Research Report

The Effect of Music Therapy in Patients with Huntington's Disease: A Randomized Controlled Trial

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Abstract.
Background: Music therapy may have beneficial effects on improving communication and expressive skills in patients with Huntington's disease (HD). Most studies are, however, small observational studies and methodologically limited. Therefore we conducted a multi-center randomized controlled trial.

Objective: To determine the efficacy of music therapy in comparison with recreational therapy in improving quality of life of patients with advanced Huntington's disease by means of improving communication.

Method: Sixty-three HD-patients with a Total Functional Capacity (TFC) score of ≤ 7, admitted to four long-term care facilities in The Netherlands, were randomized to receive either group music therapy or group recreational therapy in 16 weekly sessions. They were assessed at baseline, after 8, 16 and 28 weeks using the Behaviour Observation Scale for Huntington (BOSH) and the Problem Behaviour Assessment-short version (PBA-s). A linear mixed model with repeated measures was used to compare the scores between the two groups.

Results: Group music therapy offered once weekly for 16 weeks to patients with Huntington's disease had no additional beneficial effect on communication or behavior compared to group recreational therapy.

Conclusion: This was the first study to assess the effect of group music therapy on HD patients in the advanced stages of the disease. The beneficial effects of music therapy, recorded in many, mainly qualitative case reports and studies, could not be confirmed with the design (i.e. group therapy vs individual therapy) and outcome measures that have been used in the present study. A comprehensive process-evaluation alongside the present effect evaluation is therefore performed.

Keywords: Behavior, communication, Huntington's disease, music therapy, quality of life, RCT

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INTRODUCTION

Huntington's disease (HD) is an autosomal dominant inherited, progressive, neurodegenerative disorder, characterized by a triad of motor, cognitive and psychiatric signs and symptoms [1, 2].

These characteristics often result in loss of expressive and communicative skills, especially in the advanced stage of the disease, frequently giving rise to behavioral problems such as anxiety, irritability and apathy. The gradual deterioration in communication skills, in combination with the behavioral problems in patients with HD, contributes to a decrease of functional health and a progressive inability to participate in various life situations, leading to loss of quality of life [3].

Despite the increase in number of therapeutic trials over the last 20 years, there is as yet no cure for HD, nor can its progress be reversed or slowed down. The emphasis of all forms of treatments is, therefore, to improve quality of life [2]. One of these non-pharmaceutical treatments offered to patients with HD in long-term care facilities is music therapy [4].

The American Music Therapy Association (AMTA) defines music therapy as follows:

> "Music therapy is the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program" [5].

Music therapy uses music experiences and patient-therapist relationships in order to effect therapeutic change [6]. Music therapists are part of the multidisciplinary team and participate in interdisciplinary treatment planning, ongoing evaluation, and follow-up [5].They assess emotional well-being, physical health, social functioning, communication abilities, and cognitive skills through musical responses. Music therapists design music sessions for individuals and groups based on client needs using music improvisation, receptive music listening, song writing, lyric discussion, music and imagery, music performance, and learning through music [6].

Specific literature about MT in HD is scarce. In a comprehensive systematic literature review, Van Bruggen & Roos conclude that precise music therapy aims and methods in relation to the stage of the disease are not well determined, and therefore there is a need for a systematic study to determine the effects of music therapy in HD [7].

Over the past decades, music therapy (MT) has been developed for patients with other neurodegenerative diseases [8, 9]. There is evidence that music therapy influences emotional well-being positively and that participation in music therapy increases social response in persons with dementia, thus providing additional means of communication and enabling the patient to express his or her needs and emotions [10, 11]. Through music, contact can be established, especially as language deteriorates during the later stages of the dementia process [12]. The patient can be stimulated to recall life experiences through music. In the music therapy session this can be used as a catharsis to experience emotions. Furthermore, MT can reduce behavioral and psychological symptoms of dementia [4–16].

Finally, enhancing the ability for self-expression, contributing to improvement of the quality of life, has been reported by Lee and McFerran who in a multiple case study describe five females with profound and multiple disabilities using song-choices in music therapy [13].

Based on the aforementioned benefits, the assumption can be made that music therapy is potentially a valuable non-pharmacological intervention to improve communication skills and thus possibly reduce behavioral problems, leading to a better quality of life (QoL) overall, in people with HD.

The aim of the present study is to evaluate the effect of group music therapy (MT), compared to group recreational therapy (RT), on communicative and expressive skills in relation to behavior changes. The research questions are

1) Does MT improve expressive and communicative skills in people with HD?
2) Does MT reduce behavioral problems in patients with HD?

METHODS

An extensive description of the protocol has been published elsewhere [17].

Participants

Sixty-three patients with a clinically and genetically confirmed diagnosis of HD, 18 years and older, with a maximum TFC-score of 7 [18] were included. They were recruited from four different long- term care facilities in The Netherlands which specialize in HD-care. Patients with poor comprehension of the Dutch language or with hearing-impairments were excluded. Patients with other neurological disorders and patients who had received music therapy within the three months prior to the study were also excluded. Patients were allowed to continue their regular medication during the study, and any change

in use was carefully registered. All patients and/or their legal representatives gave informed consent. The study was approved by the medical ethical committee of the LUMC (registration # P14.038) and all local committees in the four nursing homes.

Patients were allocated to either the intervention group (music therapy) or the control group (recreational therapy). Recreational therapy was chosen over "no intervention/treatment as usual" because being a complex, multi-faceted intervention as is music therapy, recreational therapy to us seemed to be the most appropriate control intervention to make the two groups as homogeneous in personal attention and thus as comparable as possible.

Patients in both groups participated in group interventions with three to five participants. The decision to use group therapy instead of individual therapy was based on Magee [19, 20] who recommends music therapy group intervention in the mid- and late stage of the disease.

Randomization

Participants were randomized using stratified permuted block randomization with a 1 : 1 ratio of music therapy to recreational therapy. For details see the flowchart in Fig. 1.

The participants were stratified per center. Two independent persons per center conducted the randomization. The block-size varied from three to five persons, depending on the total number of participants in the center. The date of signing the informed consent was used to determine the sequence in which the participants were randomized. The decoded allocation was revealed after all baseline measurements had made. After randomization, the participants were considered part of the study, regardless of whether they decided to leave the study prematurely (intention-to-treat principle).

Data collection

All measurements were collected in patients' files and stored in locked cabinets. Data were entered into SPSS version 22 by an independent research assistant.

Blinding

The assessors conducting the measurements were kept unaware of the patient's allocation, as was the principal investigator and the statistician. The allocation was not revealed until all analyses had been completed and conclusions drawn. Blinding the nursing staff, who were responsible for some of the measurements, was not always feasible as they were also responsible for transporting the patients to and from the therapy rooms, as the number of available nurses on the ward was limited. Furthermore, blinding of the principal researcher and the statistician, who were responsible for the statistical analysis, was guaranteed: all data were coded, ensuring both were unaware of the allocation, the institute, the gender, the age and the use of medication of each participant. The dataset was not decoded, nor were the allocations revealed until the analysis had been completed.

Baseline assessments

Clinical and demographic variables (gender, age, use of psychotropic medication) were assessed at baseline (see Table 1). The Mini Mental State Examination (MMSE) [21] was assessed at baseline to determine whether the cognitive functioning of the patients in the intervention group was different than those of the patients in the control group after randomization. Assessment of the MMSE was carried out by a psychologist at the start and at the end of the study. Due to the severe cognitive state of the participants, the MMSE could not be assessed for 22 participants in the first assessment and for 26 in the second assessment. The missing scores were set to zero.

Outcome parameters

For a comprehensive description of the used items of the two measurement tools, see Supplementary Material 1.

The primary outcome measure of the study was the social-cognitive functioning subscale of the Behaviour Observation Scale Huntington (BOSH) [22]. This scale consists of 15 items which were expected to detect changes in communicative and expressive skills. We choose this subscale as the primary outcome measure because it was hypothesized that through stimulation of these skills, activities of daily life and social-cognitive functioning will improve. As a result, behavioral problems (being the secondary outcome measures, see below) will reduce, overall leading to an improvement in the quality of life [17]. The scores of this subscale range from 1 (unaffected) to 4 (contact no longer possible); the sum score may range from 15 to 60. The
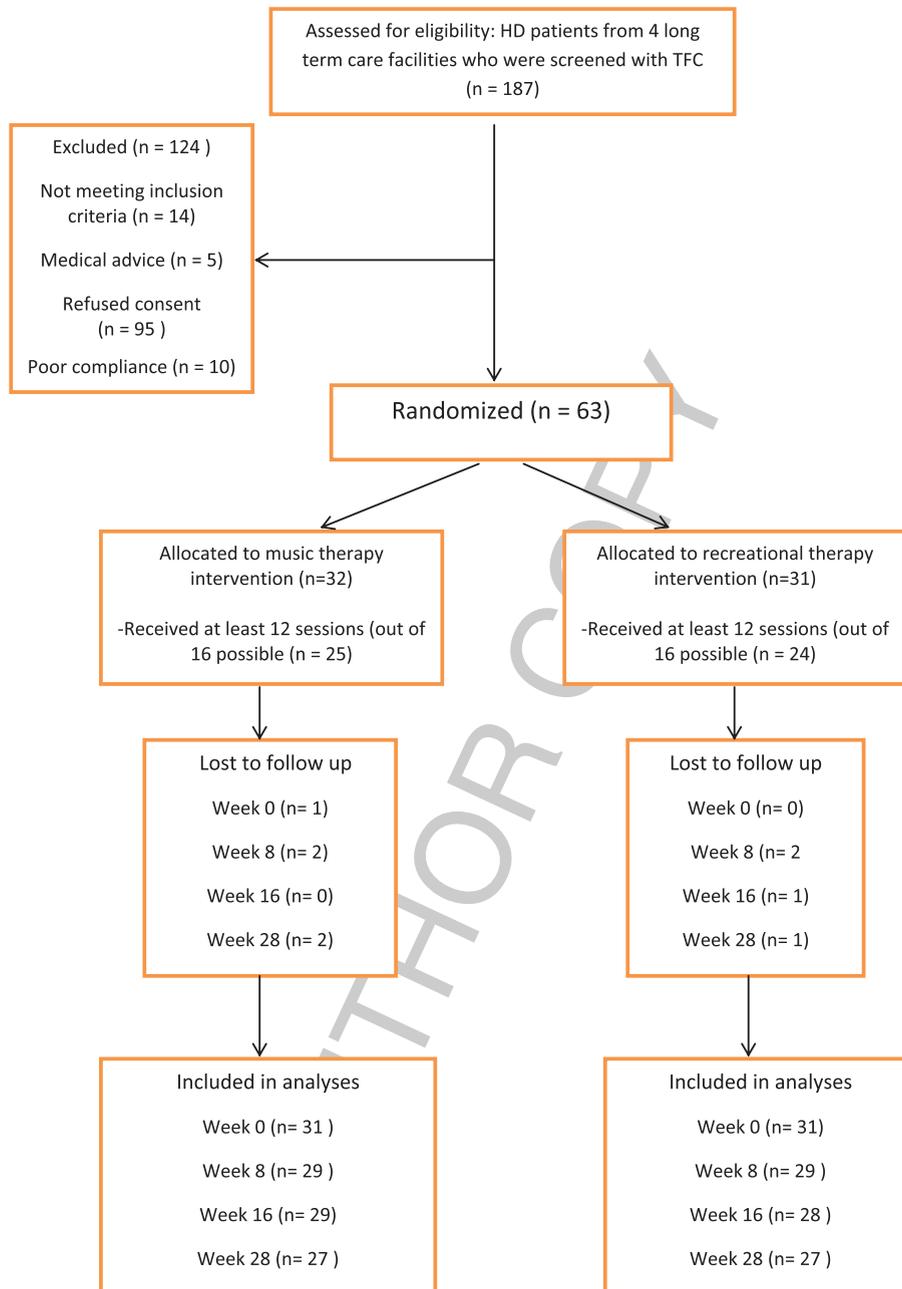
Fig. 1. Flowchart.

BOSH-assessments were administered by previously trained nursing staff in charge of the daily care of the patients. Assessment of the BOSH took place at a random time point, one week before the first intervention (baseline assessment), and was repeated after the 8th and the 16th intervention. Finally, the last BOSH-assessment took place 12 weeks after the last intervention (week 28).

The secondary outcome measures, behavioral problems, were assessed by the third subscale of the BOSH [18] and the Problem Behaviours Assessment-short version (PBA-s) [23, 24].

This subscale of the BOSH, the mental rigidity and aggression subscale, consists of 12 behavior-related items; the scores range from 1 (never) to 4 (always); the sum score can range from 12 to 48.

Table 1
Demographic and clinical characteristics of the study population

	Music therapy ($n = 32$)	Recreational therapy ($n = 31$)	Total ($n = 63$)
Total number of sessions			
– Attended/maximum	410/512	383/496	793/1008
– Missed (%)	102 (19,9%)	113 (22,8%)	215/(21,3%)
Mean age (years)	54,5	54,3	54,4
n (%) men	10 (31,2%)	10 (32,3)	20 (31,7)
n (%) women	22 (68,8%)	21 (67,7%)	43 (68,3)
Mean TFC-score at baseline	1,0 (S 1,48)	1,90 (SD 1,72)	1,44 (SD 1,65)
Mean MMSE-score			
– at baseline	14,9 ($n = 18$)	18,7 ($n = 23$)	16,8 (SD 8,09)
– after session 16	13,5 ($n = 17$)	18,0 ($n = 20$)	15,8 (SD 9,25)
Mean MMSE-score after setting missing scores to 0			
– at baseline	8,34 ($n = 32$)	13,87 ($n = 31$)	11,11
– after session 16	7,19 ($n = 32$)	11,58 ($n = 31$)	9,39
No. of patients who received psychotropic medication throughout the trial (week 0 – week 28)	25 (78,1%)	23 (74%)	24 (76%)
– antipsychotics	19	17	18
– antidepressants	18	18	18
– anxiolytics	19	12	16
– hypnotics	8	7	8
– anti-epileptics	2	4	3

The PBA-s consists of 11 semi-structured interview items and assesses behavioral problems in the 4 weeks prior to the interview. After consulting the PBA-workgroup, however, we adjusted the retrospective 4 weeks to 1 week, due to the short time-frame in which the PBA-s had to be administered. The PBA-s is a 5-point rating scale with subscales for severity and for frequency. The severity subscales uses the scores 0 (not at all) to 4 (severe/intolerable). The frequency subscale scores from 0 (absent) to 4 (all day, every day). Severity and frequency scores are multiplied to produce an overall PBA-score for each symptom. The PBA-s was scored by independent, trained psychologists who were blinded to group allocation of the patients.

The timeline of the assessment of the primary and secondary outcome measures is depicted in Fig. 1.

Intervention

The study was conducted between October 2014 and May 2016. Over a period of 16 weeks, participants received either music therapy or recreational therapy. All participants received their usual treatment while participating in the study and were not allowed to receive additional individual music therapy. Participants were free to leave the session or discontinue participation at any time. Each group consisted of three to five participants. The four

participating centers had their own professionally trained music therapist and recreational therapist. They were all fully instructed to adhere to the study-protocol.

In the music therapy group, each of the 16 music therapy interventions lasted 60 minutes and was provided weekly. The music therapy approach focused on encouraging and engaging participants in expressive musical interaction [6]. The intervention was partly described in a protocol, a treatment guide, in which the setting, goals and basic principles of the intervention were outlined, and the procedure itemised. The music therapy techniques aimed at achieving the goals were derived from the protocol "music therapy for Huntington's patients on improving and stimulating communication and self-expression" [25]. The music therapists were encouraged to be flexible while using the guidelines, allowing the "state-of-mind" of the participant, in combination with the therapist's own clinical experience, to be the guide.

While the sessions were partly standardized without limiting the music therapists in their interactions, the intervention itself was to be applied according to the protocol: each session started with the same welcome song and ended with the same farewell song. Between these two songs, the music therapist was allowed to adjust the level of each intervention according to individual capacities. The music

experiences could range from listening to music to playing or singing songs to free improvisation.

In the control group, recreational activities were offered under exactly the same circumstances as the above-mentioned music therapy sessions. As in the intervention group, a treatment guide described the procedure for the control group. The main goal of the recreational activities was to enhance communication skills by way of encouraging and stimulating the patients to interact. The activities could vary from reading the newspaper, cooking, arts-and-crafts/handwork or puzzles/games. Musical activities, such as singing along or watching a music-video, were not allowed, nor was background music to be played during the activities. Participation in musical activities in the facility (such as attending an in-house music performance) was allowed. These activities are not considered to be music therapy and are open to all patients residing in the institution,

regardless of participation in the study. Also, listening to music in the privacy of their own room was allowed throughout the study.

Statistical analysis

Sample size was determined based on the ICC of the primary outcome measurement (BOSH) [18]. We assumed that the values in the control group would not change very much over the course of the study, whereas those in the experimental group would improve by 25%. We further assumed an α of 0.05 and a ß of 0.20. Based on these assumptions, we came to the following sample size calculation:

– Social-cognitive original mean (SD) = 2.10 (1.58) and if we conservatively estimate a reduction in SD to 0.75, we would require an N of 30 per group for this subscale (for an effect size of 0.52 (moderate)).
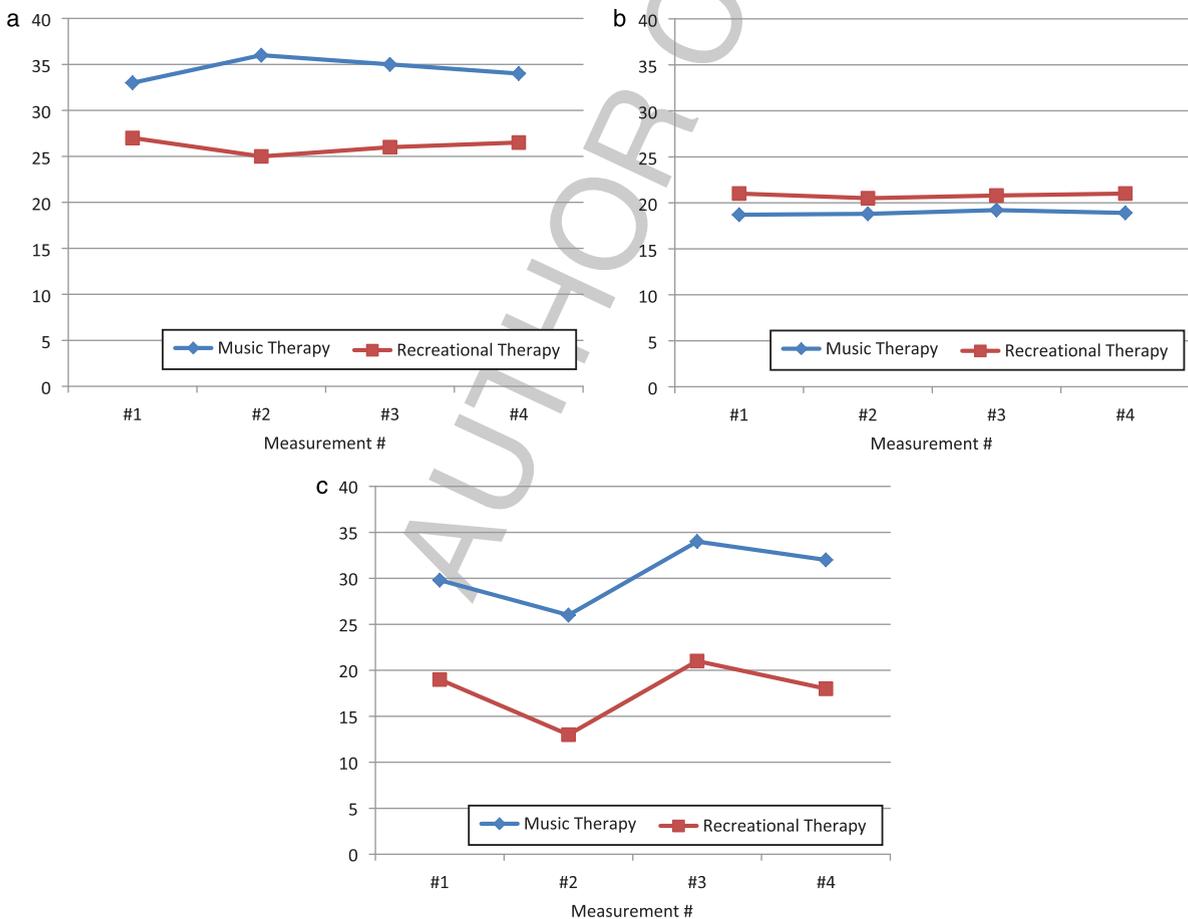

Fig. 2. (a) Mean sum scores (range 15–60) of the social/cognitive domain of the BOSH for both conditions at each of the four time-points. (b) Mean sum scores (range 12–48) of the mental rigidity/aggression- domain of the BOSH for both conditions at each of the four time-points. (c) Mean sum scores (range 0–176) of the severity/frequency scale of the PBAs for both conditions at each of the four time-points.

We followed the same statistical procedure for all three (primary and secondary) outcome measures:

First we calculated the mean sum scores of the scale (see Fig. 2). The sum score of the baseline-values was then used as a covariate in the subsequent mixed model analysis as these baseline scores appeared to be different between the MT-group and the RT-group.

A linear mixed model with repeated measures was used to compare the four BOSH and PBA-s-scores of the experimental and the control group, fitting condition (MT or RT) and time variable (the assessment number) as fixed effects in the model.

As stratified randomisation can lead to correlation between treatment arms, we adjusted for the stratification factor (i.e. the institution) in the analysis to obtain correct confidence intervals and p-values by fitting the institution code as a factor in our linear mixed model.

All data were gathered and stored in locked cabinets in the four different participating centers and entered into SPSS version 22 by an independent research assistant.

RESULTS

A total of 187 residents from four different long-term care facilities were eligible to participate in the study. Of these, 124 residents were not included for various reasons: not meeting the inclusion criteria, refusing consent, medical advice or poor compliance. The remaining 63 participants were randomised to either music therapy ($n = 32$) or recreational therapy ($n = 31$). Of these, a total of 9 participants (5 from the MT group and 4 from the RT group) were lost to follow-up, due to death ($n = 4$), moving to another care-facility ($n = 1$), or lack of motivation ($n = 4$). This resulted in 54 participants remaining (27 randomised to MT and 27 to RT). See the flowchart in Fig. 1.

At baseline, the mean TFC-score of the MT-group (1.00) tended to be somewhat lower than that of the RT-group (1.90), indicating a lower functioning

level of participants in the MT-group. However, this difference was not significant ($p = 0.03$). For all other characteristics (gender, age) the two groups did not differ significantly.

For both conditions at each of the four time-points, the unadjusted mean sum scores of the social/cognitive subscale of the BOSH are shown in Fig. 2a, of the mental/rigidity/aggression subscale of the BOSH in Fig. 2b, and of the severity/frequency scale of the PBAs in Fig. 2c. Note that a lower score means improvement for all three outcome measures.

Linear mixed models analyses showed that

– the difference between conditions at the three post-baseline time points, after correction for the difference in baseline values, can assumed to be constant as there was no effect-modification (interaction) of these differences by time (see Fig. 2);
– the difference between the estimated means of the scores of the social/cognitive subscale of the BOSH between the two conditions (2.88) at the three post-baseline time points is significant at the 0.05 level ($p = 0.042$), with a beneficial effect for the control condition;
– the difference between the estimated means of the scores of the mental rigidity/aggression subscale of the BOSH between the two conditions (4.60) at the three post-baseline time points is not significant at the 0.05 level ($p = 0.125$);
– the difference between the estimated means of the scores of the severity/frequency scales of the PBA-s between the two conditions (–1.39) is not significant at the 0.05 level ($p = 0.630$). See Table 2.

When institute was added as a fixed effect in our model, there was no interaction effect between institute and condition, i.e. the difference between the means of the sum-scores of the two conditions did not depend on the institute for any of the three domains.

Table 2
Estimate of the fixed effects of the primary and secondary outcome measures

	Estimate	Significance	95% Confidence interval	
			Upper bound	Lower bound
SocCog[1] (Primary Outcome)	2.88	0.042	0.108	5.65
MentRigAggr[2] (Secondary Outcome)	4.60	0.125	–1.32	10.52
PBAsSevFreq[3] (Secondary Outcome)	–1.39	0.630	–7.16	4.38

[1]Social/cognitive subscale of the Behavioural Observation Scale Huntington. [2]Mental rigidity/aggression subscale of the Behavioural Observation Scale Huntington. [3]Severity/frequency scale of the Problem Behaviour Assessment-short version.

DISCUSSION

In the present study we have looked for answers to the following three research questions:

1) Does MT improve expressive and communicative skills in people with HD?
2) Does MT reduce behavioral problems in patients with HD?

Music therapy offered to patients with Huntington's disease once weekly for a period of 16 weeks had no additional beneficial effect on improving expressive and communicative skills or on reducing behavioral problems when compared to recreational therapy. A slight clinical effect was found in the primary outcome measure (the social and cognitive subscale of the BOSH) in favor of recreational therapy. In our opinion, the clinical relevance of this outcome is negligible as the difference in outcome between the two conditions was very small. No significant effect could be found for the two secondary outcome measurements (the mental rigidity/aggression subscale of the BOSH and the severity/frequency scale of the PBA-s) in favor of MT or RT.

There seems to be a discrepancy between subjective (qualitative) positive evaluations that have been published and the objective (quantitative) outcome measures that are reported in this study. This is also highlighted in a comprehensive literature review [7]. Possible explanations of this apparent discrepancy are that this study is the first randomized controlled trial applying music therapy for patients in the advanced stage of Huntington's disease, involving a relatively large number of participants. The strength of the study is three-fold:

First: The design: randomization took place separately in each participating facility. Anticipating the possibility of unbalanced and missing data, we decided to use a linear mixed model to analyze the results.
Second: The fact that we used an active condition in the control group, providing similar degrees of attention and group contact in both groups. Most studies to date have used "treatment as usual" as the control condition.
Third: The fact that on the one hand, the clinical method was clearly defined: both interventions were (partly) protocolled, guiding all therapists to conduct a similar and thus comparable procedure during the sessions. On the other hand, the therapists had the freedom to elaborate during each

session as long as each of them aimed for the same goals.

It should also be mentioned that conducting an RCT with vulnerable late stage HD-patients is very challenging. The burden of participating in such studies is heavy, especially for the patients in the more advanced stages of the disease as in our study, who are more likely to drop out before completing the trial [1].

Several limitations of the present study may be the cause of the above-mentioned discrepancy between quantitative and qualitative evidence:

A. The vulnerability of the target population in relation to compliance with treatment.

Considering the low scores on both the MMSE and the TFC, the severity of the cognitive impairments at this stage of the disease is obvious. In the literature review [7], the HD-patients included in the studies were in the early or mid-stage of the disease, while in the present study, all participating patients were in the advanced stage.

Although participants were allocated to the groups by randomization, the scores of those in the music therapy group were somewhat lower in both the MMSE and the TFC, indicating a more severe functional and cognitive state in the MT-group. Adjustment for TFC-scores however did not provide different results, indicating that the functional difference was not a confounder.

The factors mentioned here might also explain the large number of sessions missed and hence the missing data (see Table 1). The strength, however, of performing a mixed model technique is that it is less sensitive to missing data than "classical" techniques through its restricted maximum likelihood estimation of effects.

B. The sensitivity of the measurement tools for the advanced stage of the target population.

The assessment tools (BOSH and PBA) might not have been the most eligible, as they might not be sensitive enough to detect marginal clinical effects in the later stages of the disease. However, the tools that were available at the time of designing the study were expected to be not eligible to use in advanced stage patients (the target population of the presented study). The choice for the BOSH and the PBA-s was based on the expectation that the items of (the subscales of) these tools would detect changes in communication and expressiveness, as well as in behavior, see Supplementary Material 1. A good alternative for future studies might be the UHDRS-FAP

(Unified Huntington's Disease rating Scale - For Advanced Patients) [26]. This is the only scale that detects decline in patients with a TFC-score ≤1. The UHDRS-FAP was adjusted in 2013 and appeared to be more sensitive to change than the original UHDRS for cognitive and motor domains. Also, a pilot validation study of the Music Therapy Assessment Tool for Advanced Huntington's Disease (MATA-HD) has just finished in the UK [27]: preliminary data indicate that the MATA-HD is a promising tool for measuring patient responses to music therapy interventions across psychological, physical, social and communication domains of functioning in patients with advanced HD. Neither tool was available yet when designing the present study.

Furthermore, validated measurement tools that are sensitive for emotional and social cognitive responses in dementia (see introduction) might be suitable to use in future studies with HD-patients.

C. The short-term effect of the intervention.

It would be quite valid to raise questions about the frequency and the time-points of the assessments. It is possible that the short-term effect of the intervention might not have been detected in the present study. In a comparable study which determined the effects of music therapy in reducing behavioral problems in elderly people with dementia, measurements were taken one hour before the session, and one, two and four hours after the session [28]. In our opinion this was not feasible in the present study due to the severity of the participants' condition.

D. Group-intervention versus individual intervention.

Group intervention, even though the group-size was small, might not have been the best option. In our opinion, contrary to Magee [19, 20], at this late stage of the disease, individual therapy might be preferable.

Finally: when designing the study protocol we initially developed a third research question: 'does MT improve quality of life of patients with HD?'. We decided to omit this third question, as the relation between the primary and secondary outcome measures and improvement of the quality of life of patients with HD could not be evaluated in the present study with the assessment tools that were used. However, this third research question remains open for discussion. However, the lack of quantitative outcome measures supporting the beneficial effects of music therapy on communication and behavior in patients with HD does not implicate that music therapy does not have a beneficial effect on improving quality of life. When evaluating interventions that have the potential to improve quality of live, finding the best research designs and the best outcome measures for patients in the advanced stage of HD remains a major challenge.

CONCLUSION

This was the first study to assess the effect of group music therapy on HD patients in the advanced stages of the disease. The beneficial effects of music therapy, recorded in many, mainly qualitative case reports and studies, could not be confirmed with the design (i.e. RCT, group therapy vs individual therapy) and outcome measures that have been used in the present study. A comprehensive process-evaluation alongside the present effect evaluation is therefore performed. The outcome of this process evaluation is expected in the Spring of 2017 and will be published elsewhere. This will result in recommendations for future research to strengthen the (quantitative and qualitative) evidence for implementing music therapy in rehabilitation for persons with Huntington's Disease.

ETHICAL APPROVAL

The study has been approved by the Medical Ethics Review Committee of the Leiden University Medical Center, registration number P14.038, and by all four centers. The study has been registered in the Dutch Trial Register (NTR 4904).

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CONFLICT OF INTEREST

The authors have no conflict to report.

SUPPLEMENTARY MATERIAL

The supplementary information is available in the electronic version of this article: http://dx.doi.org/10.3233/JHD-160229.

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