revise them by considering new possibilities (6).

Therapists who apply CBT assign homework outside of therapeutic sessions for clients to experience the value of the proposed changes that were developed through the collaboration between therapists and clients in therapeutic sessions. Instead of revising and restructuring the cognitive system or locus of attention, the MET aims to eliminate negative feelings represented by target symptoms. Taking the structure of CBT into account, the MET is a psychosomatic treatment that includes the academic concept of Chinese medicine in which the priority in treating a mental disorder is to heal the mind. In summary, the MET integrates traditional Chinese culture while preserving somatic relaxation and the operational process of CBT.

In 2019 and 2021, the MET operational manual was published in Chinese (7) and German, respectively. The MET goes beyond structural therapy abilities and includes attempts to discover clients' target symptoms to reduce the symptoms in a broader psychological context. Before therapeutic sessions, therapists help clients relax and lead them in being mindful of their emotions. Following this, the therapists guide the clients to identify and express their target symptoms and place them in appropriate "containers". With guidance, the

clients can move these containers back and forth before their psychological symptoms occur, and then put them even further away until they disappear in a psychological emptiness area. Using ten operational steps (see Section Measures Consultation Step), the MET, a psychosomatic therapy, can reduce or eliminate symptoms.

Compared to Western psychotherapies that focus on "existence," Chinese therapeutic skills involve both "emptiness" and "existence." "Emptiness" is a status in which only consciousness exists. At the same time, the existence mentioned here refers to transforming one mood into another or surmounting one without removing anything; for example, transforming a negative mood into a positive mood or overcoming sickness through wellness. In comparison, "emptiness" here relates to psychological emptiness. When a client in a bad mood enters the consultant room, a therapist who uses CBT will guide him or her to identify and restructure the maladaptive cognitive system. Therefore, an unchanged bad mood is covered by a good mood. Once a therapist applies the MET in counseling, the client will be guided to a state of psychological emptiness where the bad mood will disappear. If we describe the so-called state of emptiness in English, it is a neutral, non-positive, and non-negative state of existence instead of a state of action.

The psychological emptiness area can be regarded as a purely mental and emotional condition without any troubles. What must be mentioned here is that clients use their psychological emptiness area to solve their problems, which does not depend on their defensive mechanisms, such as denial, repression, projection, avoidance, transference, replacement, or sublimation. Their troubles are directly absorbed, accepted, and processed rather than being rejected or disguised.

The psychological emptiness area can provide cures because it is an infinite psychological space without any trouble to which therapists can guide clients. Therefore, the problems are put in psychological emptiness, a broader background, which vanish automatically using this skill. For example, if one spoon of salt dissolves in a cup of water, the water will be brackish. Nevertheless, the taste will not change much when the salt is put into one water tank. Moreover, if it is poured into one lake, nothing will change. Theoretically, once a mental disorder can be put into a person's massive psychological emptiness area, it can disappear automatically. In traditional Chinese medicine, the psychological emptiness area is widely proposed for solving psychological troubles (3). The MET provides clear, fast, and practical guidance to enter the psychological emptiness area. It is not only an innovative and non-antagonistic idea but also a particular way for problem solving. Moreover, the entire methodology includes Chinese traditional ideology and wisdom by summarizing the core of the ancient Chinese medical system.

GOALS OF TREATMENT WITH THE MET

As mentioned above, the main difference between the MET and CBT is that the MET directly targets symptom reduction,

while CBT focuses more on restructuring the cognitive or emotional systems.

Thus, to test the effectiveness of the MET in practical counseling applications, we sampled 107 subjects to assess whether it could work effectively for the entire group. The index of *influence* was used as the criterion. We first analyzed the immediate and long-term counseling effects of the MET using a paired-samples *t*-test. To specify the effectiveness of the MET for different symptoms, we classified all target symptoms reported into two categories based on a high and low frequency of the top three body parts with the highest presence of symptoms. Since we conducted our research during the COVID-19 pandemic, with clients losing beloved family members, we obtained the clients' familial information before treatment. Based on their backgrounds, we divided them into two groups, the bereavement group or the non-bereavement group, to determine whether the MET has different effects.

METHODS

Participants and Consultations

Participants

We started our study during the COVID-19 pandemic and recruited 107 participants and a total of 17 psychotherapists in mainland China. Notably, some detailed procedures for participants recruitment need to be introduced. Firstly, the present study was an open program to those who require trauma healing treatments due to the COVID-19 pandemic on mainland China and offers them psychological counseling services without requiring a clinical diagnosis at the time of enrollment. However, certain criteria must still be met: experiencing a distressed state of mind during the epidemic, including physical pain such as insomnia, headaches, and chest tightness, as well as negative emotions such as fear, anxiety, guilt, self-blame, irritability, loneliness, and sadness, as well as a desire to improve the psychosomatic condition. Clients in a psychoactive phase or who were unable to complete the three relaxation steps of MET and required crisis assistance were excluded.

We publicized recruitment advertisements on one online platform, and all participants joined voluntarily. The ethics committee of the corresponding author's university approved this research (Reference Number: H20006, ChiCTR2000034164).

Consultation Steps

The Trio (Body, Mind, and Breath) Relaxation Exercise

Regulate the body: Shake and relax the body, sit in the first 1/3 of the chair in a comfortable position with the neck and shoulders relaxed. Straighten the waist and back and then rest both hands on the thighs and close the eyes.

Regulate the breath: Breathe deeply, slowly, and naturally. There is no need to fill or empty the lungs to avoid blood pressure fluctuations.

Regulate the mind: Focus only on exhaling without special attention while inhaling. Empty the mind while exhaling. Practice these steps for ~3 min with the eyes closed and open the eyes when the mind is clear. The relaxation of the body, breath, and mind is the pre-consultation phase and a prerequisite of therapy

with the MET. If a client is unable to relax, he or she cannot proceed to the subsequent steps.

Select a Symptom That Causes Trouble for the Client as the Target Symptom

It could be a negative emotion such as fear, anxiety, anger, or a negative physical sensation such as tightness of the chest, shortness of breath, or pain of the body. In each session, only one symptom is treated. If there is more than one physical or mental problem, clients will be asked to choose the one that is most problematic or urgent for this session by evaluating its influence on a scale from 0 to 10. Usually, when people seek help, their target symptoms have scores of 7 or above.

Visualize and Locate the Target Symptom

There are two ways to determine the symbolic object of the target symptom. One way is to ask the client how they embody their target symptom. For example, the therapist could ask: what makes you feel bad at that body part? Asking such questions could encompass the client's physical sensations and feelings from the target symptom. The other way is to locate the emotion in one somatic part. If the client feels stressed, he or she may report that a pile of cotton is blocking his or her chest to the therapist. After a symbolic object and a certain somatic part are determined and located, the client should elaborate and highlight various dimensions of the object and embody the object. The therapist can help by asking the client to describe the size, shape, weight, sound, texture, and smell related to the symbolic object so it becomes vivid.

Visualize a Symbolic Container

A symbolic container is the device that holds that object mentioned in Step 3. It signifies a client's internal resources and energy. Clients are encouraged to create a container with rich and vivid perceptual features that are similar to the symbolic object.

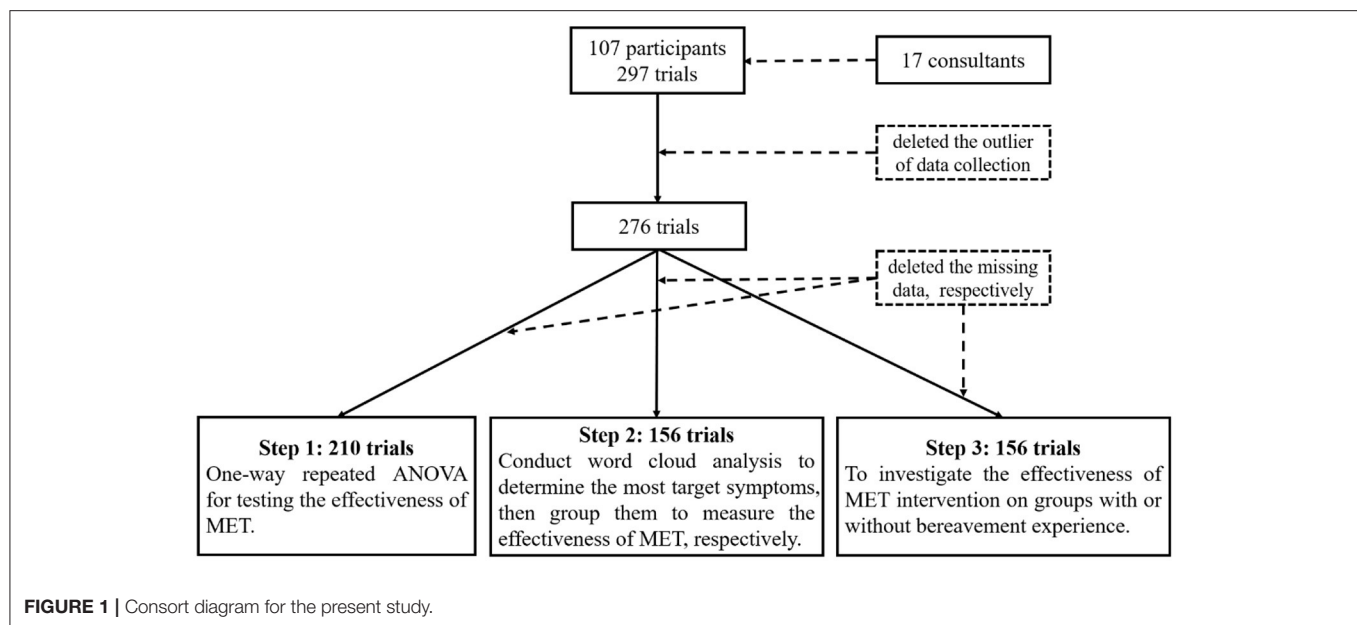
Moving the Symbolic Object Into the Psychological Emptiness Area

Guide the client to:

- i) put the symbolic object into the container in the mind;
- ii) moving the container farther and farther away psychologically and finally into the psychological emptiness area. First, move the container 3 meters away and back again. Repeat this step 2 to 3 times. Then, move the container farther away so that it will look like a small dot, then move it back. Repeat this process 10 times. Finally, move the container far enough away so the client cannot see or feel it. Clients get to the "emptiness area" where nothing exists in this stage.
- iii) When the container with the symbolic object is moved to the psychological emptiness area, clients can feel comfortable and relaxed with the target symptom leaving. The client is asked to experience the sensation of emptiness by staying there as long as they can with their eyes closed.

Assessment of Changes After the Intervention

Ask the client to score the influence of their symptoms again after the intervention. If the initial score is reduced by 50% or more,



the treatment is considered to be highly effective; if the score is reduced by 1/3 or more but by <50%, the treatment is considered to be adequately effective; and if the score is reduced by <1/3, the treatment is considered to be ineffective.

Measures

Consulting Assessment

A visual analog scale (VAS) is a Likert psychometric scale that is used to evaluate subjective characteristics or attitudes (8). These scales have previously been used to diagnose various disorders in market research and social science assessments.

First, we assessed the influence of the clients' target symptoms and scored it from 1 to 10. At the end of the MET treatment session, the client re-evaluated the impacts of their symptoms when the container was far away and invisible in their minds.

Follow-Up Feedback

The clients were asked how much the previous target symptoms had influenced them in a follow-up survey after 1 week.

Procedure

In this study, a dedicated reservationist establishes a consultation time based on the client's registration information. When the client enters the consultation room, the psychotherapists will spend about 1–3 min gathering basic information and identifying the client's primary symptoms that need to be addressed and a 1–10 rating (i.e., the influence of the clients' target symptoms). The formal consultation session is then conducted, and after the consultation, the 1–10 scale is administered once more. An average single session of ~50 min for each client.

The appointment maker will contact the visitor within about a week to inquire about the consultation's outcome and conduct a 1–10 rating. Due to the principle of respecting client's wishes, data on the effectiveness of counseling are unavailable for some visitors, as shown in **Figure 1**. In total, 297 sessions

were collected. A total of 276 sessions were collected for the final process with outlier deletion (i.e., duplicate and incorrect data rows).

Statistical Analysis

In the present study, all data were analyzed by R. We used the package of *compareGroups* (9) to collect the essential information for the participants and therapists. Then, the *WordCloud* package (10) was used to visualize the target symptoms of the participants. The *afex* package (11) was used to perform the mixed ANOVA.

RESULTS

Descriptive Demographic Analysis

As shown in Table 1, we recruited 107 participants, with the majority being female ($n = 93$; 86.9%). More than half of the participants had undergraduate and junior college education degrees ($n = 69$; 64.5%). More than half of them were employed ($n = 62$; 57.9%) and were not students ($n = 93$; 86.9%). More than 60% of them were married ($n = 69$; 64.5%). As reported in the clients' information, most of them did not have mental health issues ($n = 94$; 87.9%) or took medicine ($n = 90$; 84.1%; see **Table 1**).

A total of 17 psychotherapists worked for this study. Most of them were female ($n = 15$; 88.2%) and aged older than 40 years ($n = 15$; 88.24%). Most of them had an undergraduate education level ($n = 16$; 94.12%). More than half of them had more than 5 years of working experience ($n = 11$; 64.71%). More than half of them had worked in counseling between 1 and 3 years ($n = 11$; 64.7%) and had supervision time below 50 h ($n = 11$; 64.71%; see **Table 2**).

TABLE 1 | Summary descriptives table for clients ($n = 107$).

| | Variable | N (Proportion/SD) |
|---------------|------------------------------------|-------------------|
| Gender | Male | 14 (13.1%) |
| | Female | 93 (86.9%) |
| Age | | 40.0 (10.95) |
| Education | Below high school | 3 (2.80%) |
| | High school and polytechnic school | 3 (2.80%) |
| | Undergraduate and junior college | 69 (64.5%) |
| | Master and doctor | 30 (28.0%) |
| | Others | 2 (1.87%) |
| Occupation | Worker | 4 (3.74%) |
| | Cadre | 10 (9.35%) |
| | Technician | 16 (15.0%) |
| | Teacher | 18 (16.8%) |
| | Profession | 14 (13.1%) |
| | Others | 45 (42.1%) |
| Job status | Student | 11 (10.3%) |
| | On the job | 62 (57.9%) |
| | Unemployed | 13 (12.1%) |
| | Retire | 8 (7.48%) |
| | Others | 13 (12.1%) |
| Marriage | Unmarried | 31 (29.0%) |
| | Married | 69 (64.5%) |
| | Divorce | 4 (3.74%) |
| | Separation | 2 (1.87%) |
| | Widowed | 1 (0.93%) |
| Students | Yes | 14 (13.1%) |
| | No | 93 (86.9%) |
| Mental health | Yes | 13 (12.1%) |
| | No | 94 (87.9%) |
| Medicine | Yes | 17 (15.9%) |
| | No | 90 (84.1%) |

TABLE 2 | Summary descriptives table for psychological consultant ($n = 17$).

| | Variable | N (proportion) |
|-------------------|---------------------|----------------|
| Gender | Female | 15 (88.2%) |
| | Male | 2 (11.8%) |
| Age | 20–30 | 1 (5.88%) |
| | 30–40 | 1 (5.88%) |
| | 40–50 | 10 (58.8%) |
| | 50–60 | 4 (23.5%) |
| | Above 60 | 1 (5.88%) |
| Education | Below undergraduate | 1 (5.88%) |
| | Master | 7 (41.2%) |
| | Undergraduate | 9 (52.9%) |
| Working time | 1–3 years | 3 (17.6%) |
| | 3–5 years | 3 (17.6%) |
| | 5–10 years | 6 (35.3%) |
| | Above 10 years | 5 (29.4%) |
| Treatment time | 1–3 years | 11 (64.7%) |
| | Above 5 years | 2 (11.8%) |
| | <1 year | 4 (23.5%) |
| Supervision hours | <20 h | 7 (41.2%) |
| | 20–50 h | 4 (23.5%) |
| | Above 50 h | 6 (35.3%) |

Descriptive Analysis of the Number of MET Consultations

A single individual conducted one initial interview and three consultations in the standardized process. In particular, only a few clients required several counseling sessions to achieve the goal. Specifically, a total of 107 people were interviewed and treated first. Sixty-nine people had two sessions, and 51 people consulted three times. As shown in **Figure 2**, sessions decreased continuously with fewer clients joining subsequent counseling sessions. Three persons took nine sessions, which was the maximum number of sessions for a single person.

Overall Intervention Effect of MET

Subsequently, this study screened 276 sessions of 107 people who interviewed and consulted for the first time. Only the sessions with consultation participation were retained, and the interview data were deleted if there was no score of the influence index, which included 210 sessions. First, we tested the effectiveness of the MET intervention for participants using one-way repeated-measures ANOVA (Time: Pretest vs. Posttest vs. Follow-up). The

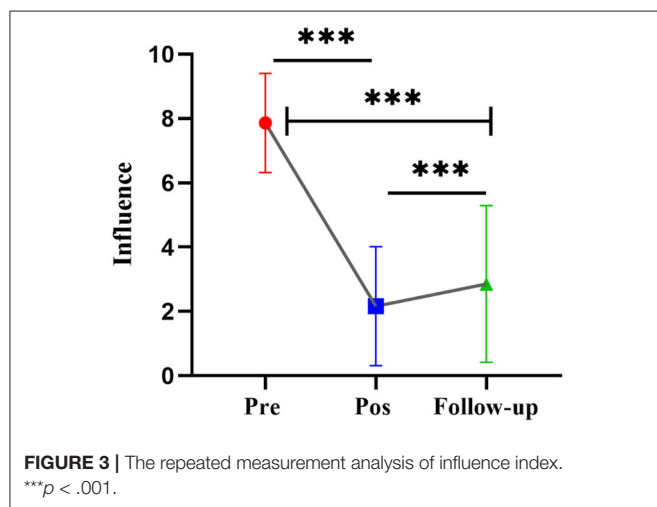
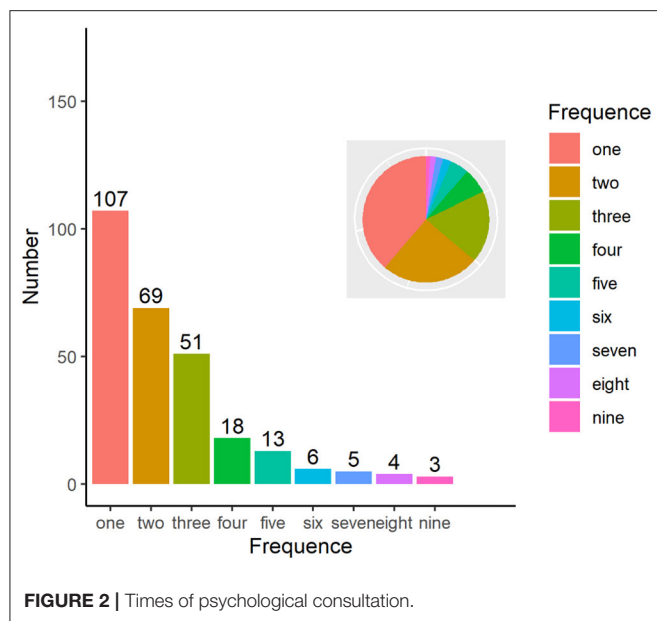
results indicated that the main effect of time was significant [$F_{(2,209)} = 651.7, p = 0.000$]. The posttest revealed that the individual influence decreased significantly after the counseling intervention ($Mean = 2.162$) compared with before consultation ($Mean = 7.861, t = 36.08, p = 0.000$). It should be noted that over time, the influence after follow-up ($Mean = 2.858$) was significantly stronger than that after the intervention ($t = 4.215, p = 0.000$), but it was still significantly lower than the influence score before the consultation ($t = 26.07, p = 0.000$; see **Figure 3**).

Word Cloud Analysis to Categorize Symptoms

Then, we deleted the missing target symptom locations, and 156 sessions were reserved for the word cloud analysis. First, we coded the target symptom locations into two parts: the body surface and internally. The results indicated that 122 symptoms were located inside the body and 34 symptoms were located outside the body (see **Figure 4A**). Considering the specific location, we coded the target symptoms into 15 parts: head, eyes, throat, neck, shoulders, back, bosom, heart, lungs, waist, stomach, abdomen, upper limbs, lower limbs, and others. The results indicated 30 symptoms for the head, 26 symptoms for the bosom, 26 symptoms for the heart, 14 symptoms for the throat, and 14 symptoms for the abdomen (see **Figure 4B**).

ANOVA Analysis for Target Symptoms

Here, it should be pointed out that this study grouped specific locations of target symptoms. The top 3 symptoms (i.e., the three parts of the body where the symptoms appeared the



most as the high-frequency group) were defined as the high-frequency group, and the rest were defined as the low-frequency group to explore whether there were differences in the index of influence between the two groups. Furthermore, to investigate the difference in the influence index between the high-frequency and low-frequency groups under three measurements, a mixed ANOVA was conducted: 2 (Group: high-frequency vs. Low-frequency) \times 3 (Time: Pretest vs. Posttest vs. Follow up).

The results showed that the main effect of the high-frequency and low-frequency groups was insignificant ($F = 0.14$, $p = 0.709$, $\eta^2 = 0.001$). However, the main effect of the time point was significant ($F = 461.14$, $p = 0.000$, $\eta^2 = 0.609$). The interaction between the high-frequency and low-frequency groups and the time point was significant ($F = 5.76$, $p = 0.005$, $\eta^2 = 0.019$). According to the comparison results, in the low-frequency group, the influence after consultation ($Mean = 2.20$, $SE = 0.204$) was

significantly lower than those before consultation ($Mean = 7.41$, $SE = 0.186$, $t = -19.841$, $p = 0.000$) and after follow-up ($Mean = 3.34$, $SE = 0.283$, $t = -12.440$, $p = 0.000$). The influence after follow-up was significantly higher than that after consultation ($t = 4.403$, $p = 0.002$).

In the high-frequency group, the degree of influence after the consultation ($Mean = 2.16$, $SE = 0.194$) was significantly lower than those before consultation ($Mean = 7.97$, $SE = 0.177$, $t = -23.303$, $p = 0.000$) and after follow-up ($Mean = 2.57$, $SE = 0.269$, $t = 17.384$, $p = 0.000$). The degree of influence after follow-up did not significantly differ from that after consultation ($t = 1.687$, $p = 0.213$). The results are shown in **Figure 5A**.

ANOVA Analysis for Bereavement

At the same time, after deleting the missing data, 156 sessions were finally obtained. Then, the participants were grouped according to whether they lost relatives during the study time. Furthermore, whether the degree of influence under bereavement was different under the three measurement time points was investigated. That is, we conducted a mixed ANOVA of 2 (Bereavement vs. No Bereavement) \times 3 (Pretest vs. Posttest vs. Follow-up). The results showed that the main effect of bereavement was not significant ($F = 0.83$, $p = 0.365$), and the main effect of the time point was significant ($F = 252.82$, $p = 0.000$), but the interaction between bereavement and the time point was insignificant ($F = 1.60$, $p = 0.206$). According to the comparison results, in the bereavement group, the degree of influence after consultation ($Mean = 2.39$, $SE = 0.34$) was significantly lower than those before consultation ($Mean = 7.39$, $SE = 0.31$, $t = -11.456$, $p = 0.000$) and follow-up ($Mean = 2.35$, $SE = 0.47$, $t = -9.056$, $p = 0.000$). However, there was no significant difference between the degree of influence after follow-up and consultation ($t = 0.086$, $p = 0.996$).

In the non-bereaved group, the degree of influence after consultation ($Mean = 2.13$, $SE = 0.15$) was significantly lower than those before consultation ($Mean = 7.77$, $SE = 0.14$, $t = -28.261$, $p = 0.000$) and after follow-up ($Mean = 3.01$, $SE = 0.22$, $t = -18.719$, $p = 0.000$). The degree of influence after follow-up was significantly lower than that after consultation ($t = 4.446$, $p = 0.000$). The results are shown in **Figure 5B**.

DISCUSSION

In summary, the MET preserves somatic relaxation and the CBT operational process while integrating traditional Chinese culture. The MET is highly effective during the COVID-19 pandemic for removing negative emotions and terrible physical feelings. As a safe, fast-acting therapeutic technique, although there is some deterioration after a week, the effects of the MET are mainly maintained, which is essential for bereaved people. Hence, some points are worthy of discussion here.

We recognize that most current counseling techniques in China are derived from the West (12). This provides us with numerous benefits, both essential to those with psychological needs and critical to developing the psychological discipline in China. For different types of clients, divergent therapeutic techniques should be applied. Hence, many people in Eastern

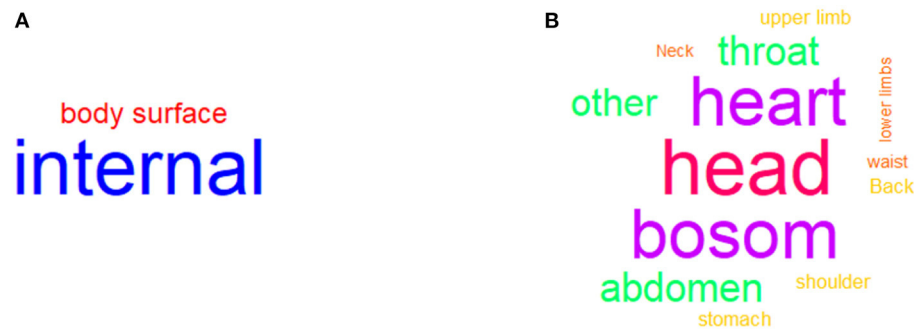


FIGURE 4 | Word cloud analysis of target symptoms. (A) indicated the frequency of approximate locations about target symptoms. (B) indicated the frequency of specific locations about target symptoms.

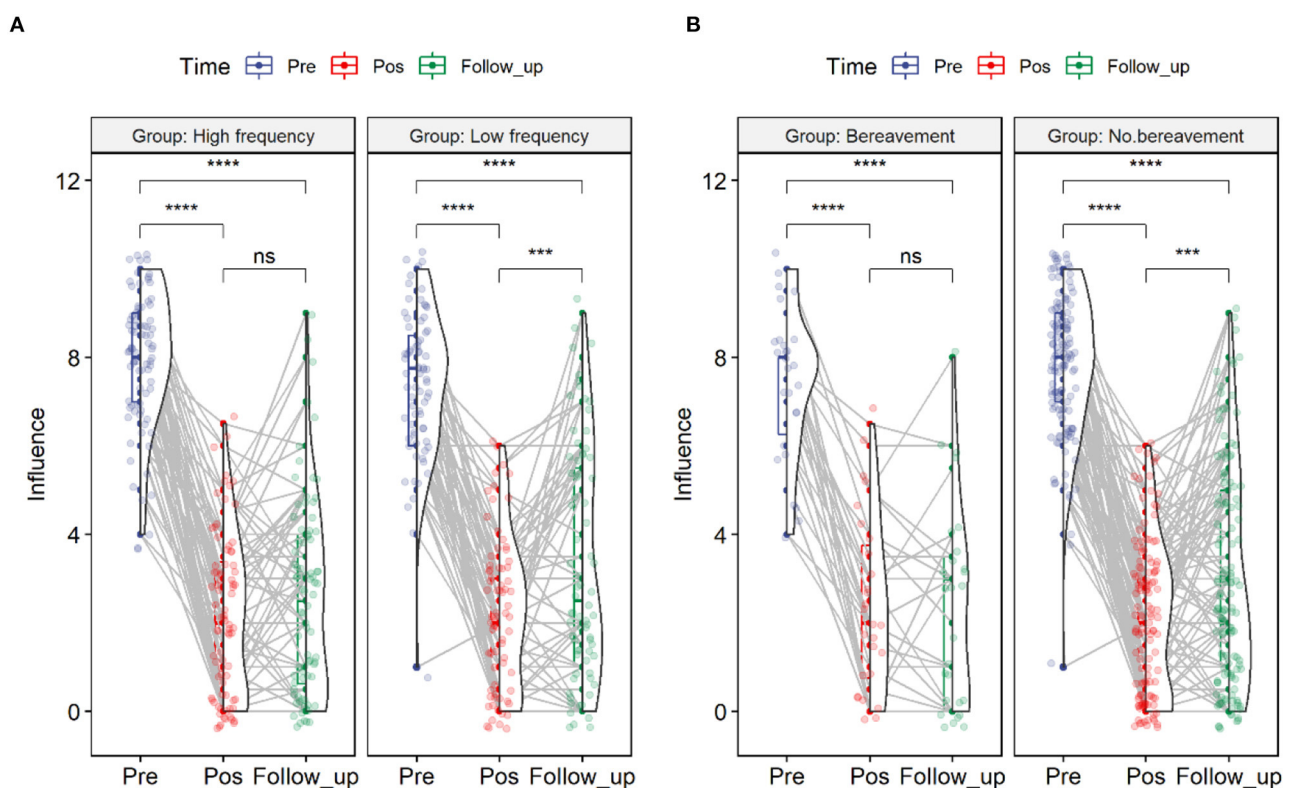


FIGURE 5 | The results of the mixed ANOVA analysis. (A) indicated the results of different degrees of frequency. (B) showed that whether bereavement or not could have a difference in influence.

cultures can be better served by the MET, which combines the fundamental logic of Western counseling techniques with Eastern philosophical principles.

In the present study, we found that the target symptoms identified by the clients decreased significantly after the intervention. What should not be overlooked is the rebound in the follow-up survey. This also highlights that our consultation outcomes were delivered promptly. According to the follow-up data, the influence of a client's symptoms returns, although it is still significantly below the initial reported levels. It is clear

that counseling is pretty successful in improving an individual's current state and that more counseling should be considered progressively over time to strengthen the treatment's benefits.

We separated the top three symptoms according to target symptoms into a high-frequency group and the remainder into a low-frequency group to verify the efficacy of the MET from multiple perspectives. Compared with those in the low-frequency group, there was no significant difference in client effect scores among the high-frequency group at post-intervention and follow-up, which indicates that the effectiveness is apparent

when the MET is evaluated from a randomized perspective. The structure of the MET is similar to that of CBT. Nevertheless, the goals are diversified. CBT assists clients in identifying illogical ideas and attempting to adjust their behavior patterns by modifying their irrational or illusory perceptions. The idea of CBT is the circulation among mood, behavior, and cognition. Compared to identifying maladaptive beliefs (13), the MET offers therapists a fresh perspective; it regards people as a whole. The therapeutic target is to remove those severe problems in personalities. CBT is rational, while MET is emotional. In other words, they have different focuses and different treatment goals. The treatment goal of MET is to bring the client to a place where there is no problem. Compared to CBT, MET has short and quick characteristics. Based on the traditional Chinese concept of emptiness, the MET leads clients to dissolve their internal problems into infinite emptiness by identifying and embodying their symptoms.

Bereavement is described as the situation of having lost a significant loved one due to death (14). Everyone will experience bereavement, which is a highly stressful event, during their lifetime. Individuals seldom experience bereavement in early childhood (~3.4%) (15). Then, as people grow, their risks of experiencing bereavement grow, with ~45% of women and 15% of men in elderly populations experiencing bereavement (16). In the present study, participants were grouped according to who had been bereaved and who had not been bereaved. There was no significant difference in the client effect scores among the group with bereavement experiences at post-intervention and follow-up, which indicates that the effectiveness is apparent when the MET is re-evaluated from a randomized perspective.

Bereavement is linked to a higher risk of mortality for a multitude of reasons, including suicide (17). Furthermore, mental and physical illness is severe and persistent in a small proportion of the population. Notably, depending on the individual and their culture, recovery might take months or even years. As a result, bereavement is both a preventative and clinical concern. However, child grief therapies do not appear to produce good results like other professional psychotherapy interventions (18). As children's early intimate relationships come to an abrupt end, early memories fade with aging. Children's bereavement experiences can be reshaped by later social attention and the formation of new personal attachments (19). However, due to the general stability of the object-subject relationship in adulthood (20), adults' memories of painful bereavement experiences are difficult to erase in a short period. They can even remain with them throughout their lives, influencing their daily emotional (21, 22) and life functions (23, 24).

Some researchers have employed a variety of psychological counseling therapies to aid persons experiencing grief who have been bereaved (25–27). Studies investigating counseling techniques refer to the dual process model and the meaning reconstruction model. However, due to cultural differences, the mainstream models in mainland China are currently cognitive behavioral therapy (CBT) and other counseling techniques. To treat and intervene Chinese people who have experienced bereavement, a counseling technique with a high degree of cultural-ecological validity is needed. The moving to the emptiness technique (MET) may be a good choice.

Limitations

However, this study has potential limitations. To begin, we presently have data on only 107 clients, although these clients reveal great demographic heterogeneity. Given that a large proportion of clients to this study received multiple counseling sessions (see **Figure 3**), we could not integrate demographic characteristics as covariates in ANOVA analysis. However, in future studies, MET should explore examining the impact of interventions on specific populations and controlling for demographic heterogeneity, such as people with depression. Second, the MET is a new counseling technique that stems from ancient Chinese philosophical thinking and Chinese medical theory, mixed with the logic of Western counseling techniques. Compared with CBT and other techniques, it is still in development. Third, although the therapeutic benefits of the MET were investigated in this study using a randomized design, more analytical approaches, such as questionnaire measurements, fMRI, fNIRS, and other similar methodologies, should be used to assess the efficacy of the MET. Furthermore, the benefits of the theoretical framework of the MET can be used in future studies concerning more clinical patients with specific medical issues, such as neurological headaches and frozen shoulder. The efficacy of the MET may be evaluated by attempting to relieve persons' somatic diseases from a psychological counseling perspective.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TL and YC: study design and critical revision of the manuscript. WZ and LL: data collection. YT and YC: analysis and interpretation. YT: drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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Hospital Culture and Healthcare Workers' Provision of Patient-Centered Care: A Moderated Mediation Analysis

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Background: Patient-centered care (PCC) is globally recognized as a high-quality and high-value healthcare service. It emphasizes the broad participation of patients and families in health-related decision-making and the provision of healthcare services that cater to patients' needs, preferences, and values. However, the mechanisms driving healthcare workers' provision of PCC are yet to be fully uncovered.

Methods: Using stratified random sampling, we recruited 1,612 healthcare workers from different levels of public hospitals in Hangzhou. We conducted survey interviews using questionnaires based on psychometrically sound scales. Structural equation modeling was used to analyze the effects of hospital culture, self-efficacy, and achievement motivation on the perceived provision of PCC by healthcare workers and to explore the mechanisms underlying their relationships.

Results: Self-efficacy had a positive mediating effect in the relationship between hospital culture and healthcare workers' perceived provision of PCC ($\beta = 0.424$, $p < 0.001$). Furthermore, the pursuit of success positively moderated the mediating role of self-efficacy ($\beta = 0.128$, $p < 0.001$), whereas, the avoidance of failure negatively moderated the mediating role of self-efficacy ($\beta = -0.017$, $p < 0.001$).

Conclusion: The findings suggest that hospitals should foster patient-centered and innovative cultures and develop strategies focusing on both internal motivation (self-efficacy and achievement motivation) and external environments (hospital culture) to help and encourage healthcare workers to implement PCC. For example, hospitals could further communication skills training, enhance leadership, build team spirit, and promote collaboration among healthcare workers.

Keywords: hospital culture, healthcare worker, patient-centeredness, self-efficacy, achievement motivation

INTRODUCTION

The notion of patient-centered care (PCC) was first proposed by Balint in 1995 to express the belief that healthcare workers—who are involved in the process of treatment—should be familiar with patients' living conditions, social environments, and disease progression; that is, healthcare workers must deliver services that recognize and cater to the preferences, needs, and values of

patients (1). PCC is a high-value healthcare service that is crucial to improving the quality of care and building harmonious doctor-patient relationships (2, 3). However, PCC calls for substantial competence among healthcare workers as it is complex and can be characterized as integrated medicine that is multi-leveled and comprehensive, covering the entire life cycle (4, 5). Therefore, clarifying the driving mechanism for the provision of healthcare is necessary to effectively intervene in the behaviors of healthcare workers. Furthermore, it is important to gain thorough and systematic insights into the factors driving PCC from different aspects, such as outer contexts and intrinsic motivation.

In recent years, many scholars have tried to elucidate the concept of PCC and explore the factors influencing behaviors of healthcare professionals pertaining to the provision of PCC; for example, in 2000, Ma studied the development and improvement of the hospital service system based on insights from the patient-centered approach, proposing a basic framework and solutions for the establishment of a patient-centered hospital service system (6). In 2002, Wang and Liu (7) argued that “patient-centeredness” involves improving doctor-patient communication, which can facilitate doctors’ understanding of their patients and help doctors and patients reach a consensus on medical decisions. In 2019, Liang (8) summarized Western studies on patient-centered medical services and administration at the theoretical level and outlined practice guidelines for the implementation of PCC in China. Gender, grade, empathy, and communication skills were found to have statistically significant effects on dental students’ attitudes regarding patient-centered services, which could be improved *via* a focus on enhancing empathy, emphasizing positive attitudes toward learning communication skills, and conducting patient-centered learning seminars (9). Furthermore, Kanat et al. (10) found that the doctor-patient relationship and communication, doctors’ characteristics, and patients’ engagement were important determinants of PCC. Paiva et al. (11) investigated the factors facilitating and inhibiting healthcare workers’ implementation of PCC; they contended that the creation of an atmosphere that is conducive to communication, engagement of patients in medical decisions, and enhancement of medical personnel’s ability to communicate effectively might foster the provision of PCC by medical workers.

Studies have linked PCC with various positive patient outcomes, including empowerment and engagement (10, 12) favorable health outcomes, diminished socioeconomic, and racial disparities, shorter hospitalization periods and earlier discharge, and lower treatment costs (13, 14). However, the existing literature on PCC has the following drawbacks. First, while many studies have identified various external (contextual) and internal (personal) factors associated with PCC provision, comparatively fewer studies have considered both contextual and personal factors holistically and identified the pathways linking them. It is extremely important to better understand how these factors interact to facilitate (or undermine) healthcare workers’ provisions of PCC. Second, among the studies focusing on the factors influencing PCC, few have focused on organizational culture, which is an important factor that facilitates service ability by valuing people, stimulating new thoughts, fostering team

spirit, and adopting systems that are recognized by employees. Third, studies focusing on the driving mechanisms of healthcare workers’ provision of PCC have not investigated the impact of their intrinsic motivation. Thus, several studies so far have revealed that self-efficacy and achievement motivation have joint effects on personal behaviors (15, 16). However, few have been conducted in the field of hospital administration, and the mechanisms underlying the synergy between self-efficacy and achievement motivation are yet to be fully uncovered; for example, it is unclear whether hospital culture has different effects on the self-efficacy of and provision of care by healthcare professionals based on their level of achievement motivation. Therefore, the pathways of effects between hospital culture and healthcare workers’ implementation of PCC are worth investigating.

Motives—both physiological and social—have been identified as major internal driving forces of human behavior in diverse domains (17). Achievement motivation refers to the perceived motivation that drives individuals to undertake challenging and meaningful work tasks and/or activities and surpass others to attain satisfactory outcomes (18). Thus, achievement motivation is an important internal variable that is positively associated with quality and initiative at work (19, 20). With regard to individual consciousness, achievement motivation is embodied in two opposing psychological tendencies: the pursuit of success and avoidance of failure (21). Schone (22) contended that strong achievement motivation is a positive predictor of employees’ job engagement, work performance, and organizational behaviors, among others. Wang (20) explored the correlation between doctors’ achievement motivation and sense of responsibility and found that achievement motivation is positively associated with service initiative. Feng (19) found that achievement motivation is one of the factors driving community practitioners to deliver first-contact services. Song et al. (23) showed that doctors with high achievement motivation maintain a positive outlook toward work, are friendlier with patients, and can overcome emotional exhaustion. According to McClelland’s (24) theory of needs (also known as the theory of motivation), healthcare workers with a high (vs. low) level of achievement motivation are more devoted to work and are more focused, proactive, and persistent in delivering PCC owing to positive feedback (25).

In light of the aforementioned findings, we advocated the importance of considering the effects of achievement motivation while assessing the influence of hospital culture on patient-centered practice among medical staff. In addition, we included self-efficacy as an essential factor in the proposed model as this—as another intrinsic variable—could reflect healthcare personnel’s level of confidence in the provision of PCC (26). Self-efficacy is an individual’s belief in their capacity to set and achieve certain goals, that is, confidence in one’s abilities (10). It is important to note that self-efficacy affects people’s mindsets, responsiveness to emotions, and choice of behaviors (27). From a behavioral science perspective, self-efficacy might be a predictive factor for the adoption of and changes in health-related behaviors (28). For example, Ham and Tak (29) suggested that low self-efficacy could lead to avoidance behaviors and ineffective communication, resulting in poor clinical outcomes.

Additionally, Afsar and Masood (30) found that enhancements in self-efficacy can facilitate innovative work-related behaviors such as PCC. Furthermore, Zhang et al. (31) demonstrated that self-efficacy is positively associated with health protection behaviors among pharmacists during the coronavirus disease 2019 pandemic.

Self-efficacy can be influenced by several contextual factors associated with hospital culture. For example, Meurling et al. (32) suggested that teamwork (or collaboration) and communication can contribute to the enhancement of self-efficacy among healthcare workers. Zhao et al. (33) proposed that the provision of external support to healthcare workers can enhance their self-efficacy and reduce job burnout. Additionally, the engagement and behaviors of leaders can influence the vitality, caliber, performance, and cohesion of their team (34). Xue et al. (35) found that leaders who favor and encourage changes can set a positive example for their coworkers and employees, fostering unity, and initiative in the organization; these factors are conducive to the organization's future. They also suggested that work atmosphere is positively correlated with initiative among employees. Furthermore, Liang and Gu (36) found that innovative organizational culture has positive effects on creativity and motivation (to perform) among employees. Therefore, an efficient hospital culture serves several functions—including guidance, bonding, stimulation, constraint, regulation, and security—which can contribute to the enhancement of self-efficacy among healthcare workers.

"Hospital culture" refers to the sum of collective consciousness, values, ethics, and norms in medical practice held by hospital employees under certain socioeconomic conditions (37). Studies have shown that hospital cultures based on internal communication, cross-team collaboration, innovation, and charismatic leadership (38–43) can facilitate the implementation of PCC by enhancing patient-centered consciousness among healthcare workers. Thus, the following hypothesis was formulated.

Hypothesis 1 (H₁): Hospital culture has a positive effect on healthcare workers' implementation of PCC. In sum, on the one hand, hospital culture has a direct positive effect on the provision of PCC by healthcare professionals; on the other hand, self-efficacy mediates the effect of hospital culture on healthcare workers' implementation of PCC. Therefore, the following hypotheses were formulated.

H₂: Hospital culture positively affects self-efficacy among healthcare workers.

H₃: Self-efficacy among healthcare workers has a positive effect on the delivery of PCC.

H₄: Self-efficacy mediates the relationship between hospital culture and healthcare workers' implementation of PCC.

Furthermore, achievement motivation moderates the relationship between hospital culture and healthcare workers' self-efficacy for the provision of PCC. Gong and Xue (44) explored the mechanism underlying the effect of empowering leadership on creativity among employees; they found that achievement motivation moderated the relationship between empowering leadership and self-efficacy. In addition,

Sommaruga et al. (45) suggested that patient-centered practice among medical personnel can be enhanced by emotional intelligence. In sum, a good hospital culture has a relatively weaker positive effect on self-efficacy among healthcare workers with low achievement motivation. On the contrary, a good hospital culture has a stronger positive effect on the self-efficacy of healthcare professionals with high achievement motivation. Therefore, the following hypotheses were formulated.

H₅: Achievement motivation moderates the relationship between hospital culture and self-efficacy among healthcare workers.

H₆: Achievement motivation moderates the relationship between self-efficacy among healthcare workers and their implementation of PCC.

Thus, we surveyed healthcare workers from 27 public hospitals (of different levels) in Hangzhou to explore the pathways linking inner communication, cross-team collaboration, innovative organizational culture, charismatic leaders, self-efficacy, and achievement motivation to healthcare personnel's provision of PCC, considering intrinsic motivation and hospital culture. In light of theories of motivation, we proposed a theoretical model with hospital culture as the independent variable, healthcare professionals' implementation of PCC as the dependent variable, self-efficacy as the mediating variable, and achievement motivation as the moderating variable (**Figure 1**).

MATERIALS AND METHODS

Sample Characteristics

Healthcare workers—including doctors, nurses, and medical technicians from different levels of public hospitals in Hangzhou city—voluntarily participated in this study. Hangzhou is a provincial capital located in coastal southeast China. It is economically well-developed and had a per capita GDP of 134,900 yuan in 2021. It is known for its quality of healthcare and high-ranked hospital administration, rendering it an apt setting for this study. The inclusion criteria were as follows: (1) providing informed consent; (2) being employed in the target hospital; and (3) having work experience of more than 6 months. The exclusion criteria were as follows: (1) being off-duty during the survey period owing to reasons like maternity leave, personal affairs, sick leave, learning, holiday, and/or business trips; and (2) questionnaires from interns or trainees from other organizations.

Stratified random sampling was used to select healthcare institutions based on three hospital levels; six tertiary and six secondary hospitals and 15 community health centers were randomly selected from among the medical organizations in Hangzhou. Convenience sampling was then used to select healthcare workers from each institution; 200 healthcare workers were selected from each tertiary hospital, 50 from each secondary hospital, and 20 from each community health center. Accordingly, 1,800 questionnaires were sent to these institutions through a face-to-face survey approach, of which 1,612 qualifying questionnaires were retrieved. The criteria for considering questionnaires invalid were: (1) incomplete responses; (2) same responses for more than 50% of the completed questions;

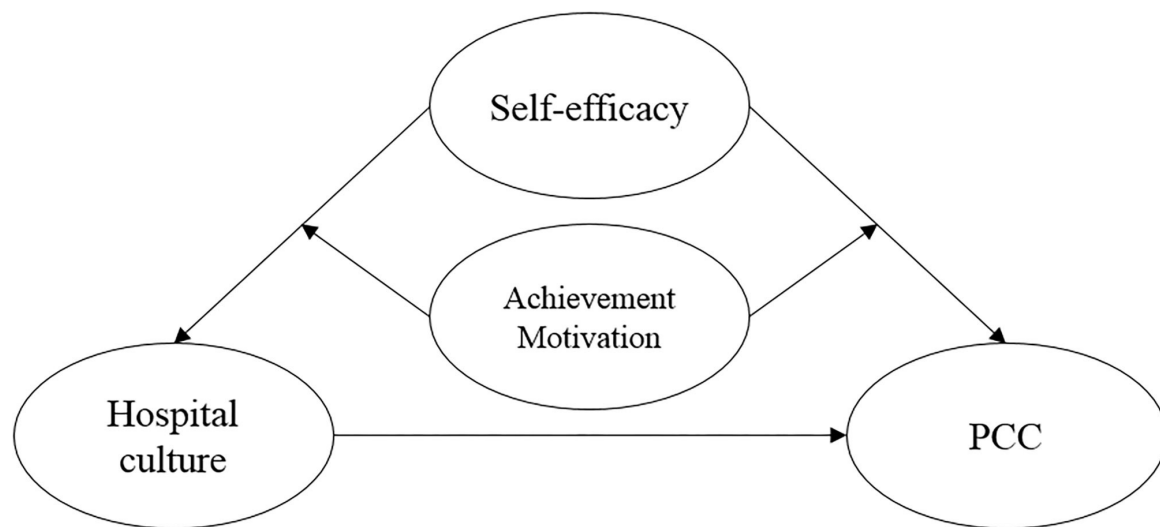


FIGURE 1 | sResearch model diagram of healthcare workers' patient-centered care.

and (3) obvious contradictions in responses across questions. If a questionnaire met even one of these criteria, it was deemed invalid.

Measures

General Information

The form for general information comprised items pertaining to gender, marital status, age, level of education, title, post, department, years of experience, type of employment, daily working hours, monthly income, hospital level, teaching status of the hospital, communication skills training, and familiarity with PCC.

Provider-Patient Relationship Questionnaire

To evaluate the healthcare personnel's perceptions of their provision of PCC, we used the Provider-Patient Relationship Questionnaire (PPRQ), developed by Gremigni et al. (46). The PPRQ includes four dimensions: effective communication (four items), interest in the patient's agenda (four items), empathy (four items), and patient involvement in care (four items). Items are scored on a five-point Likert scale, ranging from one (never) to five (always); higher scores reflect better patient-centered services. The PPRQ has good reliability and validity (Table 1).

Hospital Culture

A self-developed hospital culture questionnaire (38–43) was used to evaluate hospital culture based on four dimensions: internal communication (three items), cross-team collaboration (three items), innovative organizational culture (three items), and charismatic leadership (three items). Items are rated on a five-point Likert scale, ranging from one (strongly disagree) to five (strongly agree); higher scores represent better hospital culture. The scale had good reliability and validity (Table 1).

General Self-Efficacy Scale

Self-efficacy among healthcare workers was evaluated using the General Self-Efficacy Scale (GSES), developed by Schwarzer and Jerusalem (47). The GSES has two components: confidence about interpersonal communication (five items) and confidence about effective communication (five items). Items are rated on a five-point Likert scale, ranging from one (strongly disagree) to five (strongly agree), and higher scores represent higher self-efficacy. The scale had good reliability and validity (Table 1).

Achievement Motivation Measurement Scale

Healthcare workers' achievement motivation was evaluated using the Achievement Motivation Measurement Scale, developed by Huang (21). This scale includes two sub-dimensions: pursuit of success (four items) and avoidance of failure (four items). Items are rated on a five-point Likert scale, ranging from one ("strongly disagree") to five ("strongly agree"); items in the avoidance of failure subscale are reverse scored. Higher scores reflect higher achievement motivation. The scale had good reliability and validity (Table 1).

Quality Control

Prior to data collection, we conducted a pilot study. We gathered and analyzed the problems that were identified in the preliminary study. We then discussed the results of the preliminary study, revised the questionnaire, established a specific study plan, and finalized the questionnaire. Questionnaire distribution was performed by postgraduates with adequate experience in conducting personal surveys. The survey was conducted between July 1 and September 30, 2021. Furthermore, concentrated training sessions were conducted prior to the commencement of the official survey to ensure that the investigators had a clear understanding of the project, questionnaire, and key points during investigation; this process also ensured that they followed

TABLE 1 | Description, factor analysis, and reliability coefficients of construct measures.

| Construct | Dimension | Items | Load ^a | Cronbach's α | Correlation coefficient | Cumulative variance contribution rate (in %) | Overall α value |
|------------------------|--|---|-------------------|------------------------|----------------------------|---|---------------------------|
| Hospital culture | Internal communication | Group meetings are frequently organized in the department to discuss patients' conditions and treatment plans. | 0.763 | 0.834 | 0.719** | 75.201 | 0.944 |
| | | Resources and information can be shared within the hospital. | 0.786 | | 0.754** | | |
| | | Employees can freely point out when incidents with adverse consequences are likely to occur. | 0.735 | | 0.688** | | |
| | Cross-team collaboration | The hospital encourages transdisciplinary cooperation. | 0.862 | 0.902 | 0.791** | 83.661 | |
| | | Members in the department have mutual understanding and acceptance. | 0.86 | | 0.783** | | |
| | | Different departments cooperate effectively and efficiently to solve patients' problems. | 0.866 | | 0.813** | | |
| | Innovative organizational culture | Different departments in the hospital often collaborate with each other to develop innovative ways of providing health services. | 0.822 | 0.936 | 0.830** | 88.7 | |
| | | The hospital encourages constant innovation in health information technologies. | 0.892 | | 0.829** | | |
| | | The hospital encourages constant innovation in administrative skills and know-hows. | 0.894 | | 0.826** | | |
| | Charismatic leadership | The leaders strive to set a good example for employees. | 0.891 | 0.912 | 0.826** | 85.148 | |
| | | The leaders emphasize that employees should show respect and concern toward patients and protect their rights. | 0.845 | | 0.833** | | |
| | | The leaders encourage employees to participate in discussions and decision-making processes. | 0.851 | | 0.802** | | |
| Achievement motivation | Pursuit of success | I would be very happy to get recognized by patients. | 0.859 | 0.92 | 0.588** | 71.998 | 0.86 |
| | | I endeavor to provide personalized care for patients. | 0.892 | | 0.528** | | |
| | | I try to satisfy reasonable needs of patients and solve their problems. | 0.915 | | 0.538** | | |
| | | I prefer completing the work assigned to me as quickly as possible. | 0.862 | | 0.619** | | |
| | Avoidance of failure | I feel uneasy when treatment, examination, and/or nursing don't show clear effectiveness. | 0.821 | 0.851 | 0.586** | 74.796 | |
| | | I would feel anxious if I am unable to reach a consensus with patients on decisions about treatment, examination, and/or nursing. | 0.876 | | 0.566** | | |
| | | I dislike dealing with incidents involving malpractices and/or disputes. | 0.709 | | 0.576** | | |
| | | I would feel anxious if I am unable to immediately understand questions asked by patients. | 0.859 | | 0.616** | | |
| Self-efficacy | Confidence about interpersonal communication | I have a strong ability to build mutual trust with patients. | 0.712 | 0.893 | 0.834** | 69.321 | 0.942 |
| | | I have a strong ability to discern patients' emotions. | 0.66 | | 0.853** | | |
| | | I can solve patients' emotional issues and physical problems. | 0.522 | | 0.824** | | |
| | | Generally, I can be friendly with patients. | 0.879 | | 0.750** | | |
| | Confidence about effective communication | I understand when patients do not approve of the treatment, examination, and/or nursing plan suggested by me. | 0.643 | 0.911 | 0.745** | 81.537 | |
| | | My patients would honestly tell me their medical history if I asked them. | 0.586 | | 0.834** | | |
| | | I have a strong ability to detect non-verbal hints or actions of patients. | 0.816 | | 0.853** | | |

(Continued)

TABLE 1 | Continued

| Construct | Dimension | Items | Load ^a | Cronbach's α | Correlation coefficient | Cumulative variance contribution rate (in %) | Overall α value |
|--------------------------|-------------------------------------|--|-------------------|------------------------|----------------------------|---|---------------------------|
| Patient-centered care | Patient engagement | I possess the ability to ask pertinent questions at appropriate times. | 0.802 | 0.948 | 0.824** | 78.435 | 0.967 |
| | | I can explain medical terms in simple language. | 0.727 | | 0.750** | | |
| | | Patients would be willing to communicate with me if I asked them about sensitive or private issues. | 0.83 | | 0.745** | | |
| | | In most cases, I provide detailed information regarding treatment, examination, and nursing to patients. | 0.685 | | 0.789** | | |
| | | In most cases, I allot ample time for patients to consult with me. | 0.72 | | 0.780** | | |
| | Empathy | In most cases, I speak gently with patients. | 0.558 | 0.933 | 0.818** | 79.26 | |
| | | In most cases, I patiently listen to patients. | 0.632 | | 0.866** | | |
| | | In most cases, I care about the extent of patients' understanding about their disease status and prognosis. | 0.786 | | 0.824** | | |
| | | In most cases, I inquire about patients' preferences and needs. | 0.533 | | 0.866** | | |
| | Interest in patients' agendas | In most cases, I attach importance to the protection of patients' privacy. | 0.802 | 0.905 | 0.795** | 79.498 | |
| | | In most cases, I care about patients' expectations about the outcomes of care. | 0.753 | | 0.805** | | |
| | | In most cases, I can understand patients' negative emotions. | 0.594 | | 0.865** | | |
| | | In most cases, I can see things from the patients' perspective. | 0.612 | | 0.878** | | |
| | Effective communication | In most cases, I can bring confidence and provide a sense of security to patients. | 0.588 | 0.857 | 0.878** | 83.36 | |
| | | In most cases, I can reach a consensus and resolve conflicts together with patients. | 0.695 | | 0.892** | | |
| | | In most cases, I encourage patients to get involved in discussions and decision-making about treatment, examination, and/or nursing. | 0.78 | | 0.825** | | |
| | | In most cases, I can resolve patients' concerns about their diseases and offer timely help. | 0.774 | | 0.877** | | |
| | | In most cases, I allow patients to ask questions and express their ideas when I ask about their symptoms. | 0.764 | | 0.876** | | |
| | | In most cases, I try to determine why a patient is reluctant to receive care. | 0.766 | | 0.821** | | |

^aAll load values are significant at the 0.001 level * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

unified standards and methods. The survey was conducted *via* one-on-one interviews after obtaining informed consent from the participants. After the questionnaires were filled out, the investigators inspected them and checked with participants regarding the questionnaires that did not meet the study requirements. Subsequently, the questionnaires were coded and data were double-entered.

Statistical Analyses

Preliminary Analyses

Data were coded and entered in the database. The demographic data were evaluated and compared by descriptive analysis, one-way analysis of variance, and independent *t*-test. In addition, SPSS version 22 (IBM Corp., Armonk, NY, United States) was

used to test the Pearson's correlations between hospital culture, self-efficacy, achievement motivation, and PCC. Statistical significance was set at $p < 0.01$.

Mediation and Moderation Analyses

Structural equation modeling was used to analyze the mediating effect of self-efficacy among medical staff and the moderating effect of achievement motivation. Hayes' Process Macro Model 4 was employed to conduct mediation analysis, and Model 58 was employed for moderated mediation analysis (48). The aforementioned program is suitable for a variety of mediation, moderation, and moderated mediation models. Hypothesis testing for the regression coefficients was conducted using the bias-corrected percentile bootstrap method with 5,000 replicates

TABLE 2 | Comparison of healthcare workers' mean scores on the provider-patient relationship questionnaire based on different demographic variables.

| Variable | Categorization (n) | Total score |
|---------------------|--|---------------|
| Gender | Men (419) | 66.74 ± 9.68 |
| | Women (1,193) | 66.68 ± 9.08 |
| | <i>t</i> (<i>p</i>) | 0.12 (0.90) |
| Marital status | Married (1,154) | 66.97 ± 9.18 |
| | Single (426) | 66.05 ± 9.48 |
| | Divorced (21) | 66.24 ± 7.58 |
| | Other (11) | 64.09 ± 6.70 |
| | <i>F</i> (<i>p</i>) | 1.34 (0.26) |
| Age | ≤ 25 years (229) | 65.37 ± 10.12 |
| | 26–35 (712) | 66.10 ± 9.09 |
| | 36–45 (489) | 67.74 ± 8.83 |
| | ≥ 46 years (182) | 67.91 ± 9.49 |
| | <i>F</i> (<i>p</i>) | 5.77 (< 0.01) |
| Level of education | Junior college or below (221) | 66.93 ± 9.10 |
| | Graduate (1,142) | 66.8 ± 10.64 |
| | Postgraduate or above (249) | 66.44 ± 9.10 |
| | <i>F</i> (<i>p</i>) | 1.37 (0.25) |
| Title | None (177) | 66.01 ± 9.41 |
| | Junior (602) | 65.57 ± 9.46 |
| | Middle (556) | 67.18 ± 8.88 |
| | Sub-senior (211) | 68.53 ± 8.93 |
| | Senior (66) | 68.92 ± 9.10 |
| | <i>F</i> (<i>p</i>) | 5.99 (< 0.01) |
| Department | Internal medicine (501) | 66.20 ± 9.13 |
| | Surgery (125) | 67.35 ± 8.55 |
| | Gynecology and obstetrics (96) | 67.88 ± 7.37 |
| | Pediatrics (64) | 68.53 ± 8.56 |
| | Medical technologies (230) | 65.34 ± 11.25 |
| | Emergency room (70) | 65.50 ± 8.71 |
| | Ophthalmology and otorhinolaryngology (27) | 65.26 ± 10.14 |
| | Psychiatry (105) | 67.38 ± 8.32 |
| | Other (394) | 67.46 ± 8.93 |
| | <i>F</i> (<i>p</i>) | 2.24 (0.05) |
| Daily working hours | < 8 (277) | 65.99 ± 9.54 |
| | 8–10 (1,175) | 66.73 ± 9.21 |
| | 10–12 (128) | 67.30 ± 9.16 |
| | > 12 (32) | 69.31 ± 6.99 |
| | <i>F</i> (<i>p</i>) | 1.59 (0.19) |
| Post | Doctor (591) | 67.98 ± 8.55 |
| | Nurse (744) | 65.90 ± 9.02 |
| | Medical technician (256) | 66.08 ± 10.75 |
| | Other (21) | 66.62 ± 11.88 |
| | <i>F</i> (<i>p</i>) | 6.10 (< 0.01) |
| Level of hospital | Tertiary (1,179) | 67.77 ± 9.87 |
| | Secondary (204) | 65.15 ± 10.34 |
| | Community health center | 66.86 ± 8.75 |
| | <i>F</i> (<i>p</i>) | 3.31 (0.05) |

(Continued)

TABLE 2 | Continued

| Variable | Categorization (n) | Total score |
|---|-------------------------------|----------------|
| Teaching status of the hospital | Teaching hospital (1,259) | 66.83 ± 9.19 |
| | Not a teaching hospital (353) | 66.23 ± 9.37 |
| | <i>t</i> (<i>p</i>) | 1.07 (0.28) |
| Level of familiarity with patient-centered care | Very unfamiliar (56) | 60.32 ± 10.84 |
| | Quite unfamiliar (132) | 63.47 ± 10.17 |
| | Fairly familiar (639) | 64.42 ± 9.09 |
| | Quite familiar (653) | 67.97 ± 8.09 |
| | Very familiar (132) | 73.10 ± 8.78 |
| Work experience (years) | <i>F</i> (<i>p</i>) | 38.07 (< 0.01) |
| | < 1 (183) | 66.19 ± 9.11 |
| | 1–5 (372) | 65.97 ± 9.53 |
| | 5–10 (402) | 66.35 ± 9.25 |
| | 10–15 (287) | 66.78 ± 8.91 |
| | 15–20 (137) | 68.21 ± 8.83 |
| | > 20 (231) | 67.88 ± 9.32 |
| | <i>F</i> (<i>p</i>) | 2.20 (0.05) |

at the 95% confidence interval (CI). If it did not include 0, the difference in effect was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Review Board of Hangzhou Normal University. All participants provided informed consent, and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Demographic Characteristics

Of the 1,612 participants included in the study, 419 (54.3%) were male, 1,154 (71.6%) were married, and 182 (11.3%) were aged 46 or older. Additionally, 1,142 participants (70.8%) had a bachelor's degree, 602 (37.3%) had a junior title, 591 (36.5%) were doctors, and 501 (31.1%) were placed in the internal medicine unit. Moreover, 231 participants (14.3%) had work experience of 20 years or more, 1,199 (74.4%) held an officially budgeted post, and 1,175 (72.9%) worked for 8–10 h per day. Furthermore, 1,179 participants (73.1%) worked in tertiary hospitals and 1,259 (78.1%) in teaching hospitals; 581 participants (36.0%) had a monthly income of 5,001–7,000 yuan. Lastly, 958 participants (59.4%) had received training in patient-centered communication skills, 285 participants (17.7%) took 5–10 min on average to see one patient, and 132 participants (8.2%) were “very familiar” with PCC.

The healthcare workers' perceptions of their provision of PCC were evaluated based on their scores on the PPRQ ($M = 66.70$, standard deviation (SD) = 9.23). There were significant differences in participants' PPRQ scores based on age ($F = 5.77$, $p < 0.01$), title ($F = 5.99$, $p < 0.01$), post ($F = 6.10$, $p < 0.01$),

TABLE 3 | Means, standard deviations, and correlation coefficients of the variables.

| Variable | Mean | SD | Hospital culture | Self-efficacy | Pursuit of success | Avoidance of failure | Patient-centered care |
|-----------------------|--------|-------|------------------|---------------|--------------------|----------------------|-----------------------|
| Hospital culture | 48.561 | 7.584 | 1 | | | | |
| Self-efficacy | 38.891 | 6.228 | 0.549*** | 1 | | | |
| Pursuit of success | 16.899 | 2.647 | 0.630*** | 0.638*** | 1 | | |
| Avoidance of failure | 9.627 | 2.989 | -0.270*** | -0.326*** | -0.400*** | 1 | |
| Patient-centered care | 66.478 | 9.387 | 0.662*** | 0.559*** | 0.628*** | -0.265*** | 1 |

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. SD, standard deviation.

TABLE 4 | Testing the mediation model of self-efficacy.

| Variable | Equation 1 (PCC) | | | Equation 2 (Self-efficacy) | | | Equation 3 (PCC) | | |
|----------------------|-------------------------|-------|-----------|----------------------------|-------|-----------|-------------------------|-------|-----------|
| | β | SE | t | β | SE | t | β | SE | t |
| Constant | 23.609 | 1.339 | 17.635*** | 13.877 | 0.983 | 14.113*** | 17.721 | 1.344 | 13.186*** |
| Age | 0.628 | 0.280 | 2.241* | 0.200 | 0.206 | 0.974 | 0.543 | 0.266 | 2.038* |
| Title | 0.765 | 0.248 | 2.813* | 0.765 | 0.182 | 4.197*** | 0.373 | 0.237 | 1.576 |
| Post | -0.993 | 0.229 | -4.342*** | -0.627 | 0.168 | -3.733*** | -0.727 | 0.218 | -3.331*** |
| Familiarity with PCC | 0.520 | 0.191 | 2.730* | 0.599 | 0.140 | 4.282*** | 0.266 | 0.182 | 1.461 |
| Hospital culture | 0.815 | 0.022 | 36.681*** | 0.446 | 0.016 | 14.113*** | 0.626 | 0.025 | 24.764*** |
| Self-efficacy | | | | | | | 0.424 | 0.031 | 13.612*** |
| R ² | | 0.466 | | | 0.345 | | | 0.517 | |
| | F (5,1724) = 300.384*** | | | F (5,1724) = 181.710*** | | | F (6,1723) = 307.960*** | | |

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. PCC, patient-centered care.

and level of familiarity with PCC ($F = 38.07$, $p < 0.01$). Senior healthcare workers ($M = 68.92$, $SD = 9.10$) obtained higher scores than those with relatively junior titles ($M = 67.18$, $SD = 8.88$). Doctors ($M = 67.98$, $SD = 8.55$) obtained higher scores than nurses ($M = 65.90$, $SD = 9.02$). Furthermore, participants who were “very familiar” with PCC obtained the highest scores ($M = 73.10$, $SD = 8.78$), and those who were “very unfamiliar” with PCC obtained the lowest scores ($M = 60.32$, $SD = 10.84$) on the PPRQ. The PPRQ scores based on participants’ demographic characteristics have been presented in **Table 2**.

The means, SDs, and correlation coefficients of the variables under study have been presented in **Table 3**. Hospital culture was positively associated with self-efficacy ($r = 0.549$, $p < 0.001$) and healthcare workers’ perceived provision of PCC ($r = 0.662$, $p < 0.001$). Similarly, there was a significant positive association between self-efficacy and healthcare workers’ perceived provision of PCC ($r = 0.559$, $p < 0.001$). Additionally, significant positive correlations were observed between the variables (hospital culture, self-efficacy, pursuit of success, avoidance of failure, and PCC).

Analysis of the Mediating Effect of Self-Efficacy

First, a mediation model was constructed with hospital culture as the independent variable and the perceived provision of PCC as the dependent variable after controlling for age, title, post, and level of familiarity with PCC (**Table 4**). The results of Equation 1 showed that hospital culture had a significant

positive effect on healthcare workers’ perceived provision of PCC ($\beta = 0.815$, $p < 0.001$). Bootstrapping was performed using 5,000 bootstrap replicates (as parameter estimation). The 95% CI was 0.772–0.859 and did not include 0; thus, the results supported H1, suggesting that hospital culture had a positive effect on healthcare workers’ perceived provision of PCC.

Second, self-efficacy was entered into the model as the mediating variable. The results for the mediating effects of self-efficacy have been depicted in **Table 4** (Equations 2, 3). Hospital culture had a significant positive effect on self-efficacy ($\beta = 0.446$, $p < 0.001$) with the 95% CI within the 0.414–0.478 range; thus, the results supported H2, validating that hospital culture positively influenced self-efficacy among healthcare workers. As shown in Equation 3, self-efficacy had a significant positive effect on healthcare workers’ perceived provision of PCC ($\beta = 0.424$, $p < 0.001$); the estimated 95% CI was within the 0.363–0.485 range, and did not include zero. Thus, the results supported H3, reflecting that self-efficacy among healthcare workers had a positive effect on the delivery of PCC. Self-efficacy had a partial mediating effect in the relationship between hospital culture and PCC implementation. The size of the mediating effect has been presented in **Table 5**. Additionally, 76.81% of the total effects of hospital culture on the perceived provision of PCC were direct effects and 23.19% were indirect effects, mediated by self-efficacy. These results supported H4, suggesting that self-efficacy mediated the relationship between hospital culture and healthcare workers’ PCC implementation.

TABLE 5 | Total, direct, and mediating effects of self-efficacy in the relationship between hospital culture and healthcare workers' perceived provision of patient-centered care.

| | Effect size | Boot SE | Lower end of boot CI | Upper end of boot CI | Percentage |
|-----------------------------------|-------------|---------|----------------------|----------------------|------------|
| Total effect | 0.815 | 0.022 | 0.772 | 0.859 | |
| Direct effect | 0.626 | 0.025 | 0.577 | 0.676 | 76.81% |
| Mediating effect of self-efficacy | 0.189 | 0.024 | 0.143 | 0.238 | 23.19% |

Boot, bias-corrected percentile bootstrap method; SE, standard error; CI, 95% confidence interval. All values have been rounded up to three decimal places.

TABLE 6 | Analysis of the moderated mediation effect.

| Antecedent | Consequent | | | | | |
|--|---------------------------|-------|-----------|---------------------------|-------|-----------|
| | M (self-efficacy) | | | Y (PCC) | | |
| | β | SE | t | β | SE | t |
| Constant | 35.896 | 5.724 | 52.967*** | 49.26 | 1.425 | 34.567 |
| Age | 0.119 | 0.202 | 0.589 | 0.493 | 0.264 | 1.864 |
| Title | 0.74 | 0.178 | 4.148*** | 0.364 | 0.235 | 1.549 |
| Post | -0.603 | 0.164 | -3.664*** | -0.747 | 0.217 | -3.449*** |
| Familiarity with PCC | 0.62 | 0.137 | 4.510*** | 0.26 | 0.181 | 1.432 |
| Hospital culture | 0.405 | 0.017 | 24.047*** | 0.593 | 0.026 | 22.997*** |
| Self-efficacy | | | | 0.403 | 0.031 | 12.938*** |
| Pursuit of success | 0.211 | 0.041 | 5.171*** | 1.064 | 0.252 | 4.217*** |
| Avoidance of failure | -0.493 | 0.223 | -2.209*** | 0.574 | 0.218 | 2.631** |
| Hospital culture \times Pursuit of success | 0.022 | 0.043 | 3.479*** | | | |
| Hospital culture \times Avoidance of failure | 0.074 | 0.014 | -7.979*** | | | |
| Self-efficacy \times Pursuit of success | | | | 0.128 | 0.115 | 4.385*** |
| Self-efficacy \times Avoidance of failure | | | | -0.017 | 0.005 | -3.327*** |
| | $R^2 = 0.377$ | | | $R^2 = 0.522$ | | |
| | $F(7, 1722) = 149.017***$ | | | $F(8, 1721) = 234.921***$ | | |

All values have been rounded up to three decimal places. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Boot, bias-corrected percentile bootstrap method; SE, standard error; CI, 95% confidence interval; PCC, patient-centered care.

Analysis of the Moderating Effect of Achievement Motivation

The moderating effect of healthcare workers' achievement motivation was examined using the mediation model. The two dimensions of achievement motivation were analyzed separately as the pursuit of success was positively correlated with the perceived provision of PCC, whereas the avoidance of failure was negatively correlated with the perceived provision of PCC. A moderated mediation model was constructed after decentering the pursuit of success, avoidance of failure, and hospital culture and including the interaction terms. The results of the moderated mediation model have been displayed in **Table 6**. The interactions between hospital culture and the pursuit of happiness and the avoidance of failure had significant effects on self-efficacy ($\beta = 0.022$, $p < 0.001$; $\beta = -0.493$, $p < 0.001$). Simple slope tests (**Figure 2A**) further revealed that hospital culture had a relatively weaker effect on healthcare workers' self-efficacy when the pursuit of success was low whereas hospital culture had a relatively stronger effect on healthcare workers' self-efficacy when the pursuit of success was high. Furthermore,

Figure 2B shows that hospital culture had a relatively stronger effect on healthcare workers' self-efficacy when the avoidance of failure was low, whereas hospital culture had a relatively weaker effect on healthcare workers' self-efficacy when the avoidance of failure was high. Thus, these results supported H5, indicating that achievement motivation moderated the relationship between hospital culture and healthcare workers' self-efficacy. Additionally, the pursuit of success had a positive effect in the relationship between the aforementioned variables, whereas the avoidance of failure had a negative effect.

Moreover, **Table 6** demonstrates that the interaction effects between self-efficacy and the pursuit of success and avoidance of failure had significant moderating effects on PCC ($\beta = -0.128$, $p < 0.001$; $\beta = -0.017$, $p < 0.001$). These results indicated that the mediating effect of self-efficacy in the relationship between hospital culture and the provision of PCC was moderated by achievement motivation (comprising the pursuit of success and avoidance of failure). To further evaluate the moderating effect of achievement motivation on the mediating effect of self-efficacy, we performed bootstrap testing and explored the indirect effect

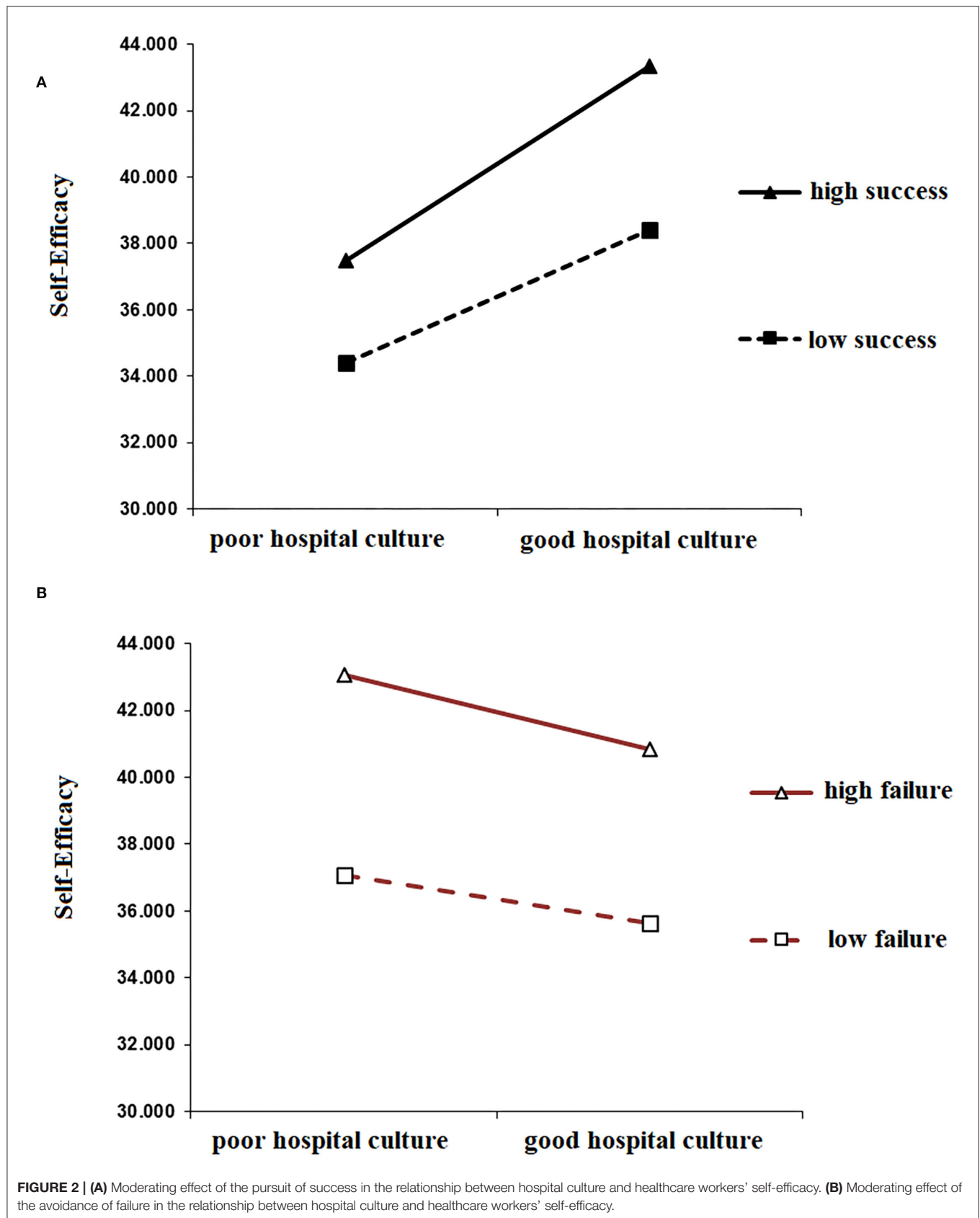


TABLE 7 | Bootstrap testing for the moderated mediation effect.

| Moderating variable | Boot SE | Effect | Bootstrap 95% CI | |
|-----------------------------|---------|--------|----------------------|-----------------------|
| | | | Lower end of Boot CI | Higher end of Boot CI |
| Pursuit of success | | | | |
| −1SD (14.253) | 0.036 | 0.190 | 0.12 | 0.259 |
| M (16.899) | 0.033 | 0.265 | 0.199 | 0.331 |
| +1SD (19.546) | 0.037 | 0.340 | 0.268 | 0.413 |
| Avoidance of failure | | | | |
| −1SD (6.637) | 0.023 | 0.190 | 0.148 | 0.239 |
| M (9.627) | 0.02 | 0.172 | 0.135 | 0.215 |
| +1SD (12.616) | 0.028 | 0.153 | 0.105 | 0.217 |

Boot, bias-corrected percentile bootstrap method; SE, standard error; CI, 95% confidence interval. All values have been rounded up to three decimal places.

of the pursuit of success and avoidance of failure on three levels of self-efficacy. As shown in **Table 7**, the results demonstrate that self-efficacy had a stronger mediating effect on the perceived provision of PCC among healthcare workers with a high need for pursuing success ($\rho = 0.340$, 95% CI not including 0) as compared to healthcare workers with a low need for pursuing success ($\rho = 0.190$, bootstrap 95% CI not including 0). On the contrary, self-efficacy had the weakest mediating effect on the perceived provision of PCC among healthcare workers with a high need for avoidance of failure; that is, the indirect effect of self-efficacy was lowest when the avoidance of failure was 1SD above the mean ($\rho = 0.153$, 95% CI not including 0).

DISCUSSION

Effects of Hospital Culture on PCC

The present study found that hospital culture played an important role in healthcare workers' care delivery. As a manifestation of healthcare personnel's collective values and norms, hospital culture can deeply influence their mindset and behaviors. Consistent with Zhang's study (13), innovative organizational culture was found to have a positive effect on healthcare workers' provision of PCC. This could be because an open atmosphere stimulates positivity and creativity among employees, creating a favorable environment for them to work on new projects and develop new skills, and especially to implement innovative patient-focused treatment plans. Additionally, the present findings are corroborated by those of Zhu's study (14) as charismatic leadership facilitated empathy for patients among healthcare workers; participants reported that they could think from the patients' perspective, and listen to and communicate effectively with them. Leaders effectively enhanced their employees' awareness of PCC and the importance of empathy by urging them to respect and care about patients and protect patients' rights.

Healthcare workers who had received training to develop their communication skills scored higher than those who had not received such training. This finding is consistent with Jeong and Park's study (49), suggesting that a healthy atmosphere

involving communication is conducive to healthcare workers' efficiency in the provision of healthcare services as it boosts understanding and togetherness, fostering tolerance and unity. Additionally, in line with the conclusions drawn by Fralicx (50), cross-team collaboration was associated with effective communication among healthcare workers. Thus, hospitals can set up multidisciplinary teams and construct streamlined communication or feedback mechanisms to enhance cooperation among different departments and facilitate the implementation of PCC.

Mediating Effects of Self-Efficacy

While exploring the mechanisms for the adoption of PCC, it is beneficial to examine the mediating effects of self-efficacy in the relationship between hospital culture and healthcare personnel's provision of PCC. Consistent with Yang et al. (51), the current study revealed that hospital culture affected healthcare workers' perceived provision of PCC, which was mediated by their self-efficacy. Self-efficacy can have direct effects on an individual's choices, goals, mindset, and attribution style, among others. Good hospital culture can foster healthcare professionals' self-efficacy, further enabling them to implement PCC.

The positive influence of hospital culture on self-efficacy can be explained in two ways. First, a supportive environment within a healthy hospital culture could increase healthcare workers' self-efficacy (52). When leaders highlight and champion the use of PCC in addition to advances in medical technologies and services that empower cross-team collaboration, healthcare workers might experience high levels of meaningfulness and confidence in completing their work; this could accelerate their ability to deliver healthcare services. Second, communication is an important factor in patient-centered medicine and calls for healthcare personnel's transition from traditional attitudes to attitudes of respect and care for patients' preferences, needs, and values (53). Open-minded leaders, innovative culture, and multidisciplinary cooperation can boost medical workers' confidence in effective communication, and thus, increase their willingness to implement PCC.

Meanwhile, self-efficacy had a positive effect on PCC; this is consistent with Sommaruga et al.'s findings (45), suggesting that healthcare providers with high self-efficacy had good interpersonal relationships and professional skills. Welsh (54) suggested that the enhancement of self-efficacy among doctors was effective in improving their communication skills; for example, doctors with high self-efficacy—consistent with the requirements of PCC—provided more disease-related information and medical knowledge to patients; encouraged them to communicate; and were responsive to their questions, suggestions, needs, and worries.

Moderating Effects of Achievement Motivation

According to McClelland's (45) achievement need theory, achievement motivation among social members stems from specific social and cultural environments. In this study, we constructed a moderated mediation model based on achievement theories. Achievement motivation exerted significant moderating

effects in the relationship between hospital culture and self-efficacy. In the same culture, healthcare workers with high achievement motivation and self-efficacy were highly willing to communicate with patients. This could be because they cared about the patients' feelings and were mindful about responding to them and meeting patients' preferences and needs. This is in line with Wang's study (20), suggesting that healthcare workers' self-efficacy, and hence, achievement motivation, are reinforced when they overcome problems and difficulties in services. On the contrary, when issues keep sustaining, achievement motivation is triggered among healthcare workers with high self-efficacy owing to their confidence, whereas healthcare workers with low self-efficacy might adopt negative attitudes concerning the provision of PCC to avoid failure.

In line with Khongsamai et al.'s findings (55), in the current study, an innovative organizational culture contributed to an increase in effective communication. This could be because an open and innovative work environment facilitates initiatives among healthcare workers, improves their consciousness about communication, fosters innovation in communication styles and skills, and thus, promotes doctor-patient communication. On the contrary, achievement motivation moderated the relationship between self-efficacy and patient-centered practice among healthcare workers. Similar to Yim and Lee's findings (56), we found that healthcare workers who pursued success tended to have strong social responsibility, introspected about their actions based on patients' feedback, showed progress in ethical values and skills, and encouraged patients to participate in discussions and express their feelings.

The avoidance of failure was found to negatively moderate the relationship between self-efficacy and the provision of PCC; this has repeatedly been demonstrated in the fields of psychology and education (57, 58). In the current study, this could be because medical personnel with a strong need to avoid failure might have anticipated job burnout owing to the patient-centered services that might require several emotional resources in addition to concentration; they might also have been worried about the status of rewards and outcomes of the long-term input. However, the negative effect of avoidance of failure was not stronger than the positive effect of pursuit of success, implying that the healthcare workers' need to pursue success primarily influenced their achievement motivation.

Implications and Limitations

We believe that the present results have theoretical and practical significance. To begin with, the findings have strong implications for the development of strategies for stimulating healthcare workers' provision of PCC, which might be effective in transforming hospital administration methods and enhancing the efficiency of healthcare services. For example, to strengthen patient services, hospitals should establish an innovative culture, constantly work on creativity, encourage healthcare workers to innovate, and stimulate healthcare workers' internal achievement motivation by challenging them. Second, hospitals should establish a charismatic leadership culture. Hospital leaders should set an example and fully mobilize healthcare workers' consciousness and enthusiasm to serve patients.

Moreover, hospital leaders should pay attention to their own quality improvement, respect healthcare workers, and be sensitive to their needs. Third, hospitals should establish a multidisciplinary diagnosis and treatment team to foster a culture of cooperation. By facilitating information exchange and providing a sharing platform for each department, a good communication and feedback mechanism is formed within the hospital, promoting internal cooperation. A good internal communication atmosphere is helpful for healthcare workers to understand each other, cultivate team spirit, and improve patient service efficiency. Our study found that the external hospital culture drives healthcare workers' attitudes and behaviors. It is not combined with the viewpoint of motivation theory, which adds further value to the literature on motivation theories.

The study also has some limitations. First, the recruited healthcare workers were from hospitals in Hangzhou; this could limit the representativeness of the sample and generalizability of our findings. Thus, further research should be conducted in other regions of China. Second, this study adopted a cross-sectional design; consequently, we could not capture the causal effect of changes over time. Therefore, future studies must adopt longitudinal, experimental, or cross-sequential designs and employ hierarchical linear models; studies must also test for the confounding and mediating effects of different variables. Third, this study explored healthcare workers' perceptions of their provision of PCC; future studies must focus on the perspectives of both healthcare providers and patients. Fourth, all the variables were assessed through self-report, and although surveys were answered anonymously, social desirability bias may still have influenced the responses to some extent.

CONCLUSIONS

The present study indicated that hospital culture can affect healthcare workers' implementation of PCC. Accordingly, hospitals could organize activities for healthcare workers to discuss hospital culture; this would strengthen their understanding of the importance of hospital culture. Additionally, hospital culture can boost the provision of PCC *via* the enhancement of self-efficacy and achievement motivation among healthcare workers. Therefore, hospital administrators should pay attention to the psychological status of their staff and develop their confidence in interpersonal networking and effective communication to help them build their self-efficacy for PCC and motivation for success.

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.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Hangzhou Normal University. All study participants provided

informed consent, and the study was performed in accordance with the Ethical Standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XH conceptualized the study, drafted the methodology, and operated the software. YG performed the statistical analysis and prepared the first draft of the manuscript. HC helped with visualization and investigation. HZ operated the software and validated the findings. XZ helped in writing, reviewing, and editing the manuscript. All authors approved the submitted version of the manuscript.

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The Integration of Assistive Technology and Virtual Reality for Assessment and Recovery of Post-coma Patients With Disorders of Consciousness: A New Hypothesis

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INTRODUCTION

Multiple disabilities due to an outcome of coma combined with severe to profound disorders of consciousness may pose serious challenges to daily medical centers and rehabilitative settings. Beside specific pharmacological treatments delivered by specialized professionals, they may need diagnostic tools and rehabilitative interventions enabling those patients with an active role, constructive engagement, positive participation, independence, and self-determination (Pistoia et al., 2008; Lancioni et al., 2014b; Formisano et al., 2018; Kulyk, 2019). Thus, two basic objectives may be targeted within this framework, namely (a) the assessment and (b) the recovery of cognitive, motor, and communicative functioning (Lancioni et al., 2009a, 2011; Kirsch et al., 2017; de Tommaso et al., 2020).

Many clinical and research efforts have recently been devoted to the aforementioned critical features (i.e., evaluation and rehabilitation). With regard to the assessment, two main viewpoints may be emphasized. First of all, the existing literature is focused on determining the patient's state of functioning. That is, it is useful to identify whether patients are in a vegetative state or a more favorable diagnosis of minimally conscious state could be made (Lancioni et al., 2008a; Formisano et al., 2011; Pistoia and Sarà, 2012). Secondly, the dichotomy between the two above clinical conditions (i.e., vegetative state or and minimally conscious state) is critically discussed and any specific need to clarify the borderline between those two states requires to rectify more straightful strategies (Kim et al., 2012).

With regard to the rehabilitation, different approaches may be acknowledged. For instance, one may envisage environmental stimulation (Lancioni et al., 2014a, 2015). Otherwise, deep brain stimulation may be adopted (Lancioni et al., 2010b). Additionally, brain computer interface strategies may be implemented (Stasolla and De Pace, 2014). Those strategies rely on different theoretical background which may have clinical and practical implications on the role of the assessment and the role of the patient. The decision on whether the person is in a vegetative state or in a minimally conscious state should be considered crucial prior to the intervention and the setup for the intervention should be highly individualized to ensure the participant with a successful learning process (Lancioni et al., 2017).

The purpose of this paper is to argue on both assessment and rehabilitative strategies, to introduce the use of the technology as crucial means for the evaluation and the recovery of post-coma patients and disorders of consciousness, either due to a stroke or a traumatic brain injury, and to propose a new hypothesis of integration between assistive technology-based devices and

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virtual reality setups to improve clinical conditions of post-coma patients diagnosed with disorders of consciousness.

ASSESSMENT STRATEGIES

Basic assessment tools for identifying with certitude whether a patient is in a vegetative state or in a minimally conscious state commonly include behavioral scales, neuropsychological evaluation, neuroimaging techniques, and behavioral data based on learning setups (Ponsford et al., 2014; Kim et al., 2022; Ngadimon et al., 2022). Frequently, more than one tool and/or strategy are used for the evaluation (Lancioni et al., 2017). Behavioral scales probably represent the most adopted approach (Pistoia et al., 2013). An illustrative example is constituted by the JFK Coma Recovery Scale-Revised (Giacino et al., 2004) to determine the patient's responsiveness on communicative, sensorial, orientation, and motor levels of functioning. Procedural difficulties may arise whenever the patient does not have head/hand control in his/her behavioral repertoire consistent with the scale's requests or is unable to understand verbal instructions (Bosco et al., 2010).

Neuropsychological procedures including event-related potentials such as P300 and/or mismatch negativity are also used to assess the responsiveness of patients with severe disorders of consciousness (Lancioni et al., 2009b, 2011). Thus, empirical evidences of P300 or mismatch negativity are usually viewed as basic signs of awareness or consciousness with meaningful implications for the recovery process (Estraneo et al., 2022; Pruvost-Robieux et al., 2022). Recent reviews (Pan et al., 2021; Aubinet et al., 2022) critically discussed the use of event-related potentials and emphasized the strengths to use multiple measures to enhance the significance of the findings (Calabrò et al., 2021).

Neuroimaging techniques (e.g., functional magnetic resonance imaging, fMRI) may be a reliable tool to identify potential capacities or skills even in cases of minimal or apparently absent responsiveness (Drayson, 2014; Kirsch et al., 2017; Corsi et al., 2020). In fact, the use of those techniques can strongly help researchers to catch relevant diagnostic outcomes (Kirsch et al., 2017). Nevertheless, their use is still difficult and the application may pose serious methodological challenges in a wide part of medical or rehabilitative settings due to the assessment of specific stimuli and/or the comprehension of verbal instructions (Schwarzbauer and Schafer, 2011). A valid alternative to the fMRI is represented by the positron emission tomography (Briand et al., 2020).

Behavioral data based on learning principles may refer to two different approaches. On one hand, based on classical paradigm they include the capacity of the patient to positively associate pairs of stimuli (Ricchi et al., 2022). On the other hand, based on the operant paradigm, they consist on the capacity of the patient to correctly match a behavioral response with an environmental consequence (Lee et al., 2021). Empirical evidences of learning between both approaches (i.e., a correct association between events or its positive achievement) may be considered as a non-reflective response and suggest a diagnosis of minimally conscious state (Lancioni et al., 2008b).

Those strategies may be acknowledged as clinically relevant for those patients who have a minimal behavioral repertoire (e.g., eyelid or lip movements) and may pose practical problems with the JFK Coma Recovery Scale accordingly. Furthermore, learning principles based on the operant paradigm may be very useful to introduce a technological-aided program focused on promoting the participant's active role, constructive engagement, and positive participation (Stasolla et al., 2015).

REHABILITATIVE STRATEGIES

Intervention solutions for persons with disorders of consciousness may include different forms of environmental stimulation, deep brain stimulation, transcranial magnetic stimulation, brain computer interfaces, and learning-based programs or technological-mediated options (Lancioni et al., 2011, 2014a; Kim et al., 2012; Pistoia et al., 2013). An environmental stimulation program is typically delivered by the therapist/professional in charge of the patient. In its basic form it includes the presentation of daily stimulus events such as familiar music and/or verbal inputs during specific intervals of time. In a more sophisticated form, it may involve specific daily sessions with an intensive multi-sensorial intervention combined with a verbal and a physical guide of relevant events provided by the therapist (Lancioni et al., 2010a, 2014b). Although the basic form is less effective with regard to the improvement on the patient's level of alert and positive involvement in the context, the intensive form of environmental stimulation is more likely to have beneficial effects on the participant's level of attention and participation (Pape et al., 2015).

Transcranial magnetic stimulation and deep brain stimulation are considered common approaches within this specific framework whose implementation does not require any specific participation by the patient exposed to such strategy. Thus, while evidence-based support is available in the literature for that approach, studies suggest caution for its implementation because the effects on the patient's awareness and/or consciousness are mixed with regard to the amplitude and clinical significance (Kulyk, 2019).

Brain computer interfaces are systems devoted to measure brain activity and convert such activity into artificial outputs that restore, replace, enhance or support natural outputs of the Central Nervous System. Accordingly, such strategy is expected to modify the ongoing interactions between the Central Nervous System and its external or internal environment. Different techniques may be included to measure brain activity for brain computer interfaces. The most frequent method is represented by electrical signals detected through electrodes fixed invasively or non-invasively on the surface of the cortex or the scalp. Additionally, a metabolic measure may be recorded through fMRI (Lancioni et al., 2015).

Learning-based strategy are widely different from the aforementioned detailed strategies. In fact, that approach emphasizes the participant's active role, constructive engagement, and social interactions, mediated by the technology. That is, the strategy is largely designed to monitor the participant's

behavioral repertoire and modify it through the manipulation of environmental consequences to ensure the participant with an independent access to positive stimulation (Stasolla et al., 2022). Those programs are aimed at fostering the participant's self-determination and reducing either caregivers or families' burden accordingly (Savoia et al., 2021). Recently, the Covid-19 pandemic outlined the development of the new technologies with an emphasis on virtual reality setups and telerehabilitation strategies to supervise patients remotely (Capri et al., 2021; Momsen et al., 2022).

VIRTUAL REALITY

Virtual reality (VR), and augmented reality (AR) setups, have currently been adopted as crucial means of new technological-aided programs in different area of public health, namely (a) assessment, (b) diagnosis, (c) recovery, rehabilitation, and wellbeing. With regard to rehabilitative programs, VR has been largely adopted to positively overcome neurological impairments including neurodevelopmental disorders, and neurodegenerative diseases (Stasolla, 2021; Stasolla et al., 2021). VR ensures persons with neurological impairments with sensory experiences, computer-mediated in artificial environments, enhancing virtual interactions similarly to the real life. AR, as part of VR, emphasizes an interaction in a physical condition, differently from the artificial context provided by VR. That is, VR usually requires the use of specific headsets, which may not be easily wearable for individuals with neurological disorders. Conversely, AR may be viewed as easier to use because it refers to I-PAD, tablets, and smartphones, which are more suitable to the real world (Bekkers et al., 2020; Held et al., 2020; Levin and Demers, 2021). Although widely used in patients with disorders of consciousness (Hinze et al., 2021; Kwok et al., 2021), to the best of our knowledge it has never been used in patients with acquired brain injuries, history of coma and post-coma outcomes, except for the contribution of Maggio et al. (2020). Although it may be considered as ethically controversial and questionable, such hypothesis undoubtedly merits to be empirically tested, eventually integrated with an assistive technology device, for both assessment and recovery goals.

DISCUSSION

Two ending conclusions may be putted forward on assessment strategies. First, using suitable corrections or supplements, behavioral scales may be considered as a practically significant solution to surpass the limitations of the scale and improve diagnostic accuracy accordingly. The aforementioned learning setups may be viewed as suitable issues in this regard (Lancioni et al., 2007a,b). Second, repeating a combined assessment between two or more strategies (i.e., behavioral scales, neuropsychological approach, and/or behavioral data), one may argue that the risk of individual's fluctuations and/or misdiagnosis might be profitably prevented (Pistoia and Sarà, 2012). Among new technologies, Hyun et al. (2021) proposed a virtual reality technology-based quantitative assessment method

combined with an eye-tracking system to minimize misdiagnosis of a patient's eye movements, such as visual startle, visual fixation, and visual pursuit. Twenty healthy patients and five chronic patients in a vegetative state were systematically compared. Three stimuli were presented and visual responses data were recorded to identify valid and accurate responses to each stimulus. The system defined three of the chronic patients as showing visual fixation, undetectable through clinical assessment beforehand. Lech et al. (2021) proposed the term "Cyber-Eye" to include the emerging cognitive applications of eye-tracking interfaces for neuroscience research, clinical practice, and biomedical industry. The perspective paper suggested a brain computer interface to become less invasive, less dependent on brain activities, and more applicable as the Cyber-Eye technologies continue to develop.

Two ending considerations may be formulated on rehabilitative strategies. First, additional data are mandatory to accurately identify the impact of the different strategies and their reliability over the time and across patients. Second, systematic comparisons between procedures may be fundamental to determine the effects on a number of dimensions such as active role and positive participation (Lancioni et al., 2017). Kujawa et al. (2022) recently investigated the outcomes of an oculomotor training course aimed at the therapy of visual-spatial functions. Five patients with brain damage who were unable to communicate verbally or motorically, diagnosed between the vegetative state and the emergence from the minimally conscious state were enrolled. Over a 6-week period, the participants underwent to solved tasks associated with recognizing objects, size perception, color perception, perception of objects structure such as letters, detecting differences between images and assembling image components into the complete image with the use of an eye tracker. Findings evidenced the effectiveness of the oculomotor training based on a longer duration of the work with the eye-tracker to improve visual-spatial functions. Sanz et al. (2021) demonstrated clinical relevance and translational potential in both diagnosis and prognosis of post-coma patients with disorders of consciousness. Magnetic resonance imaging and high-density electroencephalography provided measurements of brain connectivity between functional networks, assessment of language functions, detection of covert consciousness, and prognostic markers of recovery. Positrons emission tomography could identify patients with preserved brain metabolism despite clinical unresponsiveness and could measure glucose consumption rates in targeted brain regions. Such techniques were considered encouraging and promising for both assessment and recovery purposes in clinical settings.

Finally, our new hypothesis of the integration between assistive technology-based devices and virtual reality setups may be interesting practical implications and may be adopted for both assessment and recovery purposes. For example, it may enable post-coma patients with an independent access to immersive virtual environments similar to real life. In this regard it may be viewed as a basic option of scaffolding (Dicé et al., 2018). Otherwise, one may argue that it may constitute a further form of constructive engagement and favorable occupation (Stasolla et al., 2014a) and/or of psychological wellbeing (Freda et al., 2019). Its implementation may be helpful for communicative

purposes and/or challenging behaviors and the clinical relevance may be evaluated through social validation procedures (Lancioni et al., 2009a; Chiapparino et al., 2011; Stasolla et al., 2014b, 2017). For example, one may envisage the implementation in clinical settings of a virtual reality setup activated by an assistive technology-based device. Strategies of telerehabilitation (Zucchella et al., 2018; Raso et al., 2021) might be implemented. Moreover, cognitive and motor rehabilitation solutions may be embedded (Maggio et al., 2020; Daibert-Nido et al., 2021).

Future research perspectives within this framework should deal with the following topics: (a) an extension to new technological solutions combined to virtual reality-based setups to investigate the assessment and rehabilitation purposes of post-coma patients with disorders of consciousness, (b) differentiate between traumatic brain injuries, stroke, and viral causes of the coma, (c) integrate a multi-componential approach which should include behavioral scales with neuropsychological strategies, electrophysiological measures (e.g., event-related potentials), and behavioral data with the mediation of assistive technology-based devices and virtual reality setups to enhance cognitive, communicative, emotional, and motor skills of post-coma

individuals with disorders of consciousness in both clinical and home-based settings.

Furthermore, the sustainability of such approach with regard to (1) its costs, (2) human resources, and (3) technological solutions available (e.g., mobile devices, wearable devices, computer-based options) should be investigated. Additionally, the inclusion in medical or rehabilitative centers should be exhaustively addressed. For instance, Bhattacharya and Pradana (in press) evaluated the literacy process in a three-year old child with Rett syndrome and significant disabilities. Two different modalities were considered, namely (a) corporal, and (b) oral. It would probably be interesting to transfer such approach to post-coma individuals with extensive motor disabilities and lack of speech.

AUTHOR CONTRIBUTIONS

FS conceived and wrote the paper. LV and MC edited and revised the manuscript. All authors made a substantial contribution to the article.

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Application of the unified protocol for the transdiagnostic treatment of comorbid emotional disorders in patients with ultra-high risk of developing psychosis: A randomized trial study protocol

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Background: Cognitive Behavioral Therapy is delivered in most of the early intervention services for psychosis in different countries around the world. This approach has been demonstrated to be effective in decreasing or at least delaying the onset of psychosis. However, none of them directly affect the comorbidity of these types of patients that is often the main cause of distress and dysfunctionality. The Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP) is a psychological intervention that combines cognitive-behavioral and third-generation techniques that address emotional dysregulation as an underlying mechanism that these disorders have in common. The application of this intervention could improve the comorbid emotional symptoms of these patients.

Materials and methods: The study is a randomized controlled trial in which one group receives immediate UP plus standard intervention and the other is placed on a waiting list to receive UP 7 months later, in addition to standard care in one of our early psychosis programs. The sample will be 42 patients with UHR for psychosis with comorbid emotional symptoms. The assessment is performed at baseline, at the end of treatment, and at 3-months' follow-up, and includes: general psychopathology, anxiety and depression, positive and negative emotions, emotional dysregulation, personality, functionality, quality of life, cognitive distortions, insight, and satisfaction with the UP intervention.

Discussion: This will be the first study of the efficacy, acceptability, and viability of the UP in a sample of young adults with UHR. The results of this

study may have clinical implications, contributing to improving the model of care for young people who consult for underlying psychotic, anxiety, and/or depressive symptoms that can lead to high distress and dysfunctionality.

Clinical trial registration: [<https://clinicaltrials.gov/>], identifier [NCT04929938].

KEYWORDS

anxiety disorders, depressive disorders, ultra high risk for psychosis, unified protocol, transdiagnostic, psychotic disorders, emotional focused therapy

Introduction

In recent decades one of the main topics of research in mental health has been psychotic disorders and, more specifically, their first clinical manifestations. Cumulative research has found evidence highly suggestive of a relationship between the duration of untreated psychosis (DUP) and both short- and long-term prognosis, of a relationship between longer DUP and more severe positive symptoms, and of more severe negative symptoms and lower chance of remission at follow-up (Howes et al., 2021). For this reason, early detection and intervention programs in psychosis have been disseminated in several countries around the world (Taylor, 2016).

In this sense, most psychotic disorders do not appear abruptly. Rather, the onset is preceded by subclinical manifestations of symptoms that gradually increase in frequency and intensity (Shah et al., 2017). This period has been defined and operationalized as “Ultra High Risk” (UHR; Yung et al., 2005). Subsequently, numerous studies have been carried out with the main objective of determining the rates of transition to psychosis as the main measure of outcome (Fusar-Poli et al., 2012). Research has indicated that people that meet UHR criteria are at increased risk of developing psychosis in the short term, and this risk increases over time (Salazar de Pablo et al., 2021). Despite this association, the UHR paradigm is not without criticism. Some previous literature has argued that the “UHR for psychosis” label can be stigmatizing. First, because setting the goal of preventing transition to psychosis/schizophrenia could create a paradox or a self-fulfilling prophecy of failure. Second, because initial research led to clinical trials prescribing antipsychotic medication in the UHR/CHR population (Van Os and Guloksuz, 2017).

There are recent studies that relate the stigma associated with the diagnosis of UHR with a worse prognosis (Colizzi et al., 2020) and stimulated negative stereotypes (Woodberry et al., 2021). For this reason, alternative terms like pre-diagnosis stage’ (PDS), potential of developing a mental illness (PDMI), and disposition for developing a mental illness (DDMI) have

been proposed that generate less discomfort among patients and families (Polari et al., 2021a). Generally, pharmacological therapy with antipsychotic medication is not recommended, and psychological interventions represent a more appropriate alternative to offer treatment to people at UHR (NICE, 2014; Orygen The National Center of Excellence in Youth, 2016). In a recent meta-analysis, it was found that early interventions reduced transition rate and attenuated positive psychotic symptoms at 12 months. In addition, psychological interventions demonstrated a significant reduction in transition rates compared to pharmacological therapy (Mei et al., 2021).

Further, transition to psychosis is not the only outcome for people at UHR (Polari et al., 2021b). Some studies have shown different clinical trajectories beyond the transition to psychosis, such as no transition, chronification of attenuated symptoms or their recurrence (Lin et al., 2015), positive improvement, moderate impairment, and severe impairment (Allswede et al., 2020). Another study found 17 different trajectories in UHR patients from complete recovery to transition to psychosis, including no remission, relapse, and recurrence (Polari et al., 2018). A recent study observed that 56.8% of patients with UHR met criteria for a non-psychotic disorder at 6-years’ follow-up (Rutigliano et al., 2016). Similarly, a sample from Spain yielded comparable results (Barajas et al., 2019). Persistence or recurrence of non-psychotic comorbid disorders was associated with worse overall functioning. At baseline, they found that 70.3% of this sample had some comorbidity with a non-psychotic disorder (affective disorder 36.5%, anxiety disorder 10.8%, mixed anxiety-depressive disorder 5.4%, and personality disorder 6.8%). These results showed that although transition to psychosis may be a frequent outcome of patients at UHR, there is also a very high risk of developing another psychiatric disorder (Rutigliano et al., 2016).

Recently, a growing body of literature has suggested that the classification of mental disorders needs to shift from a categorical model (such as DSM or CIE) to a dimensional one (Van Os and Guloksuz, 2017; McGorry et al., 2018). Under this paradigm, it is proposed that there is a continuum between a complete absence of symptoms and severe psychopathology. In this continuum, patients may exhibit symptoms ranging from mild to distressing to indicating the need for specialized help

Abbreviations: UP, Unified Protocol; UHR, Ultra-high Risk (for psychosis); TAU, Treatment as Usual; ED, Emotional disorders; WL, Waiting list.

(McGorry et al., 2018), including people meeting the criteria for UHR. This clinical staging and transdiagnostic framework has led to a broader classification of subthreshold risk states (CHARMS) including the bipolar trait vulnerability group, the attenuated (hypo)manic symptom group, the moderate (attenuated) depression group, and the attenuated borderline personality group (Hartmann et al., 2019).

The development of a dimensional approach has fostered the creation of different treatment alternatives, such as transdiagnostic models (Rosellini and Brown, 2019). These models are focused on treating the etiological and maintenance mechanisms shared by different mental disorders (Sauer-Zavala et al., 2017). The Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP; Barlow et al., 2017, 2019) focuses on improving emotional regulation through acceptance, tolerance of intense emotions, and behavior modification (Barlow et al., 2019). To achieve these objectives, it uses traditional cognitive-behavioral techniques (e.g., cognitive restructuring or exposure) combined with third-generation techniques (e.g., mindfulness) (Barlow et al., 2019). This treatment is indicated for people with difficulties in emotional regulation with or without diagnostic comorbidity. Most recently, a clinical trial is under way in Spain to test the efficacy, cost-effectiveness, and implementation characteristics (acceptability, usability, and utility) of a blended intervention which will enhance face-to-face treatment by incorporating an app-based intervention in onsite treatment (Osma et al., 2021).

Current psychological interventions targeting attenuated psychotic symptoms have proved effective in reducing the rates of transition to psychosis in the medium term (Morrison et al., 2004; Van der Gaag et al., 2013b; Ising et al., 2017) and in reducing the severity of psychotic symptoms (Morrison et al., 2012) compared with treatment as usual (TAU). However, further studies are needed to demonstrate more robust results (Van der Gaag et al., 2013b). Cognitive behavioral therapy (CBT) manuals designed to treat UHR (French and Morrison, 2004; Van der Gaag et al., 2013a) do not specifically include comorbid emotional symptoms (affective or anxiety disorders) among treatment goals, although it is known that they are highly prevalent and, in many cases, are the main cause of dysfunctionality (Rutigliano et al., 2016). In the PACE-Manual-Writing Group (Nelson and Orygen Youth Health Research Centre Issuing Body, 2012) there is a module that addresses comorbidity, but in the case of the UP intervention, that is based on the transdiagnostic approach, all psychotherapy techniques have been chosen because they are associated with the core vulnerabilities and processes shared by all emotional disorders (Sauer-Zavala et al., 2017).

The UP has shown a reduction in symptoms of anxiety and depression in several mental disorders (such as major depressive disorder, obsessive-compulsive disorder, and social anxiety, among others) with a large effect size, an increase in adaptive emotional regulation strategies paired with a decrease in maladaptive regulation strategies at a moderate effect size,

and an increase in functioning and quality of life (Sakiris and Berle, 2019; Cassiello-Robbins et al., 2020; Carlucci et al., 2021). Furthermore, the benefits of the UP seem to be maintained at 6 months' follow-up for clinical outcomes and at 12–18 months' follow-up in functioning (Bullis et al., 2014; Osma et al., 2021). The UP is a standardized and manualized intervention that can be delivered in individual (Barlow et al., 2017) and group formats (Osma et al., 2022). The manual consists of 8 treatment modules.

To date, there is no published study that has used the UP in the treatment of comorbid emotional symptoms in patients that meet UHR criteria, save for a single case study using the UP in a person with treatment-resistant schizophrenia (Grasa and Corripio, 2019) with promising results. There were significant decreases between pre- and post-test measures of anxiety, depressive symptoms, emotional dysregulation, loss of control, rejection, interference scales, and hallucinations, measured with the PSYRATS, as well as a significant increase in quality of life. This work aroused interest in applying the UP to psychotic disorders.

Ultra-high risk (for psychosis) patients often have difficulties in engaging with mental health services (Ben-David et al., 2019) being this situation an important obstacle to receiving appropriate treatment. In addition, young people are often familiar with new technologies (Lupton, 2021) and because of that, we believe that the application of the UP in an online format may reduce the barriers to accessing treatment (Osma et al., 2021). We already know that evidence-based therapies can be administered online without sacrificing their effectiveness (Andersson et al., 2014; McLaren et al., 2021). In a recent review, videoconferencing interventions proved to be reliable and highly acceptable for patients with psychotic disorders (Santesteban-Echarri et al., 2020). With regard to emotional disorders, no significant differences were found in the effectiveness of face-to-face CBT and online CBT. Both of them were shown to be effective in reducing the symptoms of anxiety, depression, and stress, as well as in improving quality of life (Stubbings et al., 2013). The UP has also been shown to be effective in an online format (Carlucci et al., 2021).

A pilot study is under way to assess the feasibility and efficacy of group UP to reduce comorbid emotional symptoms in patients that meet UHR criteria. In the context of the SARS-CoV-2 pandemic, the group sessions are being conducted online. Given the evidence cited above, this method of delivering the intervention would be as effective as in-person treatment with the added benefit of encouraging the attendance of people residing in different geographic territories (Singh and Sagar, 2022).

Study aims

Given the high level of comorbid anxiety and depression among individuals meeting UHR criteria, the main objective

of our study is to evaluate the efficacy of UP in addition to TAU as compared to TAU in targeting symptoms of anxiety and depression in UHR for psychosis patients.

As secondary objectives, changes in attenuated symptoms of psychosis, transition to psychosis rates, cognitive distortions, quality of life, metacognition, personality, and psychosocial functioning, and the satisfaction of participants with the treatment, are being assessed. Further, assessment will be made of whether the results are maintained at 3 months' follow-up. Different clinical trajectories will be analyzed for comparison with previous studies (Polari et al., 2018).

Materials and methods

Study design

This study is a randomized controlled trial. All patients are assessed at baseline. Patients are assigned to either treatment group, one receiving immediate treatment with UP and treatment as usual, or to a waiting list, only receiving treatment as usual. All patients are assessed post-treatment and at 3-months' follow-up. After the final assessment, patients in the waiting list are offered the UP. A list of random numbers created for this purpose is used.

Participants

Participants are people who meet criteria of UHR for psychosis and who have comorbid symptoms of emotional disorders and are receiving treatment in one of the Early Psychosis Programs (PIPPEP) in Parc Sanitari Sant Joan de Déu.

The inclusion criteria are (1) age between 18 and 35 years old, (2) a diagnosis of UHR for psychosis in the last 3 years and inclusion in our early intervention program, (3) symptoms of a comorbid emotional disorder, (4) fluent Spanish or Catalan, and (5) signing the informed consent (IC).

The exclusion criteria are (1) a frank psychotic episode in the past or in the present, (2) intellectual disability, (3) an organic disorder that explains current symptomatology.

Measures

The variables to be studied are evaluated using the instruments described in [Supplementary Appendix A](#).

Data collection

The evaluation is being carried out at 3 time points. A detailed description of the measures used in each evaluation is reported in [Supplementary Appendix B](#).

Evaluators have been trained in psychological evaluation and specifically in the administration of the CAARMS (Yung et al., 2005). They also are blind to the condition of the study to which the participants have been assigned. In order to ensure internal consistency of the evaluations, interobserver reliability will be calculated with the Cohen kappa. At the beginning of each session with the group receiving UP, two scales are administered, the ODSIS and the OASIS, to measure the severity of depression and anxiety experienced during the previous week, in order to observe fluctuations during treatment. This procedure is performed following the recommendations of the UP manual (Barlow et al., 2019).

CAARMS scores are also collected at the time patients begin treatment in our early psychosis program, prior to entering the baseline assessment of the present study. Medication changes and number or TAU sessions will be recorded as a control variables. Types and dosages of medication will be recorded at the three time points of assessment.

Interventions

All study participants receive TAU, within our early intervention program. It includes the following interventions: psychological therapy (about 20–40 sessions of CBT) as well as psychiatric treatment (with antidepressants, benzodiazepines and only when needed antipsychotic medication), social work intervention (vocational orientation and support), nursing care (side effects monitoring and healthy habits), individual cognitive remediation (if necessary), and family therapy. The number of sessions received in TAU depends on the clinical status of each patient. The maximum duration of TAU is 5 years. CBT delivered in TAU consists of techniques such as behavioral experiments, socratic questioning, and some exposure techniques mainly focused on subthreshold psychotic symptoms (French and Morrison, 2004; Nelson and Orygen Youth Health Research Centre Issuing Body, 2012; Van der Gaag et al., 2013a). Patients receive weekly or fortnightly sessions of psychotherapy. UP includes establishment of the specific therapeutic aims of each participant, motivation techniques, emotional psychoeducation, teaching functional analysis of the emotional experiences, mindfulness techniques, cognitive flexibility, analysis of emotional behaviors, and training in opposite behaviors. We also use interoceptive exposure, which we never use in individual CBT, and we teach patients to create exposure hierarchies for intense emotions so that they can follow treatment without the continuous supervision of a therapist. The UP consists of 15 online group sessions of 2 h each week. The groups include 5–8 participants. Participants receive an additional follow-up session 1 and 3 months after the end of the program. The sessions work on the 8 modules of UP

for the transdiagnostic treatment of emotional disorders, as detailed in the reference manuals (Barlow et al., 2019). A summary of each session of the UP is detailed in [Supplementary Appendix C](#).

Fidelity to the UP treatment protocol is guaranteed through weekly supervision with an accredited therapist. In addition, the therapists who will perform the UP intervention have undergone a 20-h training course. The contents of each module are summarized in an infographic and delivered to patients after the UP session to improve adherence to the intervention and acquisition of the techniques.

Once the participants are recruited to the study, they are randomized into one of the two conditions: TAU + immediate UP (TAU + imm UP) or TAU + WL (TAU + Waiting List). The first group will receive UP immediately in addition to the TAU. The second group will do the TAU while doing the assessments. During this period these patients act as a control group. Seven months later, these patients will receive UP, in addition to TAU. Assessments will also be made at the same time points. This type of study has been carried out previously (Carl et al., 2014). The number of sessions of all the services used in TAU (in both conditions) will be recorded in order to be taken into account when statistical analyses are made. The flowchart of the trial and its different stages is detailed in [Supplementary Appendix D](#).

Sample size calculation

Accepting an alpha risk of 0.05 and a beta risk of less than 0.2 in a bilateral contrast, 21 subjects in the PU + TAU group and 21 in the WL + TAU group are needed to detect a difference equal to or greater than 1.57 units. The common standard deviation is assumed to be 1.6. A follow-up loss rate of 20% has been estimated.

Data analysis

To analyze the improvements in primary and secondary variables throughout the study, linear mixed model analysis will be used. This analysis will allow us to study the main effects of time (pre-test, post-test, 3-month follow-up), treatment condition (TAU vs. TAU + UP), and number of sessions received (CBT sessions in TAU, UP sessions, etc.). We will also calculate interaction effects (e.g., treatment condition \times time, or treatment condition \times number of sessions \times time, and the type and dosage of medication) which will reveal whether the treatment condition and the number of sessions received interacted with time in the prediction of changes in study outcomes. In the event that we observe a significant interaction, *post hoc* analysis will

be conducted. Due to the nature of the present study, we expect to identify subgroups of patients presenting differing evolutions in study variables according to the number of sessions they have received.

The rate of transition to psychosis of patients in each condition and the CAARMS symptom severity will be calculated in order to evaluate changes in subthreshold psychotic symptoms (Morrison et al., 2012). We will also analyze the different clinical trajectories in the two groups following other previous studies (Polari et al., 2018). If any participant makes a transition to psychosis during their participation in the study, they will be excluded (full-blown psychosis is an exclusion criterion) and their data will be taken into account for further analysis. Finally, satisfaction of patients undergoing group treatment will also be analyzed.

Discussion

To the best of our knowledge, this is the first study to investigate the effectiveness of UP in a sample of young adults diagnosed with UHR who also have comorbid emotional symptoms. If the results of this study show that UP is effective in treating the comorbid symptoms of UHR for psychosis, this finding could contribute to expanding the psychotherapeutic approaches that can be used with young people presenting with an at-risk mental state. UP may be complementary and/or an alternative to standard CBT approaches. This study would need to be replicated with a bigger sample.

Unified protocol has been shown to be effective in patients with a primary diagnosis of emotional disorders, including cases with comorbidity, according to the systematic review studies and meta-analyses conducted to date (Sakiris and Berle, 2019; Cassiello-Robbins et al., 2020; Carlucci et al., 2021). We hypothesize that this intervention could be equally effective in young patients because there has not been a chronification of their symptoms yet.

The UP contents and the way each emotion regulation technique is introduced and trained for helps patients to normalize their emotional symptoms or disorders, because all people can experience intense emotions and respond with emotional behaviors. It is positive for all people to improve their emotional regulation skills. This perspective focused on training skills can also help to reduce mental health stigmatization. In addition, UP uses expressions like “emotional experiences,” “intense emotions,” and “emotion driven behaviors” instead of other terms like “aggressive response” or “negative emotions.” All these aspects can help reduce the rejection of treatment by mental health services, especially in young people.

The telematic group format of the UP could improve therapeutic adherence in young people, as they are familiar with new technologies (Lupton, 2021). Further, it may encourage the recruitment of patients residing in remote areas and those without specialized care resources.

Cognitive behavioral therapy delivered in TAU is an intervention that has already been shown to be effective in patients of this type (Van der Gaag et al., 2013a). However, significant differences are expected in clinical variables in those patients who additionally receive the intervention with the UP, mainly in comorbid emotional symptomatology.

Given the high comorbidity of emotional disorders in patients with UHR (Rutigliano et al., 2016) and the presence of errors in information processing in both groups of disorders, such as jumping to conclusion, selective care, and catastrophization, as well as avoidant behaviors (Livet et al., 2020), it is likely that these share common transdiagnostic mechanisms with ED. It may be the case that improving emotional regulation will have a positive effect on cognitive biases implicated in the onset and maintenance of both emotional disorders and symptoms of psychosis. If the results show positive associations between improved emotional regulation and improvement in cognitive biases, this would provide a strong theoretical and clinical basis for offering UP to people at the UHR of psychosis.

One limitation of the study is the potential difficulty in isolating the impact of UP on outcome measures. This study is a naturalistic study, that is, it is carried out in the context of public mental health, which is why it is comparable with what has been done up to now. Clinically, it would be more ethical to offer an intervention like UP to all the participants of the study. We expect that the statistical analyses mentioned above can increase the robustness of the study results and solve this limitation.

The UP has already been shown to be effective with similar symptoms (Sakiris and Berle, 2019; Cassiello-Robbins et al., 2020; Carlucci et al., 2021) and this brings us closer to the clinical reality of mental health services for young people in public health. Furthermore, this design may make it easier to collect more samples since this type of patient is not very prevalent. There are several previous studies that have used this type of methodology (e.g., Carl et al., 2014). In this sense, this would be the first step toward obtaining preliminary data on whether the UP adds something to what is already done and to assess aspects of viability and user satisfaction. The next steps will be to compare the UP in isolation with the TAU.

Ethics statement

This study has been evaluated and approved by the Drug Research Ethics Committee (CEIm) of the Parc Sanitari Sant Joan de Déu. All participants are being provided with an information sheet explaining the objectives and procedure of

the study as well as the confidentiality of the data collected. All participants are being asked in writing for their consent in accordance with the Declaration of Helsinki (WMA, 2013) and Law 14/2007 on Biomedical Research.

Author contributions

TP was the principal investigator of the project, led the development of the manuscript, and investigator in charge of recruiting patients. TP, JO, SO, RL-C, and MF-Q did the study design and decided upon all the outcome measures. MF-Q was carrying out the evaluation process and configured the data collection system. RL-C and TP were carrying out the therapy of the UP and made the infographics of each module. JO was supervising all the therapy process and content of the infographics. SO was responsible for determining sample size and power calculation and proposing all the statistical analyses. RL-C and MF-Q kept the patients linked to the study. JO and SO supervised the development of the study. All authors contributed to the manuscript and approved the final version of the manuscript.

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Conflict of interest

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

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Supplementary material

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Effects of virtual reality natural experiences on factory workers' psychological and physiological stress

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Introduction: Manufacturing facilities and factories are stressful work environments. Interventions to improve factory workers' stress is necessary to promote occupational health. This study aimed to examine the effects of virtual reality natural experiences on furniture factory employees' psychological and physiological stress.

Methods: A single-blinded, non-randomised quasi-experimental study was conducted between July and December 2021. Factory workers were recruited from two factories, and all participants at a given factory were assigned to either an experimental group or a comparison group. The intervention was conducted in a clean conference room once a week for 12 weeks during the worker's break time. The experimental group received virtual reality natural experiences consisting of 30-minute nature-based 360° videos which were played in a headset. The generalised estimating equations were performed for the statistical analyses.

Results: In total, 35 participants completed the intervention. As to psychological stress, the experimental group showed improvements in distress, depression, and anxiety, and a positive affect after the intervention compared to the comparison group. As to physiological stress, the experimental group showed improvements in indicators of heart rate variability compared to the comparison group, including standard deviations of all normal-to-normal intervals, low-frequency power, and high-frequency power.

Discussion: Virtual reality is an innovative platform to bring the natural environment into an indoor environment to create similar health effects.

KEYWORDS

green space, heart rate variability, immersion, mental health, occupational health, virtual reality

1. Introduction

Occupational stress is a well-known issue worldwide that influences both developed and developing countries. Workplace stress occurs when work-related demands surpass a worker's capacity to manage them (World Health Organization, 2020). Moreover, globalization and dramatic changes have had direct impacts on the variety of work in terms of technological developments, higher job demands, and workloads. Also, aging populations and the demographic and systemic structure of the workforce, such as a poor work-life balance, job insecurity, and precarious employment, have resulted in a significant occupational stress epidemic worldwide (Sorensen et al., 2021). Work stress is particularly important and

significantly impacts individuals and organizations. Workplace stress causes a variety of ailments, including cardiovascular and metabolic disorders, psychological issues, musculoskeletal discomfort, reproductive issues, and occupational injuries, and also leads to a poor quality of life (Mohamed et al., 2022). These health issues are related to increased absenteeism and presenteeism, as well as decreased motivation, contentment, and commitment. These can produce increases in employee turnover and a desire to resign, resulting in low business productivity and increased medical, healthcare, and social welfare expenditures (Asplund et al., 2022; Mohamed et al., 2022; Sznajder et al., 2022).

Manufacturing is not exempt from stressful work environments. Workers in the manufacturing industry become stressed as a result of high job expectations, lengthy and irregular working hours, and tough work shift patterns in order to reach production objectives and maintain customer satisfaction. Constant work stress and pressure result in both physical and mental exhaustion, a lack of work-life balance, and decreased employee productivity (Bhui et al., 2016; Bolliger et al., 2022; Kim and Jung, 2022). Hopelessness, not feeling useful, and feeling depressed in the work environment are considered factors associated with symptoms of work-related stress among factory workers (Sznajder et al., 2022), highlighting the need for interventions to alleviate poor mental health symptoms among workers in high-pressure occupational environments.

Nature-based interventions have been studied and are considered effective strategies for alleviating stress and mental health illnesses (Picton et al., 2020; Coventry et al., 2021). Nature-based interventions provide individuals with an opportunity to explore their relationship with nature in terms of connecting to and being impacted by the natural environment to reduce negative mental health issues (Hartig et al., 2014; Owens and Bunce, 2022). However, infusing the natural environment in the workplace is challenging due to urbanization, and people who live and work in urban areas have very limited opportunities to connect with nature. A scarcity of research has been undertaken to implement nature-based interventions and build a natural environment in the factory workplace.

Virtual reality (VR) is becoming an increasingly popular technology, and a growing body of research has demonstrated the effect of using VR as a tool to enable engagement with natural environments (Li et al., 2021; Adhyaru and Kemp, 2022; Spangenberg et al., 2022). Several nature videos and applications can also be easily accessed and applied as VR technology (Adhyaru and Kemp, 2022; Calogiuri et al., 2022). Implementing a natural environment using VR is a novel approach and likely to produce psycho-physiological benefits by bringing nature into an indoor environment (Browning et al., 2019). A previous evidence-based study revealed that using VR natural experiences had positive impacts on psychological stress in terms of mood, anxiety, perceived stress, and physiological stress such as the heart rate (HR) (Adhyaru and Kemp, 2022). However, few investigations have been conducted into the impacts of VR natural experiences on biofeedback and physiological stress. A more in-depth discussion and evidence are required of the physiological changes such as the autonomic nervous system (ANS) and blood pressure (BP) measurements through VR natural experiences (Lüddecke and Felnhofer, 2022). Moreover, research touched on both psychological and physiological stress-related outcome is scarce. VR natural experiences can be considered as a simulation-based intervention contributing to mental-state attribution through the simulation of perception. According to the simulation

theory, activity in sensory cortex that resembles the perception of external stimuli can be elicited from other parts of the brain. Particularly from a simulation-based intervention, imagining, hearing, or feeling something is essentially the same as actually seeing, hearing, or feeling it (Hesslow, 2012). Therefore, VR natural experiences intervention which brought a natural environment into a workplace has a great potential and contribution to psychological and physiological stress improvement. However, research on utilizing VR natural experience on alleviating occupational stress are limited. More empirical studies on investigating the effect of VR natural experience on occupational stress are warranted. Thus, the main purpose of this study was to explore the effects of VR natural experiences on furniture factory employees' stress. Using an innovative intervention of VR natural experiences during their break time, the factory workers in the experimental group were expected to show improvements in their psychological and physiological stress compared to the comparison group. Psychological stress-related outcomes included distress, depression, anxiety, somatization, positive and negative affects, and perceived stress. Physiological stress-related outcomes included BP and HR variability (HRV).

2. Materials and methods

2.1. Study design

This was a single-blinded, two-armed non-randomized, quasi-experimental study conducted from July to December 2021. Participants were recruited from two furniture factories by convenience sampling in southern Taiwan. The supervisors of the two factories were contacted by the principal investigator, and the oral consent was obtained to invite eligible workers in the factories. Then, a researcher explained the aim and procedure of the study to all workers. All workers were required to sign an informed consent form before data collection and the intervention. The workers in the two factories were either assigned to an experimental group (VR group) and a comparison group by drawing. The minimal sample size was 34 which was calculated by medium effect sizes *via* G*power software (Faul et al., 2007). Each factory recruited 21 participants who were either in the same experimental or comparison group. Participants were not aware of the other group. Ethical approval for this study was obtained from the Taiwan Medical University-Joint Institutional Review Board (N202103114). This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Participants

Participants were factory workers who had break time in the afternoon. The inclusion criteria were participants (1) aged 20–60 years, (2) who worked on the production line, (3) who had no visual or hearing impairment, and (4) who had no serious health problems, mental illness, or disability that might influence the experiment and outcomes. The exclusion criteria were participants (1) who had gone to a natural environment for recreation in the past year, (2) who went to parks or green spaces weekly, (3) who had experiences in using any VR devices in the past year, and (4) who experienced serious VR sickness. The study flow is illustrated in Figure 1.

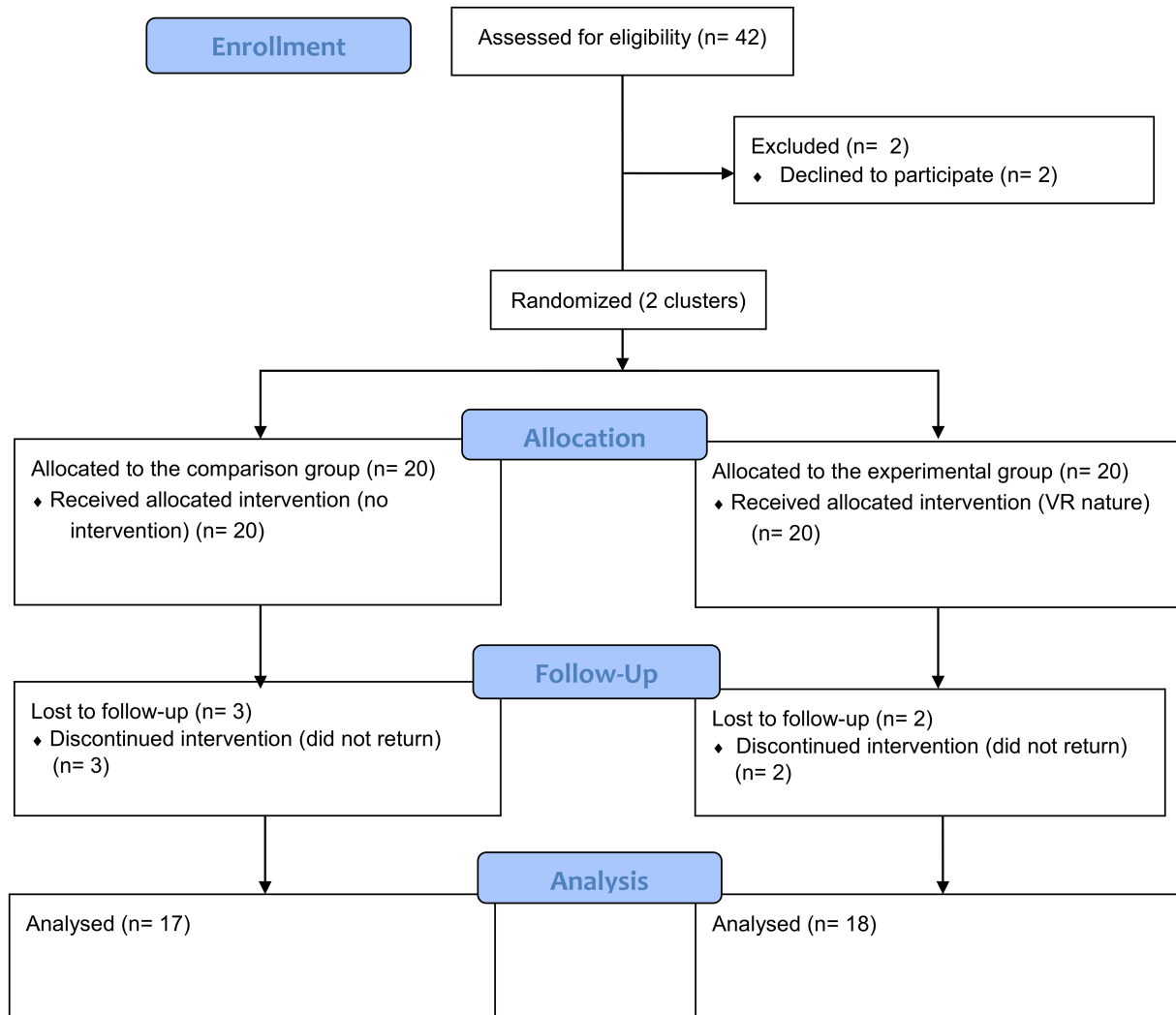


FIGURE 1
Flow diagram detailing the progress of enrolment to analysis.

2.3. The intervention

The intervention was conducted once a week for 12 weeks. To not interrupt the working time, the intervention in the experimental VR group was conducted during workers' break time. Five participants with the same break time schedule were grouped together. The group received the VR intervention in a clean conference room at the same time. The conference room was free of interference from any external visual or auditory stimulation. Participants in the experimental group were required to sit in a chair and wear a VR headset (Oculus Quest 2, META, United States) to watch 360° videos for 30 min (Figure 2). Based on the coronavirus disease 2019 (COVID-19) policy at that time, participants were also required to wear a face mask in indoor environments.

Nature-based VR videos were pre-recorded in a 360° format, including such areas as parks, hiking trails, forest paths, and bikeways (Supplementary Figures S1, S2). All videos were recorded on a sunny day in the afternoon. A different 30 min nature-based video was played in the VR headset every week. During the session, participants could freely move the direction of their head to watch the video from various angles. Participants were asked not to talk to each other during



FIGURE 2
Photo of the virtual reality (VR) natural experience intervention.

the session. A trained college student supervised every session. When using the VR headset, if a participant felt a little uncomfortable, they were told to temporarily close their eyes and then open their eyes

again. If the uncomfortable sensation continued, they were told to stop the session. The comparison group received no interventions for 12 weeks. Participants in the comparison group were free to do any activities of their choosing during their afternoon break time.

2.4. Measures

Measurements were conducted in the conference room once before and once after the 12 week intervention by a trained college student. Stress-related outcomes were measured by self-reported questionnaires, a sphygmomanometer, and an HRV analyzer. Participants' background information was collected in self-reported, structured questionnaires, including age, gender, education level, marital status, main job content in the factory, alcohol use, smoking, and chronic diseases.

Psychological measures. The Four-Dimensional Symptom Questionnaire (4DSQ) measures four common mental health problems: distress, anxiety, depression, and somatization. In total, 50 items were measured on a five-point scale. A higher score indicates worse symptoms. The 4DSQ previously presented good content validity, criterion-related validity, and construct validity (Terluin et al., 2016). Cronbach's α was 0.802 in this study. The Positive and Negative Affect Scales (PANAS) were used for measuring participants' emotions in two dimensions, including positive and negative affects. In total, 50 items were measured on a five-point scale. A higher score indicates a higher perceived affective status. The PANAS have good reliability and construct validity (Watson et al., 1988). The Perceived Stress Scale (PSS) was used for a self-evaluation of stress in the past month. In total, 10 items were measured on a five-point scale. A higher score indicates higher perceived stress. The PSS previously had good reliability, construct validity, and criterion-related validity (Cohen et al., 1983). Cronbach's α was 0.903 in this study.

Physiological measures. A BP monitor (HEM-7310, OMRON, Japan) was used to measure participants' systolic BP (SBP) and diastolic BP (DBP). The BP monitor was validated European Society of Hypertension International Protocol. by A handheld electrocardiogram (ECG) Monitor (8Z11, Wegene Technology, Taiwan) was used for ECG signal acquisition, storage, and processing of resting HRV and the ANS with the good validity (Tseng et al., 2020). Participants were requested to sit still for 5 min to record short-term HRV. After the algorithm, the selective parameters of HRV included the HR, a standard deviation (SD) of all normal-to-normal intervals (SDNN), total power (TP, 0–0.5 Hz), low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–0.40 Hz), and the ratio of LF to HF (LF/HF). Participants with a higher SDNN and LF/HF were more likely to have better ANS and lower stress, anxiety, and depression (Malik et al., 1996).

2.5. Statistical analysis

Descriptive analyzes used the frequency and percentage for categorized variables and the mean and SD of continuous variables. Chi-square tests were performed to compare participants' backgrounds between the experimental and

comparison groups. Cramer's V was calculated for effect sizes of the Chi-squared tests. Independent t-tests were performed to compare differences in participants' age and stress-related outcomes of psychological and physiological measures at the baseline. Cohen's d was calculated for effect sizes of the independent t-tests. The natural logarithms (Ln) of HRV data (TP, LF, HF, and LF/HF) were calculated for further analyzes. Analyzes were performed based on intention-to-treat principle. ITT approach provides unbiased comparisons among the treatment groups and this technique was done to avoid the effects of dropout, which the number of participants after group allocation was included in the final analysis (i.e., VR group $N=20$ and Comparison group $N=20$). Generalized estimating equations (GEEs) were performed to analyze the effect of group, time, and group-by-time interactions on stress-related outcomes. The GEEs were adjusted for participants' age and the score at the baseline. SPSS 18.0 (SPSS, United States) was used for all statistical analyzes.

3. Results

3.1. Participants' backgrounds

Table 1 reveals the participants' backgrounds. No significant differences were found in gender, smoking behavior, or chronic diseases between the VR and comparison groups. However, participants' age, education levels, marital status, and job content exhibited significant differences between the two groups. Therefore, the significant continuous variable (age) of participants' backgrounds was adjusted for in the subsequent GEE analysis. In total, 18 participants in the VR group and 17 participants in the comparison group completed the intervention.

3.2. Stress-related outcomes at the baseline

Table 2 demonstrates participants' stress-related outcomes at the baseline. Negative affect ($p=0.043$) and SBP ($p=0.043$) were found to significantly differ between the VR and comparison groups. No other variables of psychological or physiological measures were found to significantly differ between the VR and comparison groups.

3.3. Outcomes

Table 3 demonstrates the GEE-adjusted model which indicates the effects of group, time, and group-by-time interactions on stress-related outcomes, and the model was adjusted for participants' age and the outcome score at the baseline. For psychological measures, significant group effects ($p=0.021$) and group-by-time interactions ($p=0.015$) were found for distress. Significant group effects ($p=0.039$) and group-by-time interactions ($p=0.042$) were also found for anxiety. Significant group effects were found for depression ($p=0.005$) and positive affect ($p=0.035$). Mean differences indicated that distress, depression, anxiety, and positive affect in the VR group improved after the intervention compared to the comparison group. In contrast,

TABLE 1 Participants' backgrounds.

| Parameter | | VR group (N=20) | | Comparison group (N=20) | | χ^2 | p | V^1 |
|-------------------|-----------------|-----------------|----------|-------------------------|----------|----------|-------|-------|
| | | n | (%) | n | (%) | | | |
| Gender | Male | 7 | (36.84%) | 12 | (60.00%) | 2.09 | 0.148 | 0.232 |
| | Female | 12 | (63.16%) | 8 | (40.00%) | | | |
| Educational level | <high school | 13 | (81.25%) | 6 | (33.33%) | 7.89 | 0.005 | 0.482 |
| | >college | 3 | (18.75%) | 12 | (66.67%) | | | |
| Marital status | Single/divorced | 3 | (15.79%) | 10 | (50.00%) | 5.13 | 0.023 | 0.363 |
| | Married | 16 | (84.21%) | 10 | (50.00%) | | | |
| Job content | Tailor | 5 | (26.32%) | 5 | (25.00%) | 8.62 | 0.013 | 0.470 |
| | Sewing | 8 | (42.11%) | 1 | (5.00%) | | | |
| | Others | 6 | (31.58%) | 14 | (70.00%) | | | |
| Alcohol use | No | 13 | (86.67%) | 10 | (50.00%) | 5.12 | 0.024 | 0.382 |
| | Yes | 2 | (13.33%) | 10 | (50.00%) | | | |
| Smoking | No | 3 | (16.67%) | 2 | (10.00%) | 0.37 | 0.544 | 0.098 |
| | Yes | 15 | (83.33%) | 18 | (90.00%) | | | |
| Chronic diseases | No | 14 | (73.68%) | 17 | (85.00%) | 0.77 | 0.382 | 0.140 |
| | Yes | 5 | (26.32%) | 3 | (15.00%) | | | |

¹Cramer's V for effect size. VR, virtual reality.

TABLE 2 Participants' stress-related outcomes at the baseline.

| Variable | | VR group (N=20) | | Comparison group (N=20) | | t | p | d |
|------------------------|----------------------------|-----------------|---------|-------------------------|---------|-------|--------|-------|
| | | Mean | (SD) | Mean | (SD) | | | |
| Age (years) | | 55.21 | (7.71) | 36.10 | (11.12) | 6.27 | <0.001 | 1.998 |
| Psychological measures | Distress | 23.24 | (6.51) | 23.05 | (4.43) | 0.10 | 0.919 | 0.033 |
| | Depression | 8.12 | (3.30) | 6.70 | (1.42) | 1.65 | 0.114 | 0.559 |
| | Anxiety | 15.24 | (4.52) | 14.80 | (3.65) | 0.32 | 0.748 | 0.106 |
| | Somatization | 25.29 | (8.07) | 24.10 | (5.31) | 0.54 | 0.593 | 0.175 |
| | Positive affect | 2.71 | (1.06) | 2.68 | (0.70) | 0.09 | 0.930 | 0.028 |
| | Negative affect | 2.26 | (0.85) | 1.76 | (0.64) | 2.09 | 0.043 | 0.668 |
| | Perceived stress | 25.63 | (4.57) | 26.40 | (4.84) | −0.51 | 0.614 | 0.163 |
| Physiological measures | SBP (mmHg) | 132.90 | (15.73) | 118.63 | (16.09) | 2.80 | 0.008 | 0.897 |
| | DBP (mmHg) | 80.35 | (11.72) | 73.05 | (10.61) | 2.04 | 0.050 | 0.653 |
| | HR (bpm) | 75.20 | (10.13) | 80.00 | (13.73) | −1.25 | 0.220 | 0.398 |
| | SDNN (ms) | 39.02 | (17.16) | 44.75 | (19.85) | −0.97 | 0.341 | 0.309 |
| | TP [Ln (ms ²)] | 6.94 | (0.99) | 7.32 | (0.95) | −1.22 | 0.229 | 0.392 |
| | LF [Ln (ms ²)] | 5.58 | (1.31) | 6.06 | (0.84) | −1.36 | 0.181 | 0.439 |
| | HF [Ln (ms ²)] | 4.97 | (1.35) | 5.46 | (1.23) | −1.17 | 0.249 | 0.376 |
| | LF/HF [Ln (ratio)] | 0.61 | (0.70) | 0.61 | (0.79) | 0.01 | 0.990 | 0.004 |

Cohen's d for effect size; VR, virtual reality; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SDNN, standard deviation of all normal-to-normal intervals; TP, total power (0–0.5 Hz); LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.40 Hz); LF/HF, the ratio of low frequency to high frequency.

somatization, negative affect, and perceived stress revealed no significant effects.

For physiological measures, significant group effects ($p=0.031$) and group-by-time interactions ($p<0.001$) were found for DBP. A

significant group-by-time interaction ($p=0.007$) was found for SBP. HRV outcomes revealed that SDNN had a significant group effect ($p=0.030$). Both LF ($p=0.041$) and HF ($p=0.028$) had significant group-by-time interactions. Mean differences indicated that the

TABLE 3 Results of the generalized estimating equation (GEE).

| Variable | VR group (N=20) | | Comparison group (N=20) | | Group effect | Time effect | Group × Time interaction |
|-------------------------------|-----------------|---------------|-------------------------|-----------------|--------------|--------------|--------------------------|
| | MD | (95% CI) | MD | (95% CI) | <i>p</i> | <i>p</i> | <i>p</i> |
| <i>Physiological measures</i> | | | | | | | |
| Distress | −1.77 | (−0.85, 1.57) | 2.07 | (−0.72, 4.86) | 0.021 | 0.077 | 0.015 |
| Depression | −1.08 | (−5.17, 1.63) | 0.50 | (−0.51, 1.51) | 0.005 | 0.470 | 0.062 |
| Anxiety | −0.92 | (−3.66, 1.50) | 1.14 | (−1.70, 3.99) | 0.039 | 0.167 | 0.042 |
| Somatization | 0.85 | (−2.55, 0.70) | 1.71 | (−1.44, 4.86) | 0.340 | 0.062 | 0.452 |
| Positive affect | 0.22 | (−1.36, 3.05) | −0.24 | (−0.79, 0.31) | 0.035 | 0.267 | 0.095 |
| Negative affect | 0.19 | (−0.54, 0.99) | −0.21 | (−0.57, 0.16) | 0.518 | 0.371 | 0.297 |
| Perceived stress | −0.71 | (−2.40, 0.97) | 0.86 | (−1.27, 2.98) | 0.475 | 0.315 | 0.116 |
| <i>Physiological measures</i> | | | | | | | |
| SBP (mmHg) | 0.88 | (−5.91, 7.66) | 9.73 | (−0.45, 0.84) | 0.357 | 0.590 | 0.007 |
| DBP (mmHg) | 0.13 | (−7.65, 7.90) | 2.47 | (3.18, 16.29) | 0.165 | 0.031 | <0.001 |
| HR (bpm) | −1.93 | (−0.70, 5.63) | 3.63 | (−8.69, 15.94) | 0.883 | 0.404 | 0.393 |
| SDNN (ms) | 6.59 | (−5.98, 2.12) | −8.10 | (−34.22, 18.02) | 0.030 | 0.587 | 0.184 |
| TP (Ln (ms ²)) | 0.53 | (0.13, 0.92) | −0.13 | (−1.41, 1.15) | 0.585 | 0.011 | 0.545 |
| LF (Ln (ms ²)) | 0.70 | (0.15, 1.25) | −0.13 | (−1.16, 0.89) | 0.461 | 0.001 | 0.041 |
| HF (Ln (ms ²)) | 0.66 | (0.03, 1.28) | −0.36 | (−1.74, 1.02) | 0.279 | 0.006 | 0.028 |
| LF/HF (Ln (ratio)) | 0.05 | (−0.44, 0.53) | 0.23 | (−0.40, 0.86) | 0.473 | 0.534 | 0.933 |

The GEE was adjusted for participants' age and score at the baseline. The statistical significance level is set at 0.05 and the value of statistical significance is emphasized in bold. VR, virtual reality; MD, mean differences between pre- and post-test scores; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SDNN, standard deviation of all normal-to-normal intervals; TP, total power (0–0.5 Hz); LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.40 Hz); LF/HF, the ratio of low frequency to high frequency.

comparison group had higher blood pressure after 12 weeks. The SDNN, LF, and HF of the VR group had improved after the intervention compared to the comparison group. However, HR and LF/HF exhibited no significant effects.

4. Discussion

This study applied a VR device to bring the natural environment to furniture factory workers. VR natural experiences were introduced in the afternoon break time weekly for 12 weeks. Participants' psychological stress, including distress, depression, anxiety, and positive affect, improved after long-term VR natural experiences. Participants' physiological stress, including partial indicators of HRV and stabilized BP, improved after long-term exposure to VR natural experiences. VR natural experiences could potentially ameliorate factory workers' stress levels.

This study found that VR natural experiences had positive effects on psychological stress of factory workers, including distress, depression, anxiety, and positive affect. These results are in line with previous studies and demonstrate the effects of VR natural experiences on alleviating psychological stress (Li et al., 2021; Calogiuri et al., 2022; Spangenberg et al., 2022) and that it is a feasible approach which can be applied during break time in the workplace, particular in manufacturing factory settings. However, VR natural experiences did not have an effect on perceived stress. A possible reason might be that other social stressors exist, such as job content, family situations, social dynamics among colleagues, and so on, that were

potentially affecting perceived stress (World Health Organization, 2020). Both the work content and work context need to be assessed; for example, the work context includes career development, economic and payment issues, role in the organization, interpersonal relationships, organizational culture, and work-life balance (World Health Organization, 2020; Sanchez-Gomez et al., 2021). Future studies can consider evaluating other stressors to exclude stressed-out participants in order to examine the effect of VR natural experiences on perceived stress.

In addition, this study also found VR natural experiences had positive impacts on the physiological stress of factory workers, including the SDNN, LF, and HF. The SDNN is one of the important indicators of ANS functions which presents overall physiological stress measured by the HRV (Kim et al., 2018). On the other hand, participants in the experimental group had stable SBP and DBP after the intervention, while participants in the comparison group had increased SBP and DBP after 12 weeks. This is a relatively less explored area, and more biofeedback and physiological measures are encouraged to be managed by VR nature interventions. Our study adopted precise and accurate physiological measures in assessing ANS function with an evidence-based evaluation to summarize the effects of VR natural experiences (Francis et al., 2009; Guo et al., 2022). Study findings highlighted that changes in physiological outcomes can be achieved by applying a VR natural experience intervention in workplace settings which is central to promoting occupational health. As mentioned, VR natural experiences as a simulation-based intervention did contribute to psychological and physiological stress improvement. This study can be a fundamental

work in the component of simulation of perception in the simulation theory. Future studies and interventions are warranted to investigate the impacts of the simulation-based intervention on other components of the simulation theory, namely simulation of behavior and anticipation (Hesslow, 2012). It is believed that the benefits of VR natural experiences can go beyond the psychological and physiological stress improvement, for example, the enhancement in working memory, motor, sensory and cognitive function may be observed as well. In our study, the VR natural experience intervention was only implemented during break time at a factory for 30 min per session. Thus, the frequency and length were reasonable and feasible, and did not occupy much time during their break. We suggest that employers could provide VR natural experience headsets in the break space or conference room in the factory so that factory workers can have options to relieve their tense mood and improve physiological stress during their break time and have a better occupational health status.

To our best knowledge, this is the first study to explore the effects of natural experiences *via* VR devices on psychological and physiological stress for occupational health. However, there were several limitations. The study design was a clustered RCT, instead of an RCT. A few variables of participant's backgrounds significantly differed between the experimental and comparison groups, although most stress-related outcomes at the baseline did not differ between the two groups. The diverse population might have influenced the interpretation of results. The small sample size and loss of several participants after 12 weeks were also a problem. The 360° video might have been not clear enough compared to the real world. During the intervention, participants who complained about VR sickness might have missed several parts of the videos because they closed their eyes to rest. Finally, the activities of participants in the comparison group during the break time were not monitored, which might have generated a bias.

This study has implications for factory employers and occupational healthcare professionals such as public health nurses and general practitioners, and informs future studies for developing relevant interventions. Manufacturing industry employers should pay attention to employees' occupational health, especially stress. Planning regular break time in relaxed and comfortable places is important for employees' rest and further work efficacy. VR is an interesting platform that can provide an opportunity to connect with nature, activities, and games. Weekly real-world and VR-based natural experiences are both recommended for stressed workers. However, when using VR devices, the image resolution of 360° videos is still a problem that might cause VR sickness that should be overcome by future technological advances. For future studies, a study design of RCTs might provide stronger evidence. Increasing the sample size and decreasing differences in participants' backgrounds between groups are important considerations. The intervention can be conducted more frequently and longer, for example, two or three times a week for 6 months. Diverse natural environments, such as forests, waterfalls, and mountains, can be recorded in a 360° format to increase enjoyment and attraction. Besides the visual and auditory stimulation from VR, olfactory stimulation could be considered in future interventions.

VR is an innovative opportunity to bring the natural environment into an indoor environment. VR natural experiences can provide

similar effects as real-world natural experiences for relaxation. This study indicated that VR natural experiences had positive effects on furniture factory workers' psychological and physiological stress after a 12 week intervention. VR natural experiences are recommended to release stress and promote the occupational health of factory workers and heavy labors.

Data availability statement

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Taiwan Medical University-Joint Institutional Review Board (N202103114). The patients/participants provided their written informed consent to participate in this study.

Author contributions

M-HH: formal analysis and writing—review and editing. M-SW: resources and data curation. H-YY: formal analysis, conceptualization, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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.2023.993143/full#supplementary-material>

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