Research Protocol

Research Title:

Pain Acceptance Training in Patients Experiencing Emotional Distress and Somatic Symptoms: Examination of Dialectical Thinking as a Mediating Factor

Hebrew Title:

חשיבה דיאלקטית כמתווכת את יעילות אימון קבלה לכאב במטופלים עם מצוקה נפשית ותסמינים סומטיים

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STUDY SYNOPSIS

Somatic symptoms, including physical pain, are highly prevalent among mental health patients. Current treatments have limited effectiveness for these symptoms, primarily because of patients' diminished introspective capacity and lack of emotional awareness. The current study proposes pain acceptance training as a new intervention. This intervention relies on the tenets of dialectical thinking, particularly on maintaining a dialectic perspective – at once acknowledging both the desire to end the pain and the ability to accept it as it is. We aim to examine the following: (1) *the efficacy of pain acceptance training in the alleviation of somatic pain in patients with somatic symptoms; (2) the role of dialectical thinking as a mediator of pain acceptance training efficacy.*

LIST OF ABBREVIATIONS

DBT = Dialectical Behavior Therapy.

CPT = Cold Pressor Task.

STUDY AIMS

Somatic symptoms, including physical pain, are highly prevalent among mental health patients. Current treatments have limited effectiveness for these symptoms, primarily because of patients diminished introspective capacity and lack of emotional awareness. The current study proposes pain acceptance training as a new intervention. This intervention relies on the tenets of dialectical thinking, and particularly on maintaining a dialectic perspective – at once acknowledging both the desire to end the pain and the ability to accept it as it is. Our aims are to examine the following: (1) the efficacy of pain acceptance training in alleviation of somatic pain in patients with somatic symptoms; (2) the role of dialectical thinking as a mediator of pain acceptance training efficacy.

BACKGROUND

Somatic symptom disorders are among the most common mental disorders, with an estimated prevalence of 5-7% in the general population[1]. Somatic disorders are characterized by persistent, unexplained physical symptoms, such as pain and gastrointestinal and cardiovascular symptoms, which cause significant impairments to regular functioning and high burden due to multiple medical consultations[2,3]. A substantial proportion of patients also experience comorbid depression and anxiety[3,4,5].

Growing evidence indicates that specific maladaptive psychological factors (e.g., catastrophizing, emotion regulation problems, and negative physical self-concept) play a substantial role in causing and sustaining somatic symptoms[4,6]. Therefore, psychological treatments such as cognitive behavioral therapy are the first line of treatment[6]. Still, individuals with somatic symptoms exhibit limited responsiveness to conventional psychotherapeutic approaches[7].

To remedy this, one possible approach is Dialectical Behavior Therapy (DBT), which aims to enhance dialectical thinking, a cognitive process that involves the ability to hold and reconcile opposing ideas or viewpoints and reflect on them curiously[9,10]. Few studies have shown that increases in dialectical thinking during psychological treatment have positive effects on attention, coping flexibility, and self-processing[10] .

A limited number of studies have examined the effects of DBT treatment among patients with somatic symptoms. One initial study exploring the effects of DBT in individuals suffering from somatic symptoms reported reduced somatization in patients diagnosed with borderline disorder, through an increase in emotional acceptance[11].

Though promising, DBT is a long-term, in-person intervention that must be carried out by trained professionals and is, therefore, resource-intensive and inaccessible to many people. Therefore, we propose an alternative related intervention for individuals experiencing somatic symptoms, namely Pain-Acceptance Training. Similar to DBT, the Pain-Acceptance Training targets core mechanisms related to pain processing and modulation[12,13].

CURRENT INTERVENTION

Pain-acceptance training is based on dialectical thinking, particularly in maintaining a dialectic perspective, on the suffering caused by the pain - simultaneously wishing it to end and accepting it. Acceptance-based pain interventions attempt to teach patients to experience their emotions, pains, and bodily sensations more fully and without avoidance, and to notice fully the presence of thoughts without following, resisting, believing, or disbelieving them[12,13]. Accepting thoughts and feelings impedes the control these exert over behavioral tendencies and limits their impact on pursuing personal goals[14]. Thus, even though acceptance-based strategies do not aim at pain reduction, various studies have shown that these strategies can alter the pain experience and therefore may be considered regulation strategies[12,13]. This training method is also easily implemented, and can be imparted to participants both online and in person. Research shows that short trainings in pain acceptance regulation strategies increase pain tolerance, enhance recovery from pain, lower pain anxiety, distress ratings, and negative emotions related to pain, and facilitate better overall functioning despite the pain[12,13,15,16].

Prior Clinical Experience

In our recent randomized controlled single-session trial of pain-acceptance training that was conducted at the University of Haifa, healthy individuals showed reduced sensitivity to suprathreshold pain and reported an increase in pain threshold. This increase correlated with an increase in the vagal tone reactivity to pain, suggesting that the training modulates pain via the antinociceptive effect of the vagus nerve. Crucially and even more importantly, the reduction in pain sensitivity and increase in pain threshold were maintained for a month following the training, thus showing long long-lasting impact on pain perception. Furthermore, this training resulted in a decrease in pain catastrophizing levels one month later, suggesting that participants had better emotional capacities for dealing with pain[17].

RESEARCH OBJECTIVES & SIGNIFICANCE

As demonstrated, pain acceptance training showed promising results in altering the pain perception of healthy participants. The current study aims at translating these outcomes to a clinical setting; to examine a novel form of acceptance-training for pain relief in psychiatric patients suffering from somatic symptoms. We hypothesize that pain intensity, functional disability, and negative affect will decrease as a result of acceptance training, and that these changes will be mediated by an increase in patients' dialectical thinking abilities.

STUDY ENDPOINTS / OUTCOMES

To the best of our knowledge, this is the first study to examine pain acceptance training in psychiatric patients with somatic symptoms. To determine the efficacy of the training, we will utilize different pain outcome measures, and assess emotional and cognitive correlates of the change. As such, we believe this study will provide preliminary data that will serve as a basis for further randomized control trials examining the clinical implications of acceptance based training compared to other standard pain-treatment methods, and exploring the mechanisms underlying pain acceptance training for somatic symptoms relief.

Our primary training outcome measures will be pain-related, and will be conducted in three phases: Baseline, End of Intervention Assessments, and Follow-up Assessments. We expect that following two-week of acceptance training, patients will feel lower pain intensity and will show better abilities to cope with their pain. These improvements are expected to be maintained over time, and we will observe this in the follow up assessments.

These measures include pain intensity assessment, assessment of the degree of widespread body pain, pain catastrophizing levels and pain self-efficacy believes, as well as actual pain coping measurement of cold pain threshold, and cold pain tolerance.

The secondary training measures will include emotional state measures, dialectical thinking measures, and attention bias for pain. Demographic and medical records variables will serve as covariates for evaluating individual factors affecting training efficacy.

METHOD

Overall Design & Objectives

A prospective randomized two-arm controlled study assessing the effectiveness of-pain-acceptance training in patients experiencing emotional distress and somatic symptoms. The study will consist of one hundred patients suffering from significant pain symptoms (based on their medical records and verified based on self-report assessments) recruited from the Psychiatric Outpatient Clinic, the Psychiatric Day Care department, and the Pain Relief Clinic.

Study Population

Participants in the current study will consist of 100 individuals experiencing significant pain symptoms and emotional distress (based on their medical records and verified based on self-report assessments). Recruitment will take place at the Psychiatric Outpatient Clinic, the Psychiatric Day Care department, and the Pain Relief Clinic at Rambam Health Care Campus.

Eligibility Criteria:

A. Inclusion Criteria:

a. Men and Women
b. Aged 18-65
c. Able to provide a signed informed consent
d. Experiencing significant pain symptoms that interfere with daily-life functioning
e. Experiencing significant emotional distress symptoms

B. Exclusion Criteria: Patients under the age of 18 and/or diagnosed with one or more of the following diagnoses will be excluded from participation in the study:

a. Patients rating their average pain in the last week and in the last month as less than 3 in a 0-10 numerical rating scale (i.e. NPS)
b. Patients rating their emotional distress levels as less than 25 in a 10-50 numerical rating scale (i.e. Kessler Psychological Distress Scale [K10])
c. Patients diagnosed with psychotic disorders and/or suffering from psychotic symptoms.
d. Patients diagnosed with Autism Spectrum disorder.
e. Patients diagnosed with Intellectual disability.

f. Patients diagnosed with eating disorders.

g. Patients with Immediate suicidal risk.

h. Patients who initiated a new drug and/or psychotherapy treatment within the last month.

i. Pregnant women.

j. Patients currently serving in the IDF.

C. Early Discontinuation:

a. *Participant's Withdrawal*. Participants have the right to withdraw from the experiment at any time, for any reason, without facing any negative consequences. If a participant decides to discontinue their participation before the completion of the study, they are asked to inform the research team as soon as possible. The research team may conduct a follow-up assessment to gather information about the reasons for withdrawal and address any potential concerns or adverse events related to the intervention. When a participant withdraws from the experiment, they are compensated based on the parts they completed.

b. *Data collected before withdrawal*. The confidentiality of the participant's personal information will be maintained, even in the case of early discontinuation. Data collected up to the point of withdrawal will be retained and included in the analysis, ensuring that the information collected until that time contributes meaningfully to the study outcomes. The reasons for participant withdrawal will be documented in the final study report to ensure transparency and to provide a comprehensive understanding of the trial's outcomes.

D. Disqualification:

Partial Participation and Non-Response. Participants who will not finish the first assessment meeting and/or will not understand the acceptance training strategy at the first session will be disqualified from the experiment. In instances when a participant fails to respond to the online home questions on more than two occasions, the experimenter will reach out to the participant to understand any challenges they may be facing and provide necessary support. However, if a participant will not respond to the survey on more than four occasions, and they do not make an effort to follow the requirements correctly, they may be excluded from further participation. Furthermore, participants who do not complete the assessment video-call in the middle of the experiment, will be disqualified from the experiment. Disqualification criteria will be applied thoughtfully, and any instances of

partial participation or non-response will be transparently documented in the final study report. Participants will be notified about the conditions for exclusion at the beginning of the experiment to ensure clear understanding, and they will be strongly encouraged to engage seriously with the requirements of the experiment.

Study Procedure

Potential candidates suffering from significant pain symptoms will be located by the clinical staff at the Psychiatric Outpatient Clinic, the Psychiatric Day Care department, and the Pain Relief Clinic and will be referred to the research staff for a comprehensive explanation of the study goals and procedure. Those who will agree, and sign the informed consent form, will be regarded as participants.

Participants will then undergo a screening procedure that will include two stages:

(1) Assessment of psychological distress levels (via the Kessler Psychological Distress Scale [K10]; Kessler et al., 2003). A cut-off score of ≥ 25 will be utilized, indicative of moderate-to-severe distress levels. Participants scoring < 25 will be considered "disqualified" and will not proceed to the second stage.

(2) Assessment of clinical diagnosis using The Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND). This screening procedure will be delivered by an online meeting.

Those who will meet the study's criteria will undergo a battery of baseline assessments that will occur at either Rambam Hospital or the Cognition Emotion Interaction Lab at the University of Haifa – according to the participant's choice. The baseline assessments will include: (i) Completion of a battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, and dialectical thinking; (ii) Performing a short computerized cognitive task, measuring attention bias toward pain; (iii) Cold pressure task, to measure their cold pain threshold and cold pain tolerance. The CPT test is an internationally accepted test for pain assessment. The physical stimulation is in the range between pain threshold and personal endurance, so that the participant controls the duration of the stimulation and can stop it at any moment according to his will and there is no risk of harm.

Following the assessment, participants will be randomly assigned to one of the study groups: pain-acceptance intervention group (*n=50*) or treatment-as-usual group (*n=50*). The procedure of the pain-acceptance group is detailed bellow, in the 'Intervention Procedure' section. At the end of the treatment phase (i.e., 2 weeks), participants in both groups will undergo a second session of assessments, in the same location as the first assessment meeting (i.e. either in Rambam

Hospital or in the Cognition Emotion Interaction lab at the University of Haifa). This session will include: (i) Completion of a battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, and dialectical thinking; (ii) Performing a short computerized cognitive task, measuring attention bias toward pain; (iii) Cold pressure task, to measure their cold pain threshold and cold pain tolerance. At the end of this assessment session, participants from the 'treatment as usual' group will then be offered to receive the pain-acceptance treatment.

After 2 weeks from the end of intervention assessment session, participants will undergo a "follow-up" phase. As part of this phase, participants will be asked to complete a battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, and dialectical thinking. These questionnaires will be delivered online, and participants will receive a secure link via email to access and complete them remotely.

All the assessments, including the cognitive and the cold pressure tasks, will be conducted by a trained research assistant, Ph.D. or M.A. level student, from the Cognition Emotion Interaction (CEI) Lab, Psychology Department, and the Sensory Neuroscience and Pain Laboratory, Physical Therapy Department, at the University of Haifa. Furthermore, clinical data, such as diagnosis, time from first diagnosis, medications, targeted interventions for pain management, and participation in psychological treatment, will be retrieved from the medical records. All data will be collected and stored in a coded manner. No personal information will be used. For further details, please refer to the "Ethical Issues" section.

For participating in the study, participants will be remunerated with monetary compensation as follows: 100 NIS for participation in the first assessment session; 100 NIS for the daily online questionnaire (except for drop-out participants due to low adherence to the daily assessments); 20NIS for the online 15-minute video call in the middle of the training week; and 130 NIS for completing the end of intervention assessment session; 50 NIS for completing the follow-up phase. Taken together, for completing all parts of the experiment, participants will be remunerated with monetary compensation of 400 NIS, which will be funded by Prof. Irit Weissman-Fogel from Haifa University.

Intervention Procedure

Participants in the pain-acceptance group will undergo a two-week training in the pain-acceptance strategy. At the end of the first session, participants will receive a 40-minute explanation about the pain-acceptance emotion regulation strategy and will practice it with the experimenter.

The practice will start with a short conversation and inquiry about the participant's pain while continuously validating his experience and creating a shared understanding of their struggles and difficulties due to the pain. Next, the experimenter will explain the relations between distress, pain and suffering, emphasizing that in many cases trying to control our pain, emotions and thoughts leads us to undesirable results through emotional avoidance, anger and escape. This explanation will be accompanied with commonly used metaphors to enhance participants' understanding. Afterwards, participants will be familiarized with the strategy of "emotional acceptance of pain". The strategy will be comprehensively explained and participants will practice it with the experimenter twice: Firstly, by practicing with the mental exercise of "STOP" (i.e. acronyms representing **S**top, **T**ake a step back, **O**bserve, **P**rocced Mindfully); Secondly participants will be asked to immersing their dominant hand again into a bucket containing cold water, and will practice, together with the guidance of experimenter, the pain acceptance strategy while feeling moderate pain. After each practice, participants will discuss their experience with the experimenter.

Finally, in the last part of the intervention, they will be introduced to the two weeks at-home training. Participants will be asked to think of the pain acceptance training and use it for a few minutes every time they feel pain. Every time they use the pain strategy, they are asked to report it by clicking on the "Now" button found in the link that will be accessible to them through their mobile phones.

During the two-week at-home training period (including Fridays and Saturdays, unless they observe Shabbat and request an exemption), a brief online survey will be send to the participants daily in the evening via text massage. The survey will include questions about pain severity, functional disability in the past day, the frequency of using pain acceptance training in the past day, and its perceived ease. If difficulties arise in the use of the therapeutic strategy, the experimenter will contact the patient via a phone call, and will explain how the training should be carried out with the learned acceptance strategy once more. Additionally, at the end of the first week of the training, the experimenter will conduct a short 15-minute video call with the patient, to discuss the progress and the difficulties that arise in using the acceptance training.

At the end of the at-home training, participants will be asked to arrive at Rambam Hospital for the second session of the assessments (i.e., the Follow-Up assessment), which will include completing the same questionnaire battery, perform the short computerized cognitive task, and undergo the cold pressure task as in the first session.

Two weeks after the end of intervention assessment session, participants will be asked to complete the same battery of questionnaires as administered in the previous assessment session. This follow-up assessment will be conducted online.

Treatment as usual group

Participants in the 'treatment as usual' group will be also complete the daily online evaluations during two weeks. During this period (including Fridays and Saturdays, unless participants observe Shabbat and request an exemption), starting on the day after the initial assessment, a brief online survey will be sent to the participants daily in the evening via text massage. The survey will include questions about pain severity and functional disability in the previous day.

Additionally, at the end of the first week of the experiment, the experimenter will conduct a brief 15-minute video call with the participant. During this call, they will discuss the previous week and the participant's progress with the daily assessments. At the end of the at-home two-week pain evaluation, participants will be asked to arrive at Rambam Hospital for the end of intervention session of the assessments (i.e., the Follow-Up assessment). At the end of this assessment session, participants from this group will then be offered to receive the pain-acceptance treatment.

Two weeks after the end of intervention assessment session, participants will receive a link to complete online the same battery of questionnaires as administered in the previous session.

Detailed overall procedure

The overall procedure will include the following stages:

A. Screening

Participants will undergo an initial assessment of the study's criteria, including pain levels, pregnancy, initiation of a pharmacological and/or psychotherapy treatment, and psychological distress levels. Participants scoring ≥ 25 on the K10 psychological distress scale will be considered as likely to have moderate-severe distress levels, and will proceed to the subsequent screening stage. Next, participants will undergo clinical diagnosis using the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND) (i.e. a new semi-structured interview that targets the diagnostic criteria for a range of DSM-5 disorders, with additional clinical information) that will be performed by a clinician or a trained mental health professional from the research team. Those who will meet the study criteria (detailed in the

'Inclusion' & 'Exclusion' sections), will be regarded as 'Participant' and will be asked to complete the baseline evaluation.

B. Baseline Assessments

All participants who meet the study criteria will complete a battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, and dialectical thinking. Then, they will be asked to perform a short computerized cognitive task, measuring attention bias toward pain. Afterward, participants will complete the cold pressure task, to measure their cold pain threshold and cold pain tolerance.

C. Weekly Assessments

Participants allocated to the pain-acceptance group will be asked to complete a few questions assessing pain severity and functional disability, as well as their training experience and verify compliance with the training. The online questions will be sent to participants' phones daily (including Fridays and Saturdays, unless participants observe Shabbat and request an exemption) at the evening during the training weeks by a text message (see Appendix 11). In case participants report challenges in implementing the intervention routinely, the research staff will contact the patient via a phone call, and will explain once again how the training should be carried out with the learned acceptance strategy. Furthermore, in the middle of the training period, the participant will meet with the experimenter for a 15-minutes video-call meeting, in which the experimenter will explain the acceptance training again, verify compliance with the training and answer further questions aroused during the training period.

D. End of Intervention Assessments

At the end of the two-week at-home training, all participants (i.e. both from the treatment as usual and the active groups) will be asked to arrive at Rambam Hospital for the end of intervention assessment. The assessment will include performing the short computerized cognitive task measuring attention bias toward pain, followed by a second battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, dialectical thinking, and a brief questionnaire regarding their experiences in the experiment. Last, participants will complete the cold pressure task, to measure their cold pain threshold and cold pain tolerance.

E. Follow-Up Assessments

Two weeks after the end of interventionassessment session, participants from both of the groups will undergo an online follow up assessment. The assessment will include battery of questionnaires measuring pain severity, bodily dispersion of pain, somatization, pain catastrophizing, psychological symptoms, dialectical thinking, and a brief questionnaire regarding their experiences in the experiment (the same questionnaires as in the End Of Intervention Assessment). The questionnaires will be delivered online, and participants will receive a secure link via email to access and complete them remotely.

Experiment Timeline

Measures:

1. **Demographic**

The demographic questionnaire was constructed for the present study and covers inquiries about the date of birth, gender, religion, level of religiosity, marital status, number of children, economic status, years of education, medications, current treatments, and chronic disease diagnoses.

2. **Clinical Evaluations**

a) Kessler Psychological Distress Scale [K10] is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4-week period. Scores range from 10 to 50 as follows: 1) scores under 20 are likely to be well; 2) scores 20-24 are likely to have a mild disorder; 3) scores 25-29 are likely to have moderate disorder; and 4) score 30 and over are likely to have a severe disorder.

b) ***The Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND).*** The DIAMOND (Tolin et al., 2016) is a new semi-structured interview that targets the diagnostic criteria for a range of DSM-5 disorders, with additional clinical information gathered for anxiety, mood, and obsessive-compulsive and related disorders. The administration time of the DIAMOND is approximately 1 hour, making it feasible for use in research, clinical, and training settings. DIAMOND diagnoses show very good to excellent interrater reliability, and good to excellent test–retest reliability using cutoff criteria from the DSM-5 field trials (Clarke et al., 2013; Kraemer et al., 2012). Test–retest reliability of DIAMOND diagnoses ranges from good to excellent, and convergent validity was established (Tolin et al., 2018).

3. Self-Reported Questionnaires

a) Michigan Body Map. A self-report measure assesses body areas where chronic pain is experienced and specifically quantifies the degree of widespread body pain when assessing for centralized pain features[20]. See Appendix 1.

b) Pain catastrophizing scale (PCS). The PCS contains 13 items that measure catastrophic thoughts about pain in both clinical and non-clinical samples. Participants reflect on past painful experiences and indicate on a 5-point scale ranging from zero (“not at all”) to four (“always”) the degree to which they experience each of the 13 thoughts or feelings during the experience of a pain (i.e. “When I'm in pain it's terrible and I think it's never going to get any better”). Research has shown that the PCS is valid and reliable[21]. See Appendix 2.

c) Brief pain inventory - short form (BPI-SF). The BPI-SF is a well-validated, widely used, and frequently recommended instrument that measures pain severity and pain-related interference for patients with chronic pain conditions. BPI-SF evaluates pain severity at its worst, least, and average during the previous week, as well as current pain level, with 0 representing no pain and 10 the worst pain imaginable. Seven items measuring interference with daily functioning (general activity, walking, work, mood, relations with others, sleep, and enjoyment of life) are also assessed on an 11-point scale, where 0 represents no interference and 10 complete interference. The scores can be averaged to the two components of the BPI-SF score, the Pain Severity Index and the Pain Interference Index. Both BPI scales show responsivity in detecting and reflecting improvement in pain over time. See Appendix 3.

d) Pain self-efficacy questionnaire (PSEQ). The PSEQ assesses the strength of a person’s confidence in their ability to function, despite their pain. Patients are asked to rate how

confident they are so that they can do each of the 10 activities or functions at present, despite their pain, by selecting a number on a seven-point scale, where zero equals 'not at all confident' and six equals 'completely confident'. Scores on the PSEQ may range from 0 to 60, with higher scores indicating stronger self-efficacy beliefs. Good reliability and validity of the PSEQ has been reported. The test–retest reliability and internal consistency of the PSEQ in two different studies with chronic pain patients were reported as 0.79 and 0.92, respectively. See Appendix 4.

e) **The Generalized Anxiety Disorder 7-Item Scale (GAD-7).** A self-report questionnaire with 7 items describing anxiety symptoms. In this questionnaire, the participant is asked to describe how well each statement describes his situation in the past two weeks, on a 4-point Likert scale (0 - not at all, 3 - almost every day). The questionnaire is acceptable for use for research and clinical purposes to detect anxiety symptoms in general, and general anxiety symptoms in particular, both in the general population and in clinical populations. The questionnaire has good psychometric properties including high internal reliability (Cronbach's alpha index = 0.89), and high validity indices. See Appendix 5.

f) **Patient Health Questionnaire-9 (PHQ-9).** A self-report questionnaire for adults, the purpose of which is to examine the presence and severity of clinical depression[23]. The questionnaire includes 9 items that are a list of major depressive symptoms, according to the DSM. For each item, the examinee is asked to estimate how often he was bothered by the statement described in the item during the last two weeks, on a 4-point Likert scale of 3 (0 - not at all, 3 - almost every day). In addition, the examinee was asked how much the problems he reported made it difficult for him to do his job, take care of things at home or get along with others. This last item is important and significant to assess the degree of distress caused to a person by his symptoms, and the score in it is closely related to the degree of the person's quality of life. This questionnaire is frequently used, and has good psychometric data (reliability, internal consistency, Cronbach's alpha ranges from 0.86 to 0.89), and the construct and convergent validity indices are reported to be high. See Appendix 6.

g) **Acceptance and Action Questionnaire (AAQ-II).** The measure most commonly used to assess psychological inflexibility, particularly in the context of Acceptance and commitment therapy research, is the Acceptance and Action Questionnaire – II (AAQ-II)[25]. The AAQ-II has been used across nonclinical and clinical samples. The AAQ-II demonstrated factor structure stability, internal consistency, test-retest reliability and discriminant validity. The AAQ-II appears to measure a unidimensional factor across

varied samples, consistent with theory that suggests psychological inflexibility functions as a coherent construct. In addition, as predicted, the AAQ-II was associated with higher levels of depression, anxiety, stress, and overall psychological distress. See Appendix 7.

h) **The Dichotomous Thinking Inventory (DTI).** The Dichotomous Thinking Inventory (DTI) is a self-report measure used to assess a black-and-white cognitive thinking style or worldview[26]. The questionnaire assesses an individual's dichotomous thinking style in a general setting by measuring the degree of positive view of dichotomy, such as dichotomous thinking being better than other thinking styles and dichotomy being consequent, deserved, and worthy. The DTI has 15 items scored on a 6-point scale ranging from 1 = disagree strongly to 6 = agree strongly. The DTI has 3 components: preference for dichotomy, dichotomous beliefs, and profit-and-loss thinking. See Appendix 8.

i) **The Dialectical Self Scale (DSS).** The Dialectical Self-Esteem Scale (DSS) is a validated and reliable measure that assesses dialectical self-esteem as related to self-perception[27]. The DSS is a 32-item instrument using a 7-point Likert scale ranging from strongly disagree to strongly agree to measure the perception of dialecticism. Sixteen items describe scenarios that are inconsistent with naive dialecticism which are reverse-scored to determine a dialectical self-esteem rating, with high scores representing greater degrees of dialecticism (i.e. individuals who are "more dialectically oriented"). See Appendix 9.

j) **Patient's global impression of change (PGIC) scale.** Patients rate their improvement on a seven-point scale, where 0 equals "very much worse" and 6 equals "very much improved". This scale will be asked only in the last session, at the end of the intervention period. Patients themselves make a subjective judgment about the meaning of the change to them following treatment, this scale is often taken as the external criterion or "gold standard" of clinically important change. However, this method, by itself, does not indicate what has improved. See Appendix 10.

4. Tasks / Tests

a) Perception Load (PL). Patients will perform a computerized version of the emotional modification of the perceptual load paradigm[17,18,19]. In this task, participants are required to indicate whether a target letter (X or N) appears on the screen, by responding to the corresponding letter on the keyboard. The task contains two perceptual load conditions, low and high, which are determined by the number of distracting letters appearing alongside the target letter. In the low load condition, one distracting letter appears on the screen alongside the target letter, whereas in the high load condition, four distracting letters appear on the screen together with the target letter

(see figure 2). The distracting letters are chosen randomly from the letters K, H, V, Z, or W. The target and distracting letters will appear randomly in six possible locations that create an imaginary circle at the center of the screen. The distracting pictures can be either neutral or pain-related one.

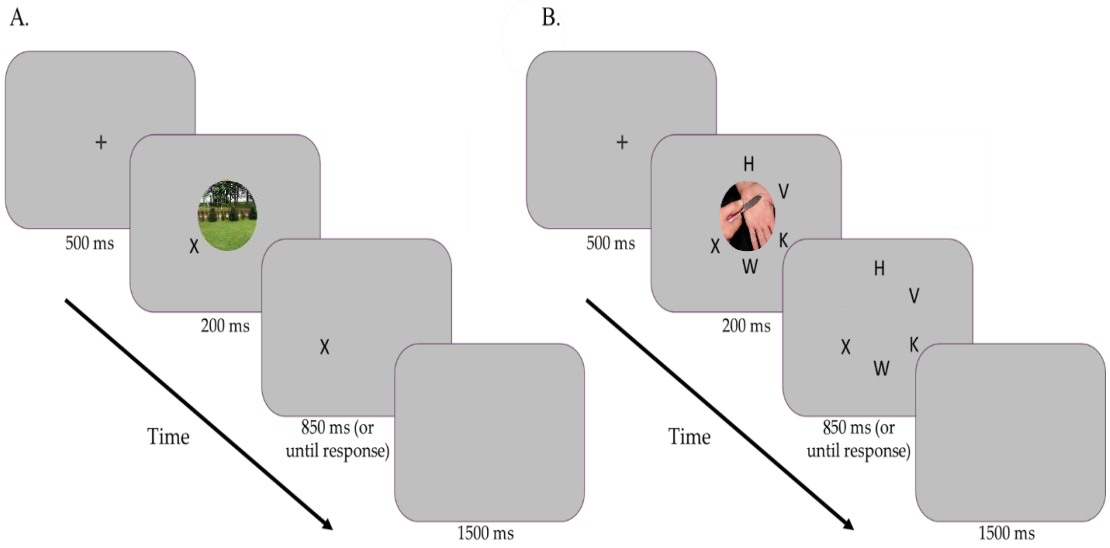

Figure 2. Examples of typical trials of the perceptual load task. A) Low load condition of the task. In the low load condition, one letter appears on the screen, and the participant needs to indicate whether it is one of two letters (either X or N). In this example, the distracting picture is neutral. ***B)*** High load condition of the task. In the high load condition, five letters appear on the screen, and the participant needs to indicate whether one target letter (either X or N) appears on the screen. In this example, the distracting picture is pain-related.

b) Cold Pressor Task (CPT). Pain will be induced with the cold pressor task (CPT). The cold pressor task consists tub containing cold water. Water's temperature will be kept at 10-12°C, to create a moderate pain sensation. This is a usual temperature range when studying pain, and based on our vast experience with this task it appropriate for the present experiment. The tub will be filled with water, and two ice bottles will be inserted in the sides of the tank to cool the water to the desired temperature. Water temperature will be assessed by a thermometer before the beginning of the session, as well as just before hand immersion to verify the stability of the temperature.

It is important to note that the CPT test is an internationally accepted test for pain assessment, and is a measure commonly used in Prof. Weissman-Fogel experiments. This task in delivered by trained experimenters and the physical stimulation is in the range between pain threshold and personal endurance, so that the participant controls the duration of the stimulation and can stop it at any moment according to his will, thus there is no risk of harm.

Participants will be seated in a chair adjacent to the container and asked to immerse their non-dominant hand into the tab for as long as they feel able to do so. Maximum duration of immersion will be five minutes. Based on our previous experience with the task, the mean immersion duration is expected to be ~20-30 seconds. The two primary outcome measures will be taken during the cold pressor task. The first will be *pain threshold*, which indicates the number of seconds from immersion in the tub that the participant first reported feeling pain. Threshold is a behavioral index of hypervigilance towards the pain experienced in the cold pressure. As such, conceptually it is the most likely to be affected by acceptance training. The second outcome measure will be *pain tolerance*, which indicates the number of seconds from immersion in the tank that the participant can tolerate the pain. As in the acceptance training participants learn and practice to accept without judging or reacting to their pain sensations and to recognize that its presence is only temporary and will soon pass, we hypothesize that the patients in the active training will be able to tolerate the cold pain for longer durations of time.

5. Clinical data

The following clinical data will be retrieved from the medical records: Listed diagnosis, time from first diagnosis, medications, targeted interventions for pain management, and participation in psychological treatment.

Safety Measures

Participants will be encouraged to report any unexpected events or concerns to the research team as soon as possible. The team will conduct a thorough assessment, providing appropriate support, and, if necessary, adjusting the intervention or involving additional healthcare professionals. The safety and well-being of participants remain our utmost priority, and every effort will be made to respond to unexpected events in a timely, ethical, and responsible manner.

Analyses

A. Calculating Sample Size:

The sample size for the current research was calculated based on our previous study examining the efficacy of acceptance training for altering pain in healthy individuals. In this study, we examined the immediate and long-term effects of a single session of acceptance training on pain perception. In a sample of 40 healthy females who completed the training, we found some

immediate pain reduction gains, and that these effects were maintained for one month after, and even increased with time. Hence, we elected to employ similar sample size for the current experiment, comprising 50 participants in both the acceptance intervention and treatment as usual groups, as it appears appropriate for discerning the anticipated pain reduction effects. Nevertheless, we chose to extend the training duration in the current experiment to amplify the assimilation and utilization of the acceptance coping strategy.

B. Change in Outcome measures:

Planned analysis:

Primary and secondary outcome analysis. To evaluate training efficacy, we will examine whether the training affected the primary outcome measures of pain sensitivity. Therefore, we will compare the pre-post difference on each measure between the active training group and treatment as usual by using repeated measures ANOVA analysis. Then, to evaluate the behavioral, affective and cognitive effects of the acceptance training, we will use the same analysis method to examine whether the training affected the secondary training outcomes (i.e., emotional state measures, attention bias toward pain-related information, and dialectical thinking).

Mediation analysis. Next, we will examine whether the changes in pain and mood following the acceptance are mediated by an increase in patients' dialectical thinking abilities. For this aim, we will conduct a multilevel mediation analysis in R.

Regression analysis. To examine which individual differences contribute to the acceptance training efficacy, we will conduct stepwise regression analyses between the primary pain outcomes and the demographic and trait self-report variables. In addition, for comprehensiveness, we will explore the correlation matrix between all the measures taken in this study. Furthermore, additional exploratory analyses will be conducted between the individual variables and the secondary training outcomes.

Trajectories of change in pain following the acceptance training. In a further analysis, we will analyze the patterns of change following the use of the acceptance coping strategy. For this aim, we will analyze the daily data gathered from participants during the training phase, to examine whether changes in acceptance abilities predict subsequent changes in pain intensity, pain disability, and mood. These analyses will be conducted by using linear mixed model analyses.

All data analyses for this study will use IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, United States) and R Statistical Software (v4.1.2; R Core Team 2021).

PESONNEL TRAINING

The research team will undergo comprehensive training to ensure precise and consistent administration of the DIAMOND interview, tasks, and questionnaires at the initiation of the experiment. Additionally, the team will engage in practice sessions to proficiently convey explanations related to the pain-acceptance training, with a focus on clarifying and refining instructions during training. Furthermore, the research team will be equipped with training to adeptly address patients' needs and handle any challenges that may arise throughout the study.

ETHICAL ISSUES

Participants will be allowed to withdraw or discontinue their participation in the study at any time. Early discontinuation will not affect the participant's existing medical care or relationship with their healthcare provider.

To guarantee the anonymity and confidentiality of all participants across both study groups, each of them will be coded in the following way:

1. The pain-acceptance intervention group will be identified by the code “P”, followed by sequential numbers representing the number of participants (i.e., P1-P50)
2. The ‘treatment as usual’ group will be identified by the code “C”, followed by sequential numbers representing the number of participants (i.e., C1-C50)

All participant data will be exclusively recorded and stored in the database using this coding system. First names, IDs, and other personal identifiers that will be obtained in this study will be kept confidential and separate from the identifying details of the patients. Only the PI and Sub-PIs will have access to this information.

All questionnaire data will be collected through Qualtrics, a secure platform with a username and password. The questionnaire will be sent to the patient's phone number and will have a unique link that identifies him with his subject number.

Participation payment will follow the rules of the Rambam Hospital for paying research participation.

The cold stimuli employed for assessing patients' pain threshold and tolerance in the current experiment (i.e., the CPT task) are controlled and widely utilized in laboratories globally, including Prof. Irit Weissman-Fogel's laboratory. These stimuli fall within the range of pain threshold to moderate intensity, ensuring they pose no risk of harm. Participants retain the autonomy to cease the cold stimulation at any point during the experiment.

If abnormal findings indicative of any psychiatric state or suicidal risk emerge during the Diagnostic Interview for Anxiety, Mood, OCD and Related Neuropsychiatric Disorders

(DIAMOND), participants will be immediately referred to the PI, a qualified psychiatrist, for further examination.

Finally, during the two weeks of the training, patients will be able to contact the PI in case of exacerbation of pain. Moreover, during the training period, patients are asked to complete 5-times weekly questions. Thus, in case participants report difficulties or exacerbation of pain, they will be contacted by the research team.

Research protocol number: 0062-24

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