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RESEARCH PAPER

EFFICACY OF A FUNCTIONAL THERAPY PROGRAM FOR DEPRESSION AND C-REACTIVE PROTEIN: A PILOT STUDY

Giuseppe Maniaci, Caterina La Cascia, Alessandra Giammanco, Laura Ferraro, Zaira Sardella, Giulia Bivona, Marcello Ciaccio, Daniele La Barbera

Abstract

Objective: Affecting more than 264 million people, depression is a systemic and multifactorial disorder that represents one of the leading causes of illness and disability worldwide. Several studies showed an inflammatory response in depressed patients, including the involvement of both chronic low-grade inflammatory response and activation of cell-mediated immunity. The present study aimed to verify the efficacy of a structured functional therapy program for patients with depressed mood, and to determine whether this program can significantly reduce levels of C-reactive protein.

Method: 28 outpatients with depressed mood received 20 individual sessions of Functional therapy. Data about socio-demographic variables, depression, self-esteem, and quality of life were collected; moreover, blood specimens were collected before and after treatment, and CRP measurement was performed by immunoenzymatic method. All measures were administered at baseline, at the end of treatment (i.e., 3 months after baseline), and at follow-up (i.e., 6 months after baseline).

Results: A repeated measures ANOVA showed a significant difference after treatment on depression levels, levels of self-esteem, and all dimensions of quality of life, such as physical, psychological, social relationships, and environment. Furthermore, a statistically significant difference on levels of CRP was found. Moreover, at follow-up, improvements were maintained.

Conclusions: The study revealed initial evidence of the efficacy of a functional therapy program on treating depression and its psychological and inflammation-related markers.

Key words: depression, inflammation, C-reactive protein, CRP, self-esteem, quality of life, psychotherapy, functional therapy

Giuseppe Maniaci[1], Caterina La Cascia[1], Alessandra Giammanco[1], Laura Ferraro[1], Zaira Sardella[1], Giulia Bivona[2], Marcello Ciaccio[2,3], Daniele La Barbera[1]

[1] Section of Psychiatry, Department of Biomedicine, Neuroscience, and Advanced Diagnostic, University of Palermo, Palermo, Italy

[2] Institute of Clinical Biochemistry, Clinical Molecular Medicine and Laboratory Medicine, Department of Biomedicine, Neurosciences and Advanced Diagnostics, University of Palermo, Palermo, Italy.

[3] Department and U.O.C. Laboratory Medicine, University Hospital "Paolo Giaccone" of Palermo, Palermo, Italy.

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Corresponding author

Giuseppe Maniaci
E-mail: giuseppe.maniaci02@unipa.it

Introduction

Affecting more than 264 million people (James et al., 2018), depression has been recognized as a leading cause of illness and disability worldwide by World Health Organization (WHO), which indicated it as one of the priority conditions covered by WHO's mental health Gap Action Programme (World Health Organization, 2020).

It is generally agreed that multiple factors contribute to the etiology of depression, such as genetic (Dunn et al., 2015), environmental (Infurna et al., 2016), anatomic and biochemical factors (Oakes et al., 2017), and personality traits (Goldstein et al., 2019). However, current research pointed out the systemic complexity of this disorder, by highlighting the association between depression and inflammation (Dowlati et al., 2010; Huang et al., 2019; Maes et al., 2011).

Several studies showed the involvement of both chronic low-grade inflammatory response and activation of cell-mediated immunity in depression (Berk et al., 2013; Köhler et al., 2017). Low-grade inflammatory response is characterized by high levels of acute phase reactants, such as C-reactive protein (CRP) (Haapakoski et al., 2015), and inflammatory cytokines, such as tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) (Dowlati et al., 2010). In this regard, current research found increased levels of CRP in depressed patients (Khandaker et al., 2014; Osimo et al., 2019), and higher levels of CRP were associated with depressive symptom severity (Köhler-Forsberg et al., 2017). Moreover, recent reviews highlighted the role of pro- and anti-inflammatory cytokines in the etiopathogenesis of depression, showing that they

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represent an important predictive marker in order to identify patients who could benefit from tailored therapeutic approaches (Liu et al., 2020; Petralia et al., 2020a). Additionally, it was suggested that the pro-inflammatory cytokine Macrophage migration inhibitory factor (MIF), as well as D-dopachrome tautomerase, could play a role in induction and maintenance of the major depressive disorder (Petralia et al., 2020b), by upregulating production of interleukin-1β and TNF-α (Günther et al., 2019). Recent research, indeed, showed high blood levels of MIF in depressed patients (Bloom & Al-Abed, 2014; Musil et al., 2011).

Several psychotherapy programs have demonstrated effectiveness in treating depression, including cognitive behavioral therapy (Crail-Meléndez et al., 2010; Twomey et al., 2017), Eye Movement Desensitization and Reprocessing (EMDR) (Carletto et al., 2017), and psychodynamic approaches (Driessen et al., 2015). Recent studies have also shown the efficacy of mind–body approaches in treating depression – among them, yoga (Chan et al., 2016; Cramer et al., 2017), meditation (Annells et al., 2016; Carpena et al., 2019), and mindfulness-based interventions (Kuyken et al., 2016; Reangsing et al., 2020). However, it is well established that a combination of psychotherapy and pharmacotherapy is the most effective treatment for depression (Cuijpers et al., 2020; Kamenov et al., 2017). Furthermore, a recent study found that combining psychotherapy and a healthy diet leads to a significant improvement of depressive symptoms, self-esteem and quality of life (Maniaci et al., 2020), focusing attention on the relevance of practicing healthy lifestyle behaviors for improving the treatment outcome. To date, only few studies have tried to test the hypothesis that psychotherapy can reduce depression-related inflammation, highlighting mixed results. Indeed, while some studies highlighted decreased serum levels of TNF-α, IL-6 (da Silva et al., 2016; Moreira et al., 2015; Walsh et al., 2016), and CRP (Eisendrath et al., 2016) at the end of psychotherapy, other research found no effects on interleukin-8 and CRP (Memon et al., 2017).

Functional therapy (FT) is an integrated mind-body approach that takes into account the human organism's deepest psycho-biological mechanisms – the so-called functional processes – such as body memory and peripheral memory, which together constitute the Self (Rispoli, 2008). Some studies showed the efficacy of FT programs in reducing pathological gambling behaviors (Maniaci et al., 2018) and in reducing psychological and physiological correlates of stress (Perciavalle et al., 2017).The main goal of FT for depression, is the increasing of mood and self-esteem via several bodily, cognitive and emotional techniques geared towards helping patients to improve the basic experiences of the self altered by the disorder (for an explanation of Functional theory, see Di Pasquale et al., 2019; Rispoli, 2016).

Given those premises, the present study had two aims: (a) to verify the efficacy of a structured FT program delivered in individual sessions for patients with depressed mood; (b) to determine whether this program can significantly affect levels of CRP in those patients. Specifically, the first outcome was a significant reduction of depressive symptoms and an improvement in self-esteem and quality of life; the secondary outcome was a significant reduction in levels of CRP after treatment.

Materials and Methods

Procedure

From September 2018 to February 2020, patients were recruited as they responded to an advertisement posted in the outpatient clinic and on social media, and on flyers distributed to medical offices and pharmacies. All volunteers were subjected to structured telephone screening in order to determine their eligibility in terms of the following inclusion and exclusion criteria: aged from 18 to 60 years old, seeking treatment for mood problems, not receiving any concurrent treatment, not receiving any psychopharmacological treatment for depression in the previous 12 months, and not practicing yoga or meditation. Moreover, they had to score >13 points on the Beck Depression Inventory-II (BDI-II) and report a body mass index (BMI) between 18.5 and 40 at the initial assessment, in order to exclude individuals who had high inflammatory parameters because of their high BMI (e.g. Ambrosio et al., 2018).

Individuals with past or current drug abuse or addiction (excluding nicotine), chronic inflammation disease, severe hepatic failure, serious infection (e.g., hepatitis B), cancer in the previous 6 months or regular use of anti-inflammatory drugs for >15 days per month were excluded. Other exclusion criteria were: an intelligence quotient <65, active suicidal ideation with a plan, and a current or lifetime diagnosis of any psychotic disorder, bipolar disorder, primary anxiety disorder, or a borderline, schizotypal, or antisocial personality disorder. To further examine other eligibility criteria and depression, consultations with a clinical psychologist and psychiatrist were organized together with the administration of the psychological tests. All participants provided their written informed consent, and all measures were administered with respect for their privacy. Blood samples were collected in dry tubes before and after treatment (T0, T1, and T2, respectively). Serum was obtained by centrifugation for 10 minutes at 3350 g at room temperature and then stored in aliquots at −80 °C until testing. CRP measurement was performed by immunoenzymatic methods. All participants received the FT protocol. All measures were administered at baseline, at the end of treatment (i.e., 3 months after baseline), and at follow-up (i.e., 6 months after baseline).

This study was part of a larger research project including the evaluation of depression as a systemic disorder and it was approved by the ethical review board of the Policlinico "P. Giaccone" in Palermo, Italy (07/2017). All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments.

Measures

Screening measures

Sociodemographic questionnaire. An ad-hoc sociodemographic questionnaire was used in order to collect data including the age, sex, marital status, occupation, and socio-economic status of the patients.

Wechsler Adult Intelligence Scale – Revised (WAIS-R) – short version. The Italian version of WAIS-R was administered to measure intelligence and cognitive ability (Wechsler, 1981). According to the Velthorst method (Velthorst et al., 2013), we used a well-established and well-validated short version of

the instrument that consists of the following tests: Digit Symbol, Arithmetic, Information, and Block Design. The short version proposed is a useful screening device of general intellectual ability in research settings, in order to minimize fatigue and possibly study participant frustration that could bias the results, while providing a reliable estimate of current intellectual ability.

Millon Clinical Multiaxial Inventory-III (MCMI-III). This self-report questionnaire allows an assessment of personality disorders and main psychiatric disorders on the basis of DSM-IV criteria. It consists of 175 true-false items, 14 personality pattern scales, 10 clinical syndrome scales and 4 validity scales (Millon & Davis, 1997). The Italian version of the questionnaire was found to have good psychometric properties: Cronbach's alpha values ranged from 0.66 to 0.90; test-retest reliability was between 0.82 and 0.96 (Zennaro et al., 2008).

Outcome measures

Beck Depression Inventory-II (BDI-II). The BDI-II measures depressive symptoms severity. It is composed of 21 items, rated along a four-point Likert scale, reflecting cognitive, affective, behavioural and somatic symptoms. Items are summed up in order to obtain an overall index; the final score can be interpreted in the following way: no depression (0–13 points), mild depression (14–18 points), moderate depression (19–29 points) and severe depression (30–60 points) (Ghisi et al., 2006). The Italian version of the BDI-II has shown a one-factor structure, adequate internal consistency (in the range 0.80-0.87), test-retest reliability ($r = 0.76$) and construct validity (Sica & Ghisi, 2007).

Basic Self-Esteem Scale (Basic SE). This self-report questionnaire measures that particular type of self-esteem which develops during childhood and which is independent of personal skills, achievement or outside validation. The test is composed of 22 items rated along a five-point Likert scale. The Italian version of the instrument has shown good psychometric properties (Cronbach's alpha = .85; test–retest reliability = 0.81-0.83) (Forsman et al., 2003).

World Health Organization Quality of Life–BREF (WHOQOL–BREF). The WHOQOL-BREF was derived from the WHOQOL-100. It is composed of 26 items and it produces scores for 4 domains related to quality of life: physical health, psychological health, social relationships, and environment. This instrument emphasizes the subjective perception of the quality of life, by allowing the clinician to evaluate the impact of the disease on the patient's life (The WHOQOL Group, 1998). The Italian version of the WHOQOL-BREF has shown good internal consistency, ranging from 0.65 for the social relationships domain to 0.80 for the physical domain; test-retest reliability values range from 0.76 for the environment domain to 0.93 for the psychological domain (De Girolamo et al., 2000).

Intervention

Five clinical psychologists with 4 years postgraduate training in functional therapy implemented the intervention after receiving refresher training in the application of the structured functional therapy protocol for depression. Prior to the study, therapists received training in the application of the structured protocol for depressive symptoms. Moreover, during the treatment phase, they participated in weekly clinical supervision with a senior clinical psychologist with specialist functional therapy training, in order to maintain fidelity to the manualized intervention. Two of the therapists were men and three were women. Their average age was 41.6 years ($SD = 4.97$) and their mean level of postgraduate training experience was 12.6 years ($SD = 5.45$).

FT protocol was administered during a 3-month period over the course of 20 individual sessions, scheduled to occur twice weekly for the first 2 months and once weekly for the last month. The intervention protocol was tailored in order to treat depressive symptoms by increasing mood, self-esteem, and quality of life (Rispoli, 2008). Specifically, the protocol aimed to reduce or eliminate depressed mood and to improve assertiveness and social abilities through several bodily, cognitive, and emotional techniques, such as deep breathing and specific guided imagery (please see the supplemental materials if you are interested in learning more about the focus of each session).

Statistical analyses

In order to evaluate any statistically significant difference in depression, self-esteem, quality of life, and levels of CRP, a repeated measure analysis of variance (ANOVA) was used at baseline, after treatment, and follow-up. In order to test the assumption of sphericity, a Mauchly's test was performed; Greenhouse-Guisser and Huynh–Feldt corrections were applied where appropriate. Moreover, the sample was split into three subgroups according to the severity of depressive symptoms evaluated by BDI-II, and a one-way repeated ANOVA analysis was conducted to analyze differences between groups after treatment. In addition, the least significant difference (LSD)-adjusted pairwise comparisons were used for analyzing differences between groups before and at each time point during the study.

Furthermore, the sample was split according to the WHO BMI classification (WHO, n.d.) and a one-way ANOVA analysis was conducted in order to analyze differences between BMI categories and levels of CRP, as well as between BMI and depressive symptoms pre- and post-treatment and follow-up.

Finally, a correlation analysis was performed using the Pearson correlation coefficient, in order to verify the presence of a correlation between depressive symptoms, BMI, and levels of CRP pre- and post-treatment and follow-up.

All analyses assumed an alpha risk of 5%. All statistical analyses were performed in the Statistical Package for the Social Sciences for Windows 22.0.

Results

Demographics

The sample consisted of 28 subjects (60.7% females), ranging from 18-59 years old, with a mean age of 33.1 years old ($SD = 11.18$). 67.9% were unmarried whereas 32.1% were married. The mean education level was 13.75 years ($SD = 3.02$). **Table 1** shows IQ levels, personality disorders, and psychiatric comorbidities of the participants at time of assessment. The final sample comprised 23 participants with depressed mood, since five patients dropped out (**table 1**).

Outcomes

Significant differences at the end of treatment were highlighted on depression, self-esteem, and all dimensions of quality of life, together with levels of

CRP. No significant differences were highlighted at follow-up (**table 2**).

Moreover, no significant differences were found between the three groups splitted according to the severity of depressive symptoms in terms of depressive symptoms F (2,20) = .764, p = .479); levels of self-esteem F (2,20) = .464, p = .635, and physical F (2, 20) = 1.824, p = .187, psychological F (2,20) = .048, p = .953, social F (2,20) = 1.523, p = .242, and environmental F (2,20) = 2.678, p = .093 quality of life. Levels of CRP between those groups did not significantly differ, either F (2,20) = .896, p = .424.

Moreover, no significant differences between BMI and levels of CRP were found before treatment F (2,24) = .130, p = .879, after treatment F (2,18) = .733, p = .494, and follow-up F (1,16) = 1.318, p = .268.

Table 1. *IQ levels, BMI, personality disorders, and psychiatric comorbidities of the participants at time of assessment*

Factors	**Participants (N=28) Mean (*SD*)**
I. Q.	103.1 (21.22)
BMI	24.23 (3.32)
Personality disorders	**Participants (N=28) Frequency (%)**
Schizoid	4 (14.3%)
Avoidant	6 (21.4%)
Depressive	11 (39.3%)
Dependent	8 (28.6%)
Histrionic	1 (3.6%)
Narcissistic	2 (7.1%)
Antisocial	-
Sadistic	-
Compulsive	2 (7.1%)
Negativistic	3 (10.7%)
Self-defeating	5 (17.9%)
Schizotypal	-
Borderline	-
Paranoid	-
Clinical Syndromes	**Participants (N=28) Frequency (%)**
Anxiety	16 (57.1%)
Somatic Symptom	5 (17.9%)
Bipolar Disorder	-
Dysthymia	8 (28.6%)
Alcohol Use	-
Drug Use	-
Post-Traumatic Stress	-
Thought Disorder	2 (7.1%)
Major Depression	8 (28.6%)
Delusional Disorder	-

Table 2. *Means, Standard deviations, and Two-Way ANOVA Statistics for study variables*

Factors	**T0 Pre-treatment (N=23) Mean (*SD*)**	**T1 Post-treatment (N=23) Mean (*SD*)**	**T2 Follow-up (N=23) Mean (*SD*)**	**Test One-way repeated measures ANOVA**		
				F	**df**	***p***
Depressed mood	28.43 (8.69)	11.56 (9.93)	11.04 (9.50)	56.1	1.5	.000
Self-esteem	21.73 (22.99)	63.04 (32.74)	51.08 (28.68)	23.78	1.61	.000
QoL – Physical	33.71 (13.93)	49.40 (15.30)	48.42 (12.17)	20.53	2	.000
QoL – Psychological	37.45 (7.44)	56.34 (15.40)	53.80 (12.33)	32.61	2	.000
QoL – Social relationships	47.30 (19.55)	67.74 (23.36)	68.15 (15.77)	21.41	2	.000
QoL – Environment	46.98 (11.23)	60.83 (15.35)	60.96 (11.37)	15.94	2	.000
CRP	3.19 (3.60)	1.55 (1.56)	1.57 (1.65)	5.99	1.14	.024

Table 3. *Bivariate Pearson's correlation between depressive symptoms, BMI, and levels of CRP*

Factors	T0 Pre-treatment (N=28)			T1 Post-treatment (N=23)			T2 Follow-up (N=23)		
	1	2	3	1	2	3	1	2	3
1. Depressive symptoms	-	-.346 NS	.428 *	-	.117 NS	.151 NS	-	.010 NS	.283 NS
2. BMI	-.346 NS	-	-.080 NS	.117 NS	-	.115 NS	.010 NS	-	.008 NS
3. Levels of CRP	.428 *	-.080 NS	-	.151 NS	.115 NS	-	.283 NS	.008 NS	-

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Furthermore, no significant differences between BMI and depressive symptoms were found before treatment F (2,25) = .963, p = .395, after treatment F (2,19) = .834, p = .450, and follow-up F (1,19) = .126, p = .727.

Data analysis revealed that depressive symptoms were positively correlated with levels of CRP r = .428, p = .026 before treatment. No significant correlation was found between depressive symptoms, BMI, and levels of CRP pre- and post-treatment and follow-up (**table 3)**.

Discussion

This is the first pilot study aimed at evaluating the efficacy of a structured FT program for patients with depressed mood in terms of its effects both on psychological and inflammation correlates. Specifically, the first outcome was a significant reduction of depressive symptoms as well as an increase of self-esteem and quality of life. As expected, at the end of the FT program a strong reduction of depressive symptoms together with an increase of quality of life was highlighted. Furthermore, these changes were stable at the 3 months follow up. The efficacy of traditional psychotherapeutic approaches in treating depression is well-established (e.g. Crail-Meléndez et al., 2010; Driessen et al., 2015); however, recent studies have focused on the efficacy of mind–body approaches (Carpena et al., 2019; Reangsing et al., 2020): in their study, Prathikanti et al. (2017) found that an eight-week hatha yoga intervention was effective in reducing depression severity in a sample of 38 adults with major depression. Moreover, Cramer and colleagues (2017) found that a six-week meditation-based program was effective in reducing depressive symptoms in a sample of university students; indeed, it seems that mindfulness meditation interventions are effective in reducing the tendency to ruminate about thoughts and emotions that contribute to depression (Nakajima et al., 2019).

Our results are in line with other studies concerning the efficacy of mind-body therapies for depression, highlighting the efficacy of a three months structured program of FT for depression and its psychological correlates, therefore confirming the role of psychotherapy for improving mood (Cuijpers et al., 2020; Carletto et al., 2017) as well as self-esteem (Ko & Hyun, 2016) and quality of life (Kolovos et al., 2016).

Furthermore, according to our hypothesis, a significant reduction of levels of CRP was found after the FT program. As several researchers have shown, there is a strong association between depression and chronic low-grade inflammation (Berk et al., 2013; Halaris, 2019; Köhler et al., 2017). Patients with depression show high levels of acute phase reactants, such as CRP (Haapakoski et al., 2015; Khandaker et al., 2014; Köhler-Forsberg et al., 2017; Osimo et al., 2019). Our data could be interpreted as a confirmation of the hypothesis that a state of vagotonia, recovered through a deep and diaphragmatic breathing and several specific body techniques based on functional approach, can positively affect markers of inflammation (Bower & Irwin, 2016; Morgan et al., 2014). Moreover, these data, highlighting an association between reduction of both depressive symptoms and CRP, could be viewed as a confirmation of the connections between immune system and nervous system and the possibility to positively affect this association through a mind-body approach such as FT. These findings are in line with previous research that observed decreased levels of CRP (Eisendrath et al., 2016) and pro-inflammatory cytokines in depressed patients after they received psychotherapeutic intervention (da Silva et al., 2016).

No significant differences between BMI categories and levels of CRP, as well as between BMI and depressive symptoms were found pre- and post-treatment and follow-up. Last, our data highlighted that depressive symptoms were positively correlated with levels of CRP. This result is in line with previous studies that found an association between levels of CRP and depressive symptom severity (Köhler-Forsberg et al., 2017).

Our pilot study confirmed the efficacy of a structured FT program for patients with depressed mood, highlighting for the first time an effect on inflammation-related markers such as CRP. Such findings would suggest the usefulness of treating depression by following an integrated approach including psychotherapy, mind-body techniques, pharmacotherapy and lifestyle behaviors in order to significantly improve the outcome.

The main limits of the present study were the small sample size and the lack of a control group. However, as a pilot study, our results are promising and consistent with our hypotheses; future research is needed in order to verify those findings in a larger group, by comparing the experimental group with a control group (e.g. treatment-as-usual control group). Future research should also evaluate other markers of inflammation, such as pro- and anti-inflammatory interleukins. Moreover, future studies could examine if functional therapy can enhance the response of patients who are non-responders to traditional pharmacological treatment: indeed, recent studies underlined that non-responders to psychopharmacological treatment become responders when they receive anti-inflammatory drugs (e.g. Kopschina Feltes et al., 2017; Petralia et al., 2020a; Petralia et al., 2020b).

Despite those limitations, our pilot study suggests that a structured program of FT, delivered in an individual

setting, may be effective in treating depression and its psychological and inflammatory correlates.

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