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Personalized cognitive training: Protocol for individual-level meta-analysis implementing machine learning methods

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ABSTRACT

Accumulating evidence suggests that cognitive training may enhance well-being. Yet, mixed findings imply that individual differences and training characteristics may interact to moderate training efficacy. To investigate this possibility, the current paper describes a protocol for a data-driven individual-level meta-analysis study aimed at developing personalized cognitive training. To facilitate comprehensive analysis, this protocol proposes criteria for data search, selection and pre-processing along with the rationale for each decision. Twenty-two cognitive training datasets comprising 1544 participants were collected. The datasets incorporated diverse training methods, all aimed at improving well-being. These training regimes differed in training characteristics such as targeted domain (e.g., working memory, attentional bias, interpretation bias, inhibitory control) and training duration, while participants differed in diagnostic status, age and sex. The planned analyses incorporate machine learning algorithms designed to identify which individuals will be most responsive to cognitive training in general and to discern which methods may be a better fit for certain individuals.

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1. Background

Cognitive training comprises a class of relatively new therapeutic interventions that target mechanisms implicated across different mental health conditions. Cognitive training programs are designed to enhance emotional functioning, either directly by cultivating different strategies for emotional processing and/or responses or indirectly by bolstering cognitive control processes in a non-emotional context, which in turn should improve emotional functioning (Cohen and Ochsner, 2018). Extensive research indicates that cognitive enhancement methods have the potential to promote well-being and emotional functioning (Au et al., 2015; Cohen et al., 2016; Koster et al., 2017; Linetzky et al., 2015). Nevertheless, questions remain regarding the efficacy and generalizability of these methods (Cristea et al., 2015; Hallion and Ruscio, 2011; Melby-Lervag et al., 2016; Schwaighofer et al., 2015).

Inconsistent outcomes that have arisen across the field of cognitive training may result from individual differences in response to training (Shani et al., 2019). Previous studies suggest that certain subgroups may benefit more from cognitive training than others (Dolcos et al., 2020; Menne-Lothmann et al., 2014; Studer-Luethi et al., 2012). For instance, in a patient-level meta-analysis conducted by Price et al. (2016), socially anxious young adults (37 years of age and younger) benefitted more from cognitive training in which participants were trained to focus their attention away from threatening stimuli than did older adults. Moreover, cognitive training characteristics may also affect training efficacy. For example, longer cognitive training duration may lead to enhanced efficacy (Schwaighofer et al., 2015). Yet few investigations have examined possible moderators associated with individual differences in training outcomes.

Furthermore, researchers have begun to acknowledge the need to complement traditional theory-driven analyses with data-driven techniques. Traditional approaches in the field of cognitive training usually test the effect of one predictor at a time on training efficacy (e.g., training duration) or the differential effects of training efficacy (e.g., comparing training and control groups). These approaches can lead to erroneous conclusions due to multiple comparisons (inflated type I errors), model misspecification, and multicollinearity. Findings may also be affected by publication bias, because statistically significant predictors have a better chance of being published. Machine learning approaches have been instrumental in identifying predictors and moderators, whereas traditional methods have yielded few consistent findings (e.g., Cohen and DeRubeis, 2018; Zilcha-Mano et al., 2018). Therefore, machine learning methods can evaluate the contributions of multiple predictor variables and their interactions while facilitating the identification of baseline predictors of enhanced training outcomes with maximum optimization.

In this study, we seek to identify factors that influence the effects of cognitive training by applying machine learning methods to data from previous trials to answer two questions: (1) What are the characteristics of individuals who benefit from cognitive training? (2) Which subgroups benefit more from certain types of training (e.g., working memory training, interpretation bias modification)?

We detail the decisions behind data collection, processing and planned analysis. To the best of our knowledge, this study is among the first comprehensive investigations aimed at increasing well-being by comparing training programs with the goal of tailoring cognitive training on the basis of individual characteristics (i.e., demographic information and clinical status). To achieve comparability between training programs and promote personalized cognitive training, we outline several considerations for subsequent investigations.

2. Method

A large and varied dataset consisting of individual-level data can be analyzed by data-driven methods (e.g., machine learning). Thus, we sought to compile a dataset that includes information from as many participants as possible, presenting with different mental conditions and demographic backgrounds and based on several distinct cognitive training regimes (i.e., type of training, session duration, number of sessions).

Publication search. A comprehensive PubMed literature search was conducted by entering the following keywords: cognitive training, brain training, cognitive remediation, cognitive rehabilitation, cognitive enhancement, cognitive bias modification, attention bias modification, attention training, bias training, interpretation bias modification, working memory training, working memory modification, executive function training, and executive function modification. These keywords were chosen based on a review of the keywords used in published cognitive training meta-analyses (Cristea et al., 2015; Lampit et al., 2014; Motter et al., 2016). The goal was to incorporate data from different types of training (e.g., working memory training, attention bias modification) while decreasing the odds of overlooking relevant studies. The following filters were applied in the search: papers published in the past five years (2013–2018), human subjects, papers published in English, adult participants (18–65).

All papers generated by this search (N = 574) were thoroughly reviewed as follows: All the abstracts were initially reviewed by a PhD student with relevant experience and cognitive training expertise. The principal investigator resolved and clarified any ambiguity raised by the student. Then, the PhD student and two research assistants conducted a double screening of those papers that passed the initial screening. Specifically, each paper was reviewed by the one PhD student and one research assistant (i.e., a BA student with relevant expertise in cognitive training research). Again, in cases of discrepancy, the PhD student consulted with the principal investigator in reaching a decision.

Inclusion-exclusion criteria. The following inclusion criteria were used: (1) **population**: Only studies that focused on healthy, sub-clinical or anxious and depressed adults between the ages of 18 and 65 were included. We excluded studies on people with neurological conditions (e.g., stroke, mild cognitive impairment, dementia, brain injury), psychosis, and substance abuse (e.g., smoking, alcohol, drugs). (2) **Intervention**: We included studies targeting specific cognitive domains (e.g., attention, working memory) and excluded studies that were not purely aimed at training cognitive functions, such as meditation, psychotherapy, and/or interpersonal training. (3) **Pre-post assessment**: Included studies that used validated questionnaires assessing emotional/mental health/well-being as outcome measures (e.g., questionnaires measuring mood, anxiety, quality of life, emotion regulation). Studies that solely relied on participants' performance on cognitive tasks as outcome measures were excluded, since it was decided that the large diversity of these measures undermines their comparability. Finally, the main outcome measures had to have published healthy population norms.

The primary investigators then contacted the corresponding authors of the qualifying published studies (N = 39) via email. These authors were asked to collaborate by providing individual-level datasets stripped of identifying characteristics. The primary investigators also invited leading researchers in the cognitive training field to contribute qualifying datasets.

This process concluded in 26 datasets from labs around the globe, including individual-level data from 1942 participants. Four datasets were excluded from the analysis: (1) Two of these datasets employed a training regime that integrated more than one task and targeted more than one cognitive process. Including such training regimes in analysis could compromise the effort to distinguish the effectiveness of different types of training (Bomyea et al., 2015; Damholdt et al., 2016). (2) To avoid a confound between certain subpopulations and a specific study, at least two datasets for each sub-population were required (e.g., depressed, healthy) (Badura-Brack et al., 2015; Swainston and Derakshan, 2018). Accordingly, studies that did not meet requirement were excluded (For further details on excluded studies see Appendix C). Consequently, analysis would involve 22 datasets consisting of individualized data from 1544 participants (Beevers et al., 2015; Bunnell et al., 2013; Clerkin et al., 2015; Cohen et al., 2015; Cohen and Mor, 2018; Course-Choi et al., 2017; Daches and Mor, 2014; Daches et al., 2015; Ducrocq et al., 2016; Ducrocq et al., 2017; Enock et al., 2014; Hotton et al., 2018; Kuckertz et al., 2014; Lee et al., 2015; McNally et al., 2013; Owens et al., 2013; Rohrbacher et al., 2014; Sari et al., 2016; Williams et al., 2013; Williams et al., 2015; Yang et al., 2015). Appendix A summarizes the details of the included studies and Fig. 1 summarizes the data search and collection process.

Outcome measures. Because main outcomes must be determined before analysis, the following guidelines were formulated to direct the authors in designating one main outcome measure for each included study: (1) The variable must be a specific score on a standardized questionnaire related to mental health/emotions/well-being and have healthy population norms (for comparability purposes). (2) This variable should match the investigators' initial focus in their published paper. In some cases, however, this was not possible for various reasons (e.g., the researchers based their main outcome investigation on variables that were measured through performance on computerized cognitive tasks and did not administer a standardized self-report questionnaire measuring their defined main outcome). In these cases, symptomatic levels that characterized the investigated population served as the outcome measure. For example, if a study examined the effect of training on individuals diagnosed with social anxiety, the score on a social anxiety questionnaire was chosen as the dependent variable. When a study included more than one questionnaire assessing the same construct, we selected the one most common in the sample of collected studies as the main outcome measure.

Secondary outcomes. These variables include all other standardized questionnaire scores that were measured before and after the training but were not defined as the primary outcome measure. They will be added to a secondary analysis following the main analysis.

Potential moderators. All participating studies included data on the participant's age and gender, allowing us to study the influence of these variables at baseline. Only some studies collected additional demographic information, such as education level, marital status, and ethnicity, so it was impossible to include these important variables in the

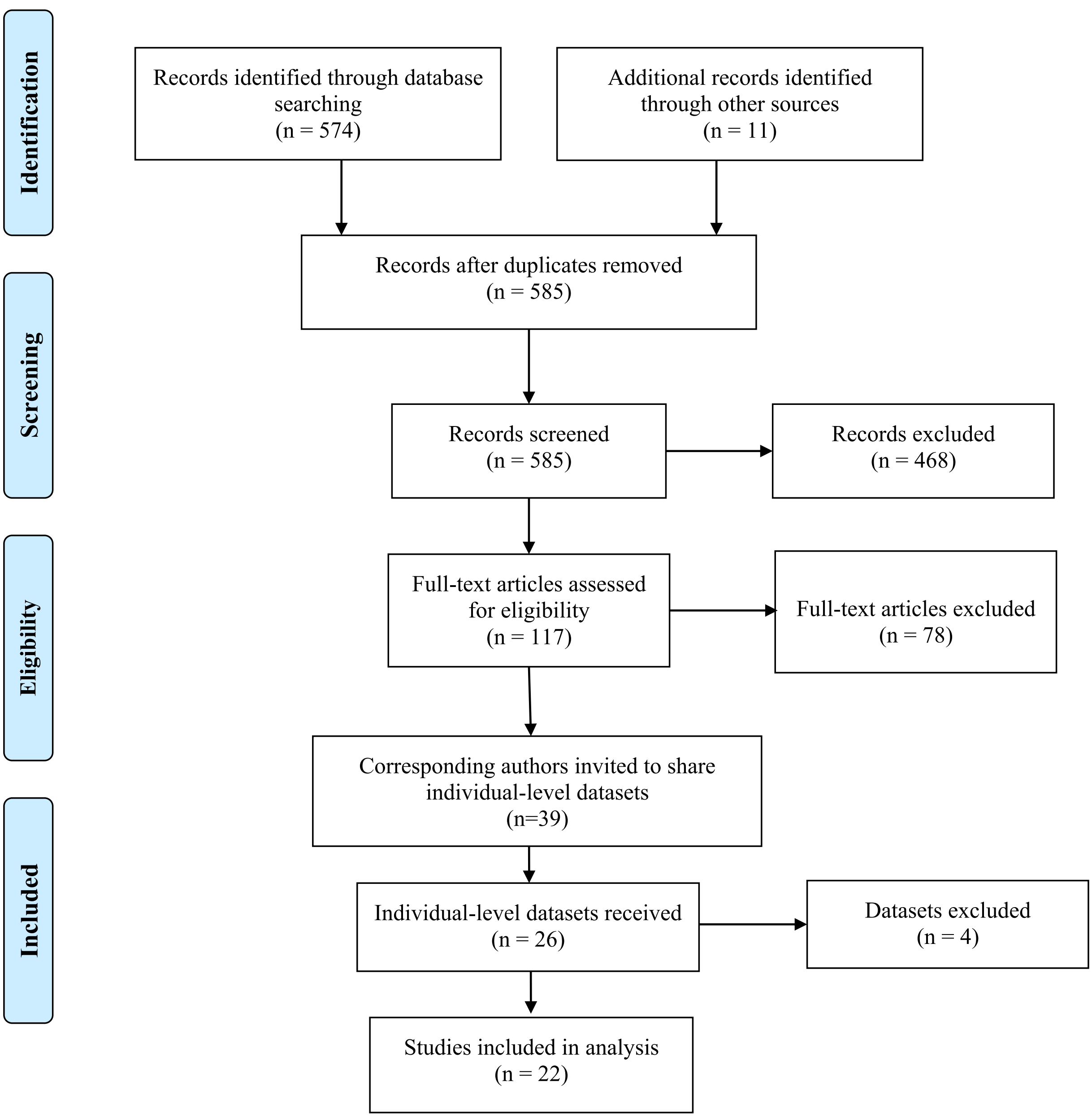

Fig. 1. Flow diagram: data search and collection.

analysis. Furthermore, the following variables were added to the original datasets based on the characteristics of each study: geographical region where the study was conducted, clinical status of participants (i.e., diagnosis, if applicable), and diagnostic method (i.e., clinical or non-clinical assessment of mental condition). For a list of each study's potential moderators, see Appendix A.

Geographical region variable: The included studies were conducted in various countries around the world: United Kingdom, United States, Israel, China, Belgium, Sweden, Australia, Denmark, and Germany. To confirm with the planned analysis methods, we had to consolidate these nine countries into a dichotomous variable. Based on the results and discussion of the meta-analysis by Au et al. (2015), we chose to divide the countries into US and international.

Clinical status variable: Included studies involved participants diagnosed with depression, dysphoria, rumination, anxiety, high worry, social anxiety, social phobia, and speech anxiety. Some studies involved psychiatrically healthy participants. To minimize the high variability among the aforementioned mental conditions, we grouped these conditions into three categories: depression, anxiety, and healthy. Studies were also classified as involving either a psychiatric interview or questionnaire-based assessment.

Intervention characteristics. Cognitive training programs were categorized into four groups: working memory training (i.e. training programs aimed at improving working memory capacity), attention bias modification training (ABM) (i.e. training programs aimed at modifying attentional bias), cognitive interpretation bias modification (CBM-I) (i.e. training programs aimed at modifying interpretation bias), and inhibitory control training (i.e. training programs aimed at improving executive control). For further details see Appendix A.

To characterize the differences in training methods, we included the following variables in each dataset: number of training sessions, average days between training sessions, average duration of each training session (in minutes), training location (home/lab), visual emotional stimuli (did the training procedure include a visual stimulus that represents specific emotions (e.g., a facial expression of disgust, a photo of a baby crying, the word "sad")? These variables were chosen based on a comprehensive literature review indicating that they predict training efficacy (Koster et al., 2017; Mogg et al., 2017; Price et al., 2016; von Bastian and Oberauer, 2014; Weicker et al., 2016). These will be added as potential moderators.

Control groups: Most included studies compared one training group to one control group, but there was significant heterogeneity among the activities performed by participants in the control groups (for further discussion see Shani et al., 2019). To increase homogeneity within each training category, we included only the most common types of control group activities. See Appendix B for further details of the included and excluded groups in each study.

Standardization. Because main outcomes are scores of different validated scales, we conducted a standardization process to compare them. To that end, we searched the literature for publications that detailed healthy population norms (i.e., means and standard deviations). When possible, we matched the country where the population norms were collected to the country where each study was conducted. For a more detailed report of each variable's population norms, see Appendix A.

For standardization calculation, the population mean was subtracted and divided by the standard deviation.

3. Data analysis

In accordance with the study goals, two analyses will be conducted. The first analysis is aimed at identifying who will benefit more from cognitive training than from control conditions (prognostic variables). The second analysis is aimed at identifying subgroups of individuals who may benefit from a certain training type rather than an alternative type of cognitive training (prescriptive variables). All analyses will be conducted after an initial data screening procedure: standardization of outcome data will be implemented in accordance with the norms of each main outcome measure, derived from the literature as mentioned above. Missing values will be imputed with an appropriate imputation method, and in accordance with the patterns of missing data apparent in the final data.

1. Identifying prognostic variables: Which individuals are most likely to benefit from cognitive training in general?

Machine learning models will be used to identify the characteristics of individuals who benefit more from cognitive training than from the control intervention. This will be accomplished by identifying the moderators of the training group effect on outcome. These moderators are responsible for the amount of difference in outcome between the training and the control groups. We will compare two models: a classical linear regression model and an ensemble method based on machine learning. The linear model identifies the moderators by adding interactions of potential moderators and training group. The ensemble method uses trees to add interactions by splitting nodes based on potential moderators, followed by splitting nodes based on treatment group.

On a randomly selected subset (70%) of the data (training set), we will apply the following procedure to select the best predictive model out of the two. An eight-fold cross-validation procedure will be used to compare the performances of the two methods. In each iteration, one-eighth of the sample will be held out and the two methods will be fitted by using the other seven-eighths of the sample. Subsequently, both fitted models will be applied on the eighth of the sample that was held out to estimate what the expected outcome of each individual would be had that individual been assigned to either the control or the training group. Repeating this on all eight folds will result in two expected outcomes for all individuals in the training set for each model. The "optimal" treatment for an individual is defined as the group in which the expected outcome is preferable. The difference between the expected outcome in the "optimal" and "non-optimal" groups is termed the Personalized Advantage Index (PAI; DeRubeis et al., 2014). The higher the PAI is, the more the individual is expected to gain if assigned to the optimal group.

The comparison between the two models will be based on an empirical average of the PAI, calculated as the difference between the average outcome of all participants in the training set who were assigned to their "optimal" treatment group and the average outcome of those assigned to their "non-optimal" treatment group. The optimal and non-optimal training group of each individual will be defined by the PAI calculated using cross-validation. Given that participants were randomly allocated to groups, this difference will represent an unbiased estimate of the average PAI and will be used to evaluate and compare the two models. More power is gained if we only compare the averages of participants with considerably higher PAI values (DeRubeis et al., 2014). After we select the model with the higher average PAI, this model will be fitted to the total training set. We will use the fit to obtain the predicted individual PAI and the average empirical PAI on the test set (the 30% left aside).

This analysis includes twelve potential moderators: age, gender (male or female), population (depression, anxiety, or healthy), diagnosis method (clinical assessment or self-report questionnaire), baseline level of outcome variable (after standardization), number of training sessions, average number of days between training sessions, average training session duration (in minutes), training location (lab or online), inclusion of a visual emotional stimulus (present or absent), condition (training or control), study ID. D ue to the distribution of each variable, minor adjustments related to specific variables may be required before analysis commences.

2. Identifying prescriptive variables: Which individuals are more likely to benefit from each type of cognitive training?

To predict who benefits more from one specific cognitive training rather than another, we will implement a data analysis process similar to the one specified above, but with several important changes. First, we will exclude individuals who were assigned to a control condition. Thus, condition (training or control) variable will be excluded from analysis due to irrelevance. Second, the search will be for variables that can moderate the effect of training type (working memory training, ABM, CBM-I, or inhibitory control training) on outcome. This will allow the algorithms to identify specific subgroups that benefit from a specific type of cognitive training. Third, the definition of PAI will be adjusted for the case of more than two treatment groups.

The above analyses will be repeated twice: once for the main outcome and once for the secondary outcome (see details above).

To further increase the strength of the findings, we will recruit a new sample of participants for a new randomized controlled trial, which will act as external validation of our results. In this subsequent study, some of the participants half of the participants will be assigned to a training regime based on the machine learning algorithm predictions. The other half will be randomly assigned to a training regime. We will then test whether assigning individuals according to the algorithm's predictions vs. random assignment will yield differential treatment benefits.

4. Discussion

Promoting effective and scalable mental health interventions is of major clinical importance. While cognitive training has emerged as a promising low-cost and (potentially) highly scalable intervention (Van den Bergh et al., 2018), inconsistent research results have led to varied interpretations about the efficacy of these interventions on the designated outcome measures (Motter et al., 2016). The striking heterogeneity in cognitive training studies (e.g., differences in training length and environment) has substantial implications for the potential therapeutic impact of cognitive training (Schwaighofer et al., 2015). This study addresses the inconsistent results and methodology across the field (Green et al., 2019; Shani et al., 2019) and simultaneously aspires to draft recommendations for future comparative investigations. Accordingly, we designed a large-scale individual-level meta-analysis study that includes individualized data from various laboratories across the globe. By tapping into the special aspects of each cognitive training field and addressing its heterogeneity by applying machine learning algorithms, we plan to investigate the following: (1) What are the characteristics of individuals who benefit from cognitive training in general? (2) Which subgroups benefit most from certain types of training programs? Central challenges in comparing between studies are discussed here, alongside suggested solutions.

Green et al. (2019) highlighted the similarity between challenges facing the cognitive training field and related domains, while suggesting to exploit the analytic guidelines of similar and related study domains to promote cognitive training research. Accordingly, the current study relies upon previous analytic practices that have been successfully implemented in the field of psychotherapy (Cohen and DeRubeis, 2018; Zilcha-Mano, 2018).

Furthermore, due to the diversity of included studies, a thoughtful and systematic *a priori* decision-making process was required. For example, some studies investigated several primary outcome measures, relying on performance on a cognitive task as an outcome measure. This resulted in a large variety of outcome measures representing significant differences in characteristics (e.g., questionnaire scores, reaction times, accuracy). To achieve comparability between these studies, we carefully outlined the designation of one outcome measure for each study. Since all outcome measures required standardization, meaningful data such as performance on cognitive tasks was omitted from analysis. This process forced us to exclude noteworthy, well-designed, cognitive training studies solely due to the absence of a standardized self-report outcome measure (i.e., a questionnaire). Therefore, one of our main conclusions is the need to establish a computerized battery of cognitive tasks to be utilized in all cognitive training studies to allow adequate comparability.

To categorize baseline and training variables, we developed a classification method for each variable (i.e., clinical status, training type). Similar to other meta-analyses, each factor had to be represented by a sufficient number of studies. Therefore, we made *a priori* decisions about how to collapse across studies and achieve a sufficiently large representation of each feature.

Decisions were determined based on consultations with cognitive training experts, thoughtful discussions, and literature reviews. These extended efforts reflect the understanding that each decision may affect the outcomes of the current study. Similar to the implementation of standard statistical methods in which decisions regarding whether to compare mean or median scores may influence results, the integration method across meta-analytic studies may dramatically affect the results. To overcome potential biases, we will analyze all available variables described above in an *a priori* manner to minimize analytic biases. Moreover, the issue of publication bias has been discussed extensively (Koster and Bernstein, 2015; Melby-Lervåg et al., 2016). By publishing a detailed protocol of a large-scale study before analysis, we aim to minimize potential biases (e.g., data mining and Type 1 error) and the odds of distorted results (Culverhouse et al., 2013; Ioannidis, 2005). Subsequently, by disclosing the full study design and all outcome variables, we hope to reduce publication bias (Green et al., 2019).

The significance of implementing investigations that compare cognitive training methods with differing methodologies, populations and outcomes is clear. Yet as mentioned above, this rich variance produces challenges when synthesizing the datasets to achieve comparability. Therefore, this study design has limitations. First, the sample of included studies is based on the researchers' willingness and ability to share their de-identified individual-level datasets. Therefore, this sample may not accurately represent all studies in the cognitive training research field. Second, the included studies represent a wide range of mood and anxiety conditions (e.g., depression, dysphoria, rumination, general anxiety, and social anxiety). Due to an insufficient number of datasets for some syndromes, we collapsed related conditions under the same umbrella term. For instance, depression, dysphoria and rumination were all allocated under the depressive condition umbrella term. Third, the diagnostic status of each individual was not thoroughly examined in all studies. For instance, studies that recruited healthy participants did not necessarily screen these participants for all mental conditions. Additionally, studies that recruited participants based on a specific clinical condition (e.g., depression) did not always screen for comorbidity with other clinical conditions (e.g., anxiety). Fourth, despite the desire to include as many variables as possible, not all studies collected the same type of data. Therefore, the baseline variables only include information common to all the included studies.

To the best of our knowledge, this is the first attempt to integrate machine learning methods in a comprehensive large-scaled study aimed at comparing cognitive training interventions to promote an individually tailored training program. In contrast to previous studies that commonly regard individual differences within the same training condition as noise, here we suggest building upon this individual variance as a source for investigating moderators that can improve training efficacy, with the long-term goal of developing effective, individually tailored cognitive training to improve well-being.

5. Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request and with permission of all involved investigators.

Ethics approval and consent to participate

The current study was approved by the Institutional Review Board

(IRB) at the University of Haifa. Moreover, full participant anonymity was maintained during dataset collection. That is, we received individual-level data files from which all identifying information had been removed.

Consent for publication

All authors approved this protocol.

Trial registration

This trial was registered with Open Science Framework (OSF): DOI 10.17605/OSF.IO/25CWE.

Authors contributions

Author RS performed data search and preprocessing, all administrative tasks required for submission and drafted the protocol. Author ST took part in data preprocessing, planning of analysis and drafting the protocol. Authors HS and SZ took part in planning, supervision, brainstorming and writing the protocol. Author EK guided some of the decisions taken while planning this study design, as well as revised this protocol. ND, NC, PE, RM, SD, AW, JY, PC, JK, WY, EC, AR, CB, and BB contributed de-identified datasets, as well as substantially revised this manuscript.

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Declaration of competing interest

The authors declare that they have no conflicting interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.03.043.

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