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A randomized clinical trial to evaluate the efficacy of cognitive rehabilitation and music therapy in mild cognitive impairment in Huntington's disease

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ABSTRACT

Background: Cognitive impairment is a core feature of Huntington's disease (HD), yet no disease-modifying or symptomatic interventions have demonstrated efficacy in addressing these deficits. Non-pharmacological interventions, particularly cognitive training (CT), are promising options for maintaining neural plasticity, enhancing cognition, and improving emotional well-being.

Methods: This 24-week, single-center, randomized, single-blind study evaluated the safety and efficacy of two cognitive rehabilitation strategies in early-to-middle-stage HD patients. Participants were randomized into a computerized cognitive training (CT; n=13) intervention or a music therapy (MT; n=16) intervention. A standard of care (SoC; n=15) group with no active intervention was also involved. Weekly 45-minute sessions were conducted. Baseline and endpoint assessments included measures of global cognition, functional, motor and neuropsychiatric assessments, along with structural and functional neuroimaging.

Results: Both CT and MT groups demonstrated significant improvements in primary and secondary cognitive endpoints, including global cognition and composite measures of disease severity. Regression analysis identified longitudinal cognitive score changes as independent predictors of the rate of atrophy in the caudate, putamen, and inferior frontal gyrus. Functional connectivity analysis showed distinct intervention-related effects: CT group exhibited increased connectivity between the central executive and sensorymotor networks, while MT group reduced aberrant connectivity between the central executive and the default mode network.

Conclusion: This is the first randomized controlled trial to evaluate two cognitive rehabilitation strategies in HD using multimodal neuroimaging. Both interventions were effective in improving cognition and modulating structural and functional brain changes in regions critical to HD.

Trial Registration

ClinicalTrials.gov (ID:NCT05769972)

INTRODUCTION:

Huntington's disease (HD) is a genetic autosomal dominant neurodegenerative disorder caused by abnormal CAG repeat expansion in the *HTT* gene [30, 44]. Although the clinical diagnosis of HD is based on the unequivocal presence of motor symptoms, progressive cognitive changes and the development of behavioral alterations are inherent features of the disease, which results in a profound impact on functional independence and on quality of life [29-31]. The first signs of cognitive deterioration can manifest several years before clinical diagnosis is made [28, 38]. Later, dementia is a practically inevitable consequence of HD, which, together with neuropsychiatric comorbidity and motor deterioration, has a devastating impact on the lives of patients and caregivers [22, 23, 30, 42].

Although eventually effective disease-modifying therapies might have a global positive effect on several signs and symptoms of the disease, including cognitive impairment, up to date, no such therapies exists. Thus, current treatments available for HD are directed to the symptomatic management of the patients [11, 37]. However, contrasting to the pharmacological treatment of motor and behavioral complications of the disease, no effective pharmacological approaches to prevent or to ameliorate cognitive decline in HD has been proven effective [4, 9, 19, 25, 35, 37]. Thus, non-pharmacological interventions appear as an option to be considered. Taking into account the positive effects seen in other neurodegenerative diseases and in acquired brain injury, cognitive training (CT) therapies have been gaining interest and have been the subject of previous studies in HD [3, 7, 12, 15, 26].

CT is based on the administration of a series of tasks whose execution requires the participation of different brain systems and processes [3]. The theory behind CT in neurodegenerative diseases is based on the idea that engaging in regular cognitive tasks can help maintain or enhance neural plasticity [5]. As a consequence, it is suggested that this may slow down cognitive decline by promoting the activation and strengthening of neural networks, compensating for damaged functions, and improving overall brain activity. Additionally, CT can also support emotional well-being, increase engagement, and reduce apathy [20]. In neurodegenerative diseases, we must assume that brain damage is extensive and diffuse, affecting multiple cognitive processes in different ways, and following a progressive course rather than remaining static. Accordingly, it is not surprising that the efficacy of CT in neurodegenerative diseases have been found to be mild, and that generally, most of the effects are significantly dependent on the characteristics of the population, the type of CT techniques employed and the design of the studies [10]. Therefore, doubts remain regarding the potential efficacy of this type of intervention in the field of neurodegenerative diseases.

In HD, previous studies on CT suggest that cognitive training may confer slight cognitive benefits [1, 8, 18, 40, 43]. However, several limitations such as lack of a control group or small sample size were found in most of these studies. Moreover, hardly any study has employed neuroimaging measures that

would allow exploration of the effect of interventions on brain structure or function. In this sense, a recent study conducted in a small sample of HD patients, demonstrated positive changes in the putamen and better cognitive performance after a 3-month period of 1h/week of computerized CT [17].

To overcome some methodological limitations of previous studies, we considered that a design allowing the comparison of different types of active interventions against the natural course of the disease or the standard of care (SoC) is mandatory. Secondly, confounding factors that are not strictly cognitive, but may have a direct effect on cognitive function such as depression or apathy should be considered. Finally, to understand the mechanisms involved in an eventual positive or negative effect of CT on cognition, it is necessary to explore the impact of the intervention on brain structure and function, and how it relates to the observed cognitive effects.

Thus, the main aim of the present study was to investigate, in early-to-middle HD population, the effects of two different CT techniques over cognition, functional status, brain structure and function. To do so, we administered an intensive computerized-based CT program and an active and demanding music-therapy (MT) program to a group of participants, and compared the results of these two therapies with respect to a SoC group.

METHODS:

Study design:

We conducted a single-center, 24-weeks, randomized, single-blind, parallel-group study to assess the efficacy of a computerized CT program and MT, versus SoC. Eligible patients were randomized (1:1) in the CT or MT group. Then, a sample matched for the main clinical and sociodemographic variables was identified to be part of the SoC group. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Ordinance. The study protocol (IIBSP-MOV-2021-28) was reviewed and approved by the ethics committee of our center, and all participants read, approved, and signed the corresponding informed consent.

Sample and Assessments:

The study sample consisted on twenty-nine participants who were randomized to receive CT or MT. In parallel, fifteen HD participants were enrolled in the SoC group. In this case, no particular intervention was carried out beyond the usual clinical management.

In all cases there was availability of a genetic study confirmatory for CAG > 39. Per protocol, and to avoid the particularities of the clinical phenotypes associated with juvenile onset HD, subjects with a CAG repeat-length beyond 55 were excluded.

The severity of motor symptoms was addressed through the Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS). Disease stage was determined as a function of the Total Functional Capacity (TFC), using the Shoulson and Fahn criteria for HD staging (TFC > 10 for stage I, TFC 6–10 for stage II and TFC < 6 for stage III). Functionality was also assessed using the UHDRS Functional Independence Scale (FIS) [14].

The CAG-Age-Product (CAP score) was calculated using the formula based on age and CAG repeat length: $[\text{age} \times (\text{CAG} - 33.66)]$ [45]. Global cognition was assessed using the Parkinson's Disease – Cognitive Rating Scale (PD-CRS) to address limitations regarding sensitivity by instruments such as the MMSE or MoCA [27]. The PD-CRS addresses global cognition through the administration of nine subtests and previous studies on HD, demonstrated that the PD-CRS have good psychometric properties to capture the cognitive status of HD participants and to track longitudinal change [16, 21]. To also focus on cognitive measures with demonstrated sensitivity to change in HD, we collected data from the Symbol Digit Modalities Test (SDMT) and the Stroop word-reading (SWRT) test. The UHDRS-TMS, the TFC, the SDMT and the SWRT were used to calculate the UHDRS composite score (cUHDRS) as a reliable measure of clinical progression [34].

The severity of neuropsychiatric symptoms were assessed with the Problems Behaviour Assessment scale in its short form (PBA-s) [6, 24]. This instrument evaluates, in the presence of a reliable informant, the frequency and severity of a whole series of neuropsychiatric symptoms in HD. To further assess apathy, the Starskein Apathy Scale (SAS) was used [36].

Inclusion criteria:

Inclusion criteria were: (1) CAG repeat-length between 40 and 54 (both included); (2) Patients fulfilling diagnostic criteria for clinically symptomatic HD based on a diagnostic confidence level (DCL) score of 4; (3) Shoulson & Fahn stages of I-II at baseline according to a Total Functional Capacity (TFC) score > 6; (4) PD-CRS score between 64-83 or subjective cognitive complaints; (4) Patient to be able and willing to comply with the study visits.

Exclusion criteria:

Exclusion criteria were: (1) Illiterate patients; (2) Severe vision or hearing impairment; (3) Diagnosis of dementia (possible or probable) associated with HD; (4) Patients with active psychosis or delusional

ideation; (5) Patients who were under experimental treatment in the 2 months prior to the selection period; (6) Patients with a life expectancy less than 6 months or with any severe or uncontrolled medical condition; (7) Patients with a history of poor therapeutic compliance or drug/alcohol abuse that may interfere with the patient's ability to comply with the study protocol or give informed consent; (8) Contraindications or impossibility to undergo a MRI study; (9) Patients who required a modification of pharmacological treatments during the study period.

Primary efficacy endpoint:

The primary efficacy endpoint was determined as the percentage of change from baseline to week 24 in the PD-CRS total score.

Secondary endpoints:

As clinical secondary endpoints were explored the percentage of changes from baseline to week 24 in: SDMT, SWR; Starkstein Apathy Scale (SAS); Problem Behavior Assessment-short version (PBA-s), and on the cUHDRS. We also assessed the percentage of change on the TFC, on the Functional independence scale, and on the Clinical Global Impression of Change (CGIC).

Magnetic resonance imaging endpoints:

MRI-based secondary endpoints were explored in the participants included in the MT or CT groups. Unfortunately, there was no access for MRI in the SoC group. In terms of imaging endpoints, we focused on grey matter volume (GMV) changes pre – post intervention, and on resting-state functional MRI (rs-fMRI) changes pre – post intervention.

Safety, tolerability and adherence to treatment:

Safety and tolerability were assessed through adverse event (AE) reporting and physical examination. Adherence to treatment was assessed taking into account the session attendance rate. A measure of satisfaction with the intervention program was also obtained.

Study intervention:

After baseline data collection, participants were randomized (1:1) to CT (N = 13) or MT (N = 16) using a random block design. In order to maintain the single-blind condition of the study, the research team was composed of two independent and blinded sub-teams. One was in charge of conducting and implementing the interventions and the other was in charge of the assessments. In both cases, both the computerized CT and the MT interventions were conducted in groups of 4 to 5 participants per group.

Computerized Cognitive Training:

Computerized CT intervention comprised a 24-week program participation in one computerized CT session per week using the NeuronUp® neurorehabilitation software (NeuronUP SL; <https://neuronup.com>). NeuronUp® is a specialized tool designed for neuropsychological stimulation and rehabilitation, boasting over 250 tasks developed by professionals in neuropsychology. The CT program implemented was standardized across all participants, with individuals completing identical tasks in a consistent order over the 24-week period. Each session consisted of 7 tasks meticulously selected based on current insights into the cognitive aspects primarily associated with HD and their significant impact on functionality. Accordingly, tasks were categorized into 5 major blocks aligning with cognitive domains: executive functions, attention and processing speed, visuospatial abilities, language, memory, and social cognition. Emphasis was placed on tasks from the executive functions block. Tasks within each block remained constant throughout the program and were dynamically adjusted in difficulty based on individual performance. As participants demonstrated proficiency and progressed, task complexity increased incrementally to maintain engagement and challenge levels, allowing for the observation of individual learning curves and fostering participant motivation as milestones were achieved. To mitigate monotony, tasks were strategically distributed across different weeks of the month according to their respective domains, ensuring each week offered a diverse range of activities compared to the previous one. The CT sessions had a duration of 45 minutes, were performed in the facilities of our site, and were fully supervised by a trained neuropsychologist. The specific characteristics of each task is detailed in Supplementary material 1.

Music therapy intervention:

MT intervention spanned a 24-week period, conducted once weekly, with each session lasting 45 minutes. To initiate the intervention, participants completed a Music Preference Questionnaire (MPQ) aimed at assessing their individual musical preferences, thereby customizing the musical selection for each session. Sessions were led by a certified music therapist proficient and specialized in neurological disorders according to the study's protocol. Throughout each session, participants engaged in a series of cognitive music therapy exercises, including Auditory Perception Training (APT), Musical Sensory Orientation Training (MSOT), Musical Attention Control Training (MACT), Musical Executive Function Training (MEFT), Musical Mnemonics Training (MMT), and Mood and Memory Association Training (MMAT). The description of each exercise is detailed in Supplementary material 2. These exercises were meticulously tailored based on participants' specific needs and emotional states, facilitating a standardized yet adaptable intervention approach. The methodological framework adopted

aimed to investigate the effects of music therapy on participants' emotional and cognitive well-being, with a particular emphasis on tailoring interventions to optimize therapeutic outcome.

Sample size:

The sample size was calculated according to data on the minimally clinically important difference (MCID) of the PD-CRS in HD at 6-month and 12-month follow-up [16]. Assuming an alpha and a beta risk of 0.05 and 0.2, respectively, in a two-tailed hypothesis test, with a 1:1 distribution between both independent groups, 16 subjects were necessary in each of the groups to recognize a statistically significant difference greater than or equal to 12 units in the PD-CRS. The standard deviation was assumed to be 11.2, and a dropout rate of 10% was expected.

Statistical analysis:

Differences between treatments were examined using standard methods for analysis of the variance (ANOVA). Post hoc comparisons were performed using Student's paired t-test or Wilcoxon test when appropriate. P values for the ANOVAs were calculated after Greenhouse–Geisser corrections. The data that support the findings of this study are available from the corresponding author upon reasonable request. Data are presented as mean $\pm$ SD unless otherwise stated. Data were analyzed using SPSS 24 software.

Neuroimaging acquisition parameters, preprocessing and statistical analyses:

T1-weighted MRI images were acquired on a 3T Philips Achieva using an MPRAGE sequence (TR/TE=8.5/3.9 milliseconds, flip-angle= 8°, field of view=23cm, matrix=232x180 and voxel size=1mm).

Resting-state functional MRI (rs-fMRI) BOLD (Blood-Oxygen-Level-Dependent) images during 12 minutes were also obtained using the following parameters: TR=2000ms, TE=30ms, FOV 240mm, voxel size 3.75mm, flip angle 78°).

Structural changes in gray matter were assessed by a longitudinal voxel-based-morphometry (VBM) pipeline as described in our previous works [33]. Briefly, using the SPM12 software package, the following preprocessing steps were applied to the T1-MRI scans: pairwise registration, Jacobian difference images computation restricted to gray matter, and subsequent normalization to MNI space using DARTEL.

Resting-state connectivity changes were assessed by the default longitudinal seed-to-voxel pipeline implemented in the CoNN-NITR-MIT v18 software package, as detailed in our previous work [32].

Briefly, BOLD scans were first slice-timing corrected, realigned, motion-corrected, denoised, spatially normalized MNI space and smoothed using the default CoNN parameters. Then, seed-to-voxel fisher-transformed correlation coefficients (Z-maps) were derived for each participant and condition (pre and post intervention) using the main node of the Central Executive Network as a seed.

Regarding the statistical analyses, voxelwise longitudinal changes in gray matter were computed using a paired t-test of the GMV loss maps. Voxelwise resting-state connectivity changes were assessed by an analogous paired t-test on the Z-maps. Only clusters surviving $p < 0.05$ and false discovery rate (FDR) correction for multiple comparison using a cluster gathering threshold of $p < 0.01$ were considered significant. Lastly, in order to investigate potential associations between imaging changes and clinical changes, scalar average connectivity and GMV changes were computed at the significant clusters obtained in the voxelwise analyses.

RESULTS:

A total of 44 subjects assessed for eligibility accomplished criteria for inclusion and 29 subjects were randomized into the active treatment arms (CT; $n=13$ and MT; $n=16$). A total of 15 subjects were allocated into the SoC group. 1 subject from the CT group discontinued the study due to lost of follow up and 3 subjects discontinued the study from the MT group: 1 due to MRI incompatibilities and 2 to lost of follow up (Fig. 1). The main clinical and sociodemographic characteristics of the sample indicated a mean age of 53.70 (9.26), mean UHDRS-TMS of 34.05 ± 18.12 , mean TFC was 10.70 ± 1.68 and mean PD-CRS total score of 79.88 ± 16.32 (Table 1). Accordingly, the mean disease stage of the sample was stage I, and the mean global cognitive status was on the range of mild cognitive impairment associated to HD [21]. A SAS mean score of 17.55 ± 11.9 was found indicating that, on average, the sample exhibited clinically significant apathy (SAS cutoff > 13), with 58.6% of the participants showing clinically significant apathy. Regarding the other neuropsychiatric symptoms assessed using the PBA-s, the highest scores were found for depression, apathy, and perseverative behavior.

At baseline, no significant differences were found between groups for age, CAG repeat length, CAP score and UHDRS-TMS. Focusing on neuropsychiatric symptoms, no differences were found in any of the PBA-s domains, nor in the SAS.

Significant differences between the three groups were found for TFC [$F(2,41) = 4.53$; $p = 0.019$], FIS [$F(2,41) = 9.1$; $p = 0.001$] and PD-CRS total score [$F(2,41) = 4.2$; $p = 0.020$]. Post-hoc t-test analysis showed that these differences were driven by lower score in the MT group compared to the SoC group on FIS [$t(31) = 13.5$; $p < 0.0001$], TFC [$t(31) = 1.58$; $p = 0.015$] and PD-CRS total score [$t(31) = 15.5$; $p = 0.016$]. Due to these differences, all these variables were used as covariates in the subsequent

analyses to minimize possible effects mediated by baseline cognitive and/or functional status. Thus, results are presented in terms of corrected mean percentage of change.

[Insert Figure 1 about here]

[Insert table 1 about here]

Primary efficacy measures:

The ANOVA showed a significant effect on the mean change between baseline visit and follow-up visit in the PD-CRS total score [$F(2,35)=3.68$; $p=0.035$]. Post-hoc t-test comparisons showed that this effect was driven by a significantly better performance at follow-up in the MT group compared to SoC [$t(28)=2.1$; $p=0.038$], and by a significantly better performance at follow-up in the CT group compared to SoC [$t(27)=3.9$; $p=0.001$] (Fig. 2). A pattern of equivalent positive effects were found for the two intervention groups with respect to baseline. A trend for a significant improvement of 3.9 (6.9) points was found in the CT group [$t(12)=-1.0$; $p=0.07$], and also a trend for a significant improvement of the 3.9 (7.3) points in the MT group [$t(14)=-1.9$; $p=0.06$] on the PD-CRS. Conversely, a worsening of 0.67 (4.3) points was found in the SoC group reflecting an absence of change compared to the baseline visit [$t(15)=0.6$; $p=0.953$]. No differences on the percentage of change of the PD-CRS total score was found between MT and CT groups.

[Insert Figure 2 about here]

Secondary efficacy measures:

A significant interaction was found for the mean change on the SDMT [$F(2,35)=5.5$; $p=0.008$]. Post-hoc analysis showed that this effect was driven by a significant worse performance post intervention in the SoC group compared to MT group [$t(28)=2.46$; $p=0.017$], and compared to the CT group [$t(25)=3.2$; $p=0.003$]. At a group level, a significant better performance in the SDMT of 4.5 ± 6.5 points was found in the CT group with respect to baseline [$t(25)=2.3$; $p=0.03$], and also a significant better performance of 2.4 ± 3.8 points was found in the MT group [$t(26)=2.3$; $p=0.04$]. No differences were found in the SoC group in the comparison between baseline and post intervention SDMT score. In terms of apathy severity, the SAS was only available for the CT and MT groups. Repeated measures ANOVA showed

no effects between treatment groups. However, at a group level, although non significant, both treatment groups showed lower apathy scores post intervention, with a mean reduction of 1.4 ± 5.5 points. Focusing on the PBA-s, repeated measures ANOVA showed a significant interaction between the factors “treatment group” and “visit” [$F(2,35)=3.27$; $p=0.049$]. Post-hoc analysis showed that this effect was driven by a significant lower apathy score, with respect to baseline, in the CT group compared to SoC [$t(27)=1.9$; $p=0.04$] and in the MT group compared to SoC [$t(28)=2.1$; $p=0.03$]. At a group level, a significant change of 0.31 ± 0.4 was found in the MT group [$t(26)=2.3$; $p=0.04$], and a trend to a significant changes of 0.25 ± 0.45 was found in the CT group [$t(24)=1.9$; $p=0.08$]. No effects were found for the other PBAs components. On the cUHDRS, no significant interactions were found. However, post-hoc analysis revealed significant differences on the change to lower cUHDRS post intervention in the CT group compared to the SoC group [$t(27)=2.1$; $p=0.046$]. At a group level, a significant change of 1.35 ± 1.3 points in the cUHDRS with respect to baseline was found in the CT group [$t(24)=3.4$; $p=0.006$]. No significant differences were found in the MT and SoC groups. No other effects were found for any of the other secondary endpoints.

Neuroimaging results:

Voxelwise paired t-test showed significant cortical and striatal GMV loss after the 6-month interval. Specifically, as seen in the section “A” of the figure 3, significant loss of GMV was found in the putamen and inferior temporal cortex. Moreover, in the MT group there was a significant lower decrease of GMV in the left caudate compared to CT group, however, this effect disappeared when GMV at baseline was included as nuisance covariate.

Taking into account the results obtained for the primary endpoint and secondary endpoints, we studied the possible relationship between the longitudinal change in GMV and the scores obtained in the endpoints of interest. For this purpose, we applied a linear regression model using as the dependent variable the GMV loss at the identified clusters and, as fixed factors, the various primary and secondary endpoints, as well as age, CAG, and CAP score as nuisance covariates. This analysis showed that, independent of age, CAG, or CAP score, the change in total PD-CRS was an independent predictor of GMV loss in the right caudate/putamen ($\beta = 0.449$; $p = 0.048$), and in the inferior orbitofrontal cortex ($\beta = 0.432$; $p = 0.045$); and that the change in cUHDRS was also a predictor of GMV loss in the right caudate/putamen ($\beta = 0.758$; $p = 0.043$).

[Insert Figure 3 about here]

Resting-state fMRI analyses showed an increase in connectivity between the posterior nodes of the central executive network (CEN) and the precentral/postcentral regions of the sensorimotor network, as well as a decrease in connectivity between the posterior nodes of the CEN and the medial frontal node of the default-mode network (DMN) after the 6-month interval. The functional connectivity changes analyzed using a 2x2 mixed ANOVA, showed different effects of the type of intervention over functional connectivity. Specifically, in the CT group, changes were observed in terms of increased connectivity along several regions of the CEN and the sensorimotor network, whereas in the case of the MT group, changes were confined to a decrease in connectivity with the middle frontal cortex node of the DMN and the CEN (Fig. 4).

[Insert figure 4 about here]

Linear regression analysis showed a significant association between the connectivity increases in the parietal regions and the changes on the PD-CRS total scores ($\beta=0.611$; $p=0.005$), and SAS scores ($\beta=0.494$; $p=0.032$). In parallel, the connectivity decreases between the CEN and the medial frontal node of the DMN was associated with the SDMT changes ($\beta=-0.460$; $p=0.047$).

Safety, tolerability and adherence to treatment measures:

In terms of safety, no AEs were reported or identified. No participants reported any issues tolerating the methodology used in CT or MT. In all cases, a high level of satisfaction with the interventions was reported.

DISCUSSION:

In this study, we administered two cognitive stimulation intervention programs over a period of six months to two groups of patients with HD, following a randomized, single-blind, placebo-controlled, parallel-group design. One group participated in a computerized CT program, while another group attended MT sessions. In parallel, a control group of patients who received no intervention beyond the usual treatment and follow-up was also included in the study. This study represents one of the few randomized controlled trials (RCTs) that has investigated the efficacy and safety of cognitive

rehabilitation in HD, using various endpoints, including cognitive functioning measures as well as structural and functional neuroimaging assessments.

No adverse events were reported during the interventions and there was a very good adherence to the study protocol, thus, demonstrating the feasibility of both interventions in HD patients. In terms of efficacy, CT and MT showed a positive and significant effect in the primary endpoint (change in the PD-CRS) compared to the SoC group. Although comparing the efficacy of the two forms of intervention was not part of the objectives, we consider it relevant that both showed similar benefits compared to the SoC group. Regarding secondary endpoints, a significant post-intervention effect was found for the SDMT in both the CT and the MT groups. Although not a statistically significant change, we observed a trend toward lower scores following both interventions.

Although the allocation of subjects to the two possible intervention arms was carried out randomly, due to probabilistic reasons, the MT group ended up consisting of individuals with more severe HD in terms of baseline cognitive impairment compared to the CT group and especially to the SoC group. These baseline cognitive differences may have influenced, to some extent, the effect of the intervention. Nevertheless, the slope of improvement following the interventions, was equivalent, with similar positive differences in the change from baseline after the intervention. Thus, regardless of baseline cognitive status, both interventions can be considered effective, as both groups, unlike the SoC group, showed significant improvement.

In terms of efficacy, the most notable effects of the interventions were observed in a reliable measure of global cognitive status, namely the PD-CRS. This cognitive scale is composed of a series of tasks that cover various cognitive domains such as memory, attention, visuoconstructive processes, language, and executive functions [21, 27]. Although originally designed to assess cognitive impairment in Parkinson's disease, various studies have demonstrated the validity, sensitivity, and reliability of this instrument for screening cognitive status in HD [16, 21]. Additionally, effects were also found in two measures that are highly specific to HD and very sensitive to its progression, such as the cUHDRS and the SDMT. The fact that these improvements appear in such specific measures, rather than in others considered more general or nonspecific, lends plausibility to the hypothesis that the interventions positively impact processes whose dysfunction is closely related to HD [23].

Although it did not reach statistical significance, we consider it interesting to take into account the observed trend toward a lower score in apathy. It is widely recognized that apathy is a cardinal symptom of HD, for which we have no effective treatments, and it tends to show a linear progression throughout the disease, in parallel with functional decline [22, 39, 42]. Therefore, the positive effect observed on such a characteristic symptom of HD reinforce the suggestion that, in some way, the interventions modulate certain typically dysfunctional processes in HD. In this sense, it is also worth considering the

possibility that including participants in a stimulating activity, such as CT and MT, may have had an effect on motivation, which could have indirectly influenced the cognitive effort exerted afterwards [13]. We also find it interesting to highlight the subtle differences observed between the two intervention groups regarding improvements in apathy, which appear to be more notable in the MT group. Although both interventions were administered in a group setting, it is evident that the structure of the MT intervention promoted richer levels of interaction and socialization compared to computerized CT. While we do not have data that would allow us to make any categorical statements on this matter, we do believe it is worth considering the potential effect of the richness of the context and the level of social interaction between the two forms of intervention on apathy.

Regarding the structural neuroimaging changes, we observed an expected decrease of GMV along the 6-month follow-up period involving several subcortical and cortical territories. Unfortunately, the lack of neuroimaging data from SoC prevented us from performing comparisons with this group. Regression analyses revealed that, regardless of age, CAG, CAP score, or baseline cognitive status, the rate of change in PD-CRS was a predictor of the rate of change in GMV in both the caudate/putamen and the inferior frontal gyrus. Similarly, the rate of change in cUHDRS was also an independent predictor of the rate of change in GMV in the caudate/putamen. These results are aligned with data from a recent study conducted in a smaller sample and suggests that the interventions may exert some positive effects of neural preservation/plasticity [17]

Regarding the functional connectivity neuroimaging analyses, we observed, particularly in the MT group, a decrease in a positive correlation between a central node of the default mode network (DMN) and various nodes of the central executive network (CEN) after the intervention, the extent of which was, in turn, associated with better performance on the SDMT. Under normal conditions, there should be no positive correlation between these two networks, but rather an anticorrelation [41]. Therefore, the reduction or loss of correlation between DMN and CEN nodes may suggest a trend towards normalization of the functional relationship between these networks. Moreover, following the intervention, particularly in the CT group, we observed an increase in functional connectivity between the CEN and the precentral and postcentral regions of the sensorimotor network which was, in turn, associated with the positive changes observed after the intervention in the PD-CRS.

Currently, no effective treatment exists to slow down or cure HD, and consequently, we also lack effective pharmacological strategies for managing the cognitive disorders associated with HD [37]. While efforts continue to develop disease-modifying treatments, it is crucial to explore other possibilities that could have a positive impact on the lives of individuals affected by HD. The results of our study provide what we consider to be new and solid evidence supporting the benefits of cognitive stimulation techniques in the context of HD. The fact that we observed this effect for computerized CT

in a group of patients with milder cognitive impairment, and also for MT in a group of patients with clearly more severe cognitive impairment, suggests that people at different disease stages can benefit from CT techniques. However, these findings should be interpreted with caution due to limitations. Although the observed changes are statistically significant and positive, they should not be construed as clinically significant, at least in terms of the changes seen in the PD-CRS. Studies on the sensitivity to change of the PD-CRS in HD suggest that over a 6-month follow-up period, a Minimally Clinically Important Difference of 10 points should be considered [16]. While the change in PD-CRS observed in this study falls short of these 10 points, we believe this does not invalidate the clear positive changes observed across various endpoints. Additionally, despite this being the largest RCT to date on cognitive stimulation in individuals with HD, the sample is still not fully representative and is somewhat heterogeneous. In line with these limitations, there are additional points to consider. Firstly, the sample size may have influenced the magnitude of the observed effects. Ideally, we would have had neuroimaging data for individuals allocated to the SoC arm. Moreover, the treatment duration was relatively short, and it would have been highly valuable to extend the period beyond six months.

We believe these limitations should not detract from the study's strengths, which, in our view, lie in the robust methodology employed for both CT and MT, as well as in the carefully chosen endpoints. Emphasizing in the design and administration of the interventions, we consider that this study presents notable strengths compared to other studies conducted in this area. In the case of CT, a highly advanced cognitive training platform was utilized under the supervision of a neuropsychologist specializing in HD, and a series of exercises were selected based on our understanding of the neurocognitive processes that are typically affected in HD [1, 2, 21, 23, 38, 39]. Furthermore, the task programming was designed to adapt in real-time to the participants' performance. Moreover, to prevent frustration stemming from poor performance, tasks were structured so that they would never end due to the accumulation of multiple errors or an inability to complete them. That is, by adapting the tasks to the individual's performance, they were calibrated to the optimal execution level of the participant, ensuring that each individual finished with a positive outcome. Regarding music therapy (MT), it is important to highlight that no passive listening to music or unstructured interventions were employed. In contrast, as detailed in the supplementary materials, a standardized and demanding methodology was used, tailored to the participants, with a focus on stimulating cognitive processes such as planning, organization, and monitoring. Evidently, the results raise new questions that warrant exploration in larger RCTs, which, among other aspects, would allow us to assess whether more frequent administration of the interventions leads to greater improvements, the stability of changes over time, or the utility of interventions conducted at home, among other considerations. In any case, the data highlight that the measures used and the techniques employed are promising for further exploring the value of cognitive intervention in HD.

In summary, the study provides evidence of safety and efficacy of cognitive interventions on cognition in HD. Both CT and MT promoted brain functional changes in large-scale cognitive networks that were specific to each intervention and that exerted positive effects over the primary and secondary cognitive endpoints. Moreover, the results also indicates possible effects over structural integrity on key HD brain regions. Taking together, although HD inevitably associates a progression of both pathology and symptoms, it is essential to recognize that the inherent brain damage caused by the disease does not entirely preclude the brain's capacity to benefit from well-designed and properly administered cognitive rehabilitation interventions. Therefore, in the absence of alternative interventions for cognitive disorders, these results underscore the necessity of incorporating such interventions into the management and treatment models for HD. Larger and longer RCT's should investigate the long-term benefit of cognitive interventions, as well as to compare the results at the level of functional brain networks and structural changes with a control condition.

Author Contributions

A.M.-V., A.P.-D., S.M.-H and J.K. contributed to conception and design of the study. A.M.-V., A.P.-D., S.M.-H., G.K., J.P.-P., A.H.-B. and G.O.-S. contributed to data acquisition. A.M.-V., A.P.-D., S.M.-H., and F.S. contributed to the design, execution and review of the statistical analysis. A.M.-V., A.P.-D, S.M.-H. and G.K. wrote the first draft. A.M.-V., A.P.-D., S.M.-H., G.K., F.S, J.P.-P., A.H.-B., G.O.-S., J.P. and J.K. contributed to the revision of the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Competing Interests

A.P.-D. is supported by a grant from the Government of Andorra (ATC027-AND/2021). S.M.-H. has received honoraria for lecturing from Teva, Zambon, UCB, Bial, and Roche, and reports grants from Huntington's disease Society of America (Human Biology Project), and from Fondo de Investigaciones Sanitarias (FIS) from Instituto de Salud Carlos III (ISCIII). J.P.-P. reports a grant from Fondo de Investigaciones Sanitarias (FIS) from Instituto de Salud Carlos III (ISCIII). JP has received honoraria for advisory boards or lecturing from: Teva, Zambon, UCB, Bial, Sanofi, and Roche. J.K. has received honoraria for advisory boards or lecturing from: Teva, Zambon, UCB, Bial, General Electric, Sanofi, and Roche, and reports grants from Fundació la Marató de TV3, Fondo de Investigaciones Sanitarias (FIS) from Instituto de Salud Carlos III (ISCIII), and Fondo Europeo de

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Data Availability

The data sets generated or analyzed during the study are available from the corresponding author on reasonable request.

Ethical standards

The present study has been approved by the Hospital de la Santa Creu i Sant Pau ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants prior to their inclusion in the study.

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Figure captions:

Fig.1: CONSORT Diagram of Participants in a Study of Cognitive rehabilitation strategies for cognitive impairment in Huntington's disease

Fig. 2: Effects of the interventions on primary endpoints: On the left side, the figure shows the percentage change from baseline in the PD-CRS across the different groups. A significant change can be observed in the active treatment groups, which is not present in the SoC group. On the right side, the raw scores obtained by the various groups before and after the intervention on the PD-CRS are displayed. It can be seen that the intervention groups exhibit a significant positive increase, which is not observed in the SoC group.

Fig. 3: Structural MRI analysis: In the upper quadrant (A), the figure displays the changes in GMV (FWE corrected) found across the entire sample between the baseline visit and the end of treatment. The heat map highlights the areas where a significant loss of GMV occurred. In the lower quadrant (B), scatter plots are shown depicting the results of the linear regression analysis between changes in PD-CRS and cUHDRS and changes in GMV.

Fig. 4: Functional connectivity analysis: In the upper quadrant (A), the figure shows the changes in functional connectivity observed across the entire sample when comparing functional connectivity before and after the intervention. In the lower left quadrant (B), the significant changes found in the CT group and their relationship with changes in the PD-CRS are illustrated. In the lower right quadrant (C), the significant changes observed in the MT group and their relationship with changes in the SDMT are shown. The heat maps depict increases in connectivity in yellow tones and decreases in connectivity in violet tones.

Table 1. Clinical and sociodemographic characteristics

	Mean $\pm$ SD			
	CT group (n=13)	MT group (n=16)	SoC group (n=15)	p
Age	53.25 $\pm$ 8.02	58.31 $\pm$ 6	50.07 $\pm$ 11.11	^a 0.058; ^b 0.086; ^c 0.413; ^d 0.025
Gender (f/m)	6/6	7/6	9/6	^a 0.869; ^b 0.848; ^c 0.603; ^d 0.743
CAG ¹	42.67 $\pm$ 1.88	41.92 $\pm$ 1.71	43.60 $\pm$ 1.92	^a 0.066; ^b 0.310; ^c 0.216; ^d 0.023
CAP ²	472.94 $\pm$ 86.27	476.21 $\pm$ 75.97	488.82 $\pm$ 116.65	^a 0.900; ^b 0.921; ^c 0.698; ^d 0.742
UHDRS-TMS ³	32.75 $\pm$ 19.91	38.85 $\pm$ 17.70	30.93 $\pm$ 17.35	^a 0.504; ^b 0.426; ^c 0.802; ^d 0.244
Disease duration	5.08 $\pm$ 2.94	4.23 $\pm$ 3.14	4.76 $\pm$ 3.04	^a 0.210; ^b 0.491; ^c 0.291; ^d 0.637
Years of education	14.25 $\pm$ 3.60	12.38 $\pm$ 3.80	13.20 $\pm$ 2.76	^a 0.394; ^b 0.221; ^c 0.398; ^d 0.517
SWR ⁴	74.83 $\pm$ 18.65	59.08 $\pm$ 24.72	71.27 $\pm$ 20.21	^a 0.161; ^b 0.087; ^c 0.642; ^d 0.163
SDMT ⁵	36.08 $\pm$ 13.04	19.69 $\pm$ 13.70	31.67 $\pm$ 12.02	^a 0.008; ^b 0.006; ^c 0.369; ^d 0.021
cUHDRS ⁶	11.18 $\pm$ 3.79	7.89 $\pm$ 4.19	10.99 $\pm$ 3.25	^a 0.053; ^b 0.059; ^c 0.888; ^d 0.037
TFC ⁷	10.92 $\pm$ 1.56	9.69 $\pm$ 1.89	11.40 $\pm$ 1.18	^a 0.020; ^b 0.092; ^c 0.369; ^d 0.007
PD-CRS Total	81 $\pm$ 13.49	71.54 $\pm$ 18.94	86.20 $\pm$ 13.52	^a 0.054; ^b 0.167; ^c 0.330; ^d 0.025
PBA ⁸ Total	13.08 $\pm$ 8.08	12.85 $\pm$ 6.77	8.93 $\pm$ 8.99	^a 0.320; ^b 0.937; ^c 0.224; ^d 0.210
Depressive mood	2.15 $\pm$ 1.9	2.13 $\pm$ 2.1	1.97 $\pm$ 2.2	^a 0.921; ^b 0.970; ^c 0.820; ^d 0.837
Suicidal ideation	0.69 $\pm$ 1.9	0.75 $\pm$ 1.6	0.4 $\pm$ 1.1	^a 0.811; ^b 0.932; ^c 0.619; ^d 0.486
Anxiety	2.15 $\pm$ 2.3	2.2 $\pm$ 1.6	1.73 $\pm$ 2.1	^a 0.457; ^b 0.207; ^c 0.538; ^d 0.487
Irritability	1.42 $\pm$ 1.9	1.38 $\pm$ 2.3	1.47 $\pm$ 1.7	^a 0.320; ^b 0.960; ^c 0.942; ^d 0.902
Aggressive behaviour	0.5 $\pm$ 0.5	1 $\pm$ 1.6	0.2 $\pm$ 0.7	^a 0.216; ^b 0.289; ^c 0.209; ^d 0.085

	Apathy	4.3 ± 2.8	4 ± 2.4	3.8 ± 2.5	^a 0.398; ^b 0.781; ^c 0.621; ^d 0.821
	Perseverative behaviour	1.92 ± 2.1	2.8 ± 2.8	1.67 ± 2.2	^a 0.329; ^b 0.286; ^c 0.761; ^d 0.223
	Obsessive-compulsive behaviour	0.3 ± 1.1	0.7 ± 1.4	0	^a 0.167; ^b 0.381; ^c 0.292; ^d 0.062
	Delusions	0	0.13 ± 0.5	0	^a 0.427; ^b 0.377; ^c na; ^d 0.445
	Hallucinations	0	0.31 ± 1.1	0	^a 0.310; ^b 0.337; ^c na; ^d 0.300
	Disorientation	0	0.13 ± 0.5	0	^a 0.427; ^b 0.377; ^c na; ^d 0.445
	SAS ⁹	17.67 ± 10.00	16.62 ± 14.25	-	^b 0.834;

¹CAG repeat length; ²CAG-Age product; ³Unified Huntington's Disease Rating Scale – Total Motor Score; ³Stroop Word-Reading; ⁵Symbol Digit Modalities Test; ⁶Composite UHDRS; ⁷Total Functional Capacity; ⁸Problems Behavior Scale; ⁹Starkstein Apathy Scale

^aWhole group differences

^bCT vs MT interventions

^cCT vs control condition

^dMT vs control condition

Fig. 1

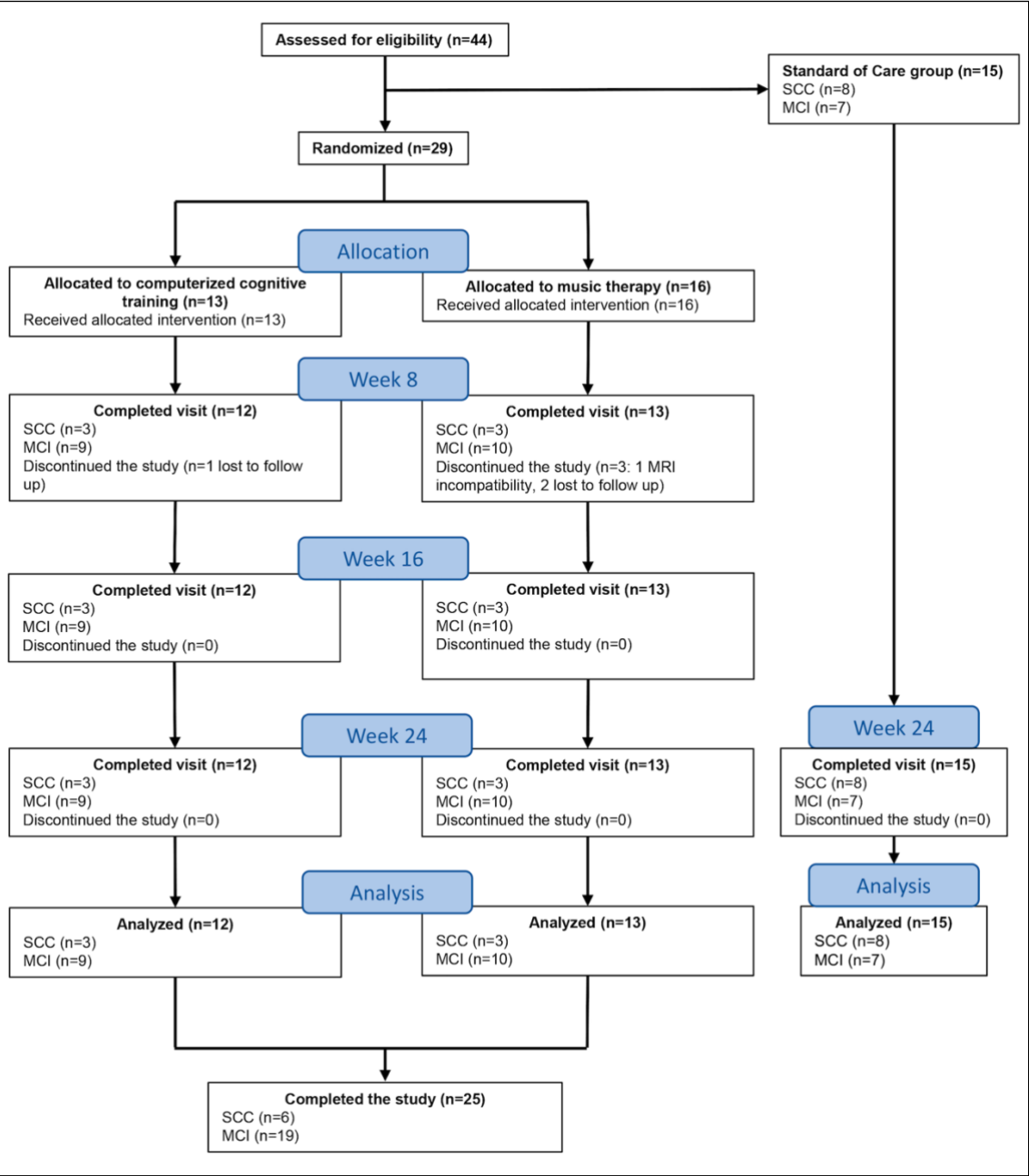


Fig. 2

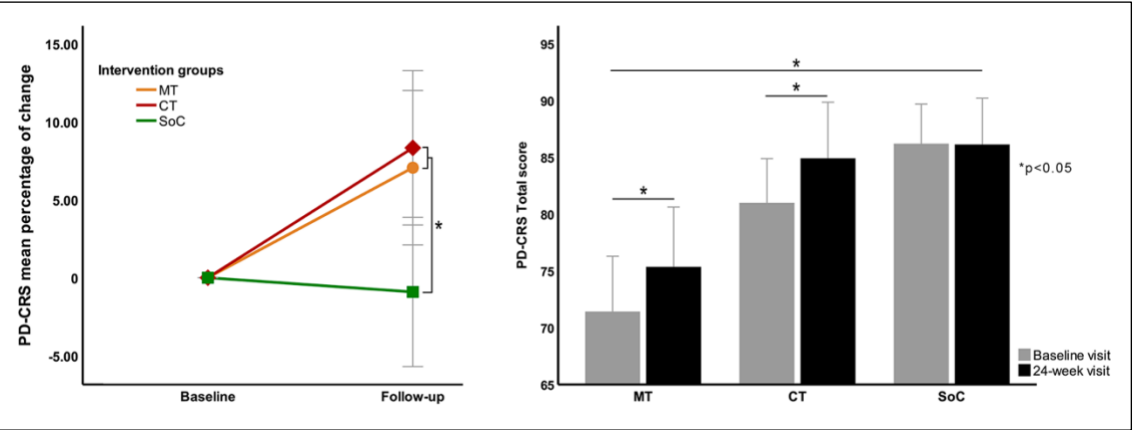


Fig. 3

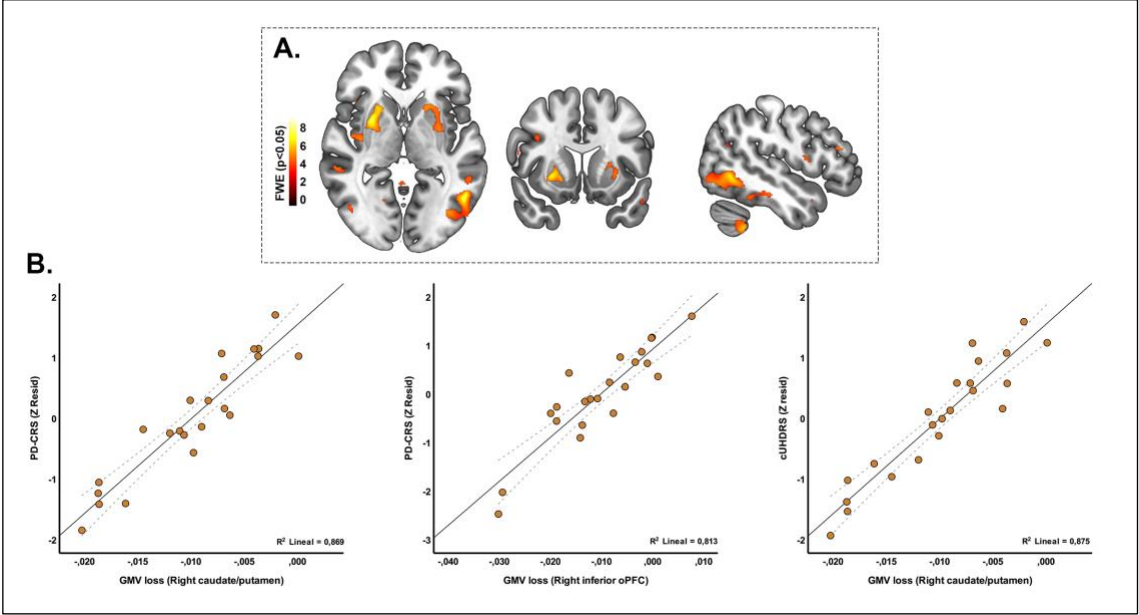


Fig. 4

