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Short communication

Individualized exergame training improves postural control in advanced degenerative spinocerebellar ataxia: A rater-blinded, intra-individually controlled trial

Cornelia Schatton [a, b, 1], Matthis Synofzik, MD [c, d, 1], Zofia Fleszar [a, b, c, d], Martin A. Giese, PhD [a, b], Ludger Schöls, MD [c, d], Winfried Ilg, PhD [a, b, *]

[a] Department of Cognitive Neurology, Hertie Institute for Clinical Brain Research, Tübingen, Germany
[b] Centre for Integrative Neuroscience (CIN), Tübingen, Germany
[c] Department of Neurodegeneration, Hertie Institute for Clinical Brain Research and Centre of Neurology, Tübingen, Germany
[d] German Research Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Germany

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ABSTRACT

Background: Treatment options are rare in degenerative ataxias, especially in advanced, multisystemic disease. Exergame training might offer a novel treatment strategy, but its effectiveness has not been investigated in advanced stages.

Methods: We examined the effectiveness of a 12-week home-based training with body-controlled videogames in 10 young subjects with advanced degenerative ataxia unable or barely able to stand. Training was structured in two 6-weeks phases, allowing to adapt the training according to individual training progress. Rater-blinded clinical assessment (Scale for the Assessment and Rating of Ataxia; SARA), individual goal-attainment scoring (GAS), and quantitative movement analysis were performed two weeks before training, immediately prior to training, and after training phases 1 and 2 (intra-individual control design). This study is registered with ClinicalTrials.gov, NCT02874911).

Results: After intervention, ataxia symptoms were reduced (SARA -2.5 points, $p < 0.01$), with benefits correlating to the amount of training ($p = 0.04$). Goal attainment during daily living was higher than expected (GAS: 0.45). Movement analysis revealed reduced body sway while sitting ($p < 0.01$), which correlated with improvements in SARA posture and gait ($p = 0.005$), indicating training-induced improvements in posture control mechanisms.

Conclusion: This study provides first evidence that, even in advanced stages, subjects with degenerative ataxia may benefit from individualized training, with effects translating into daily living and improving underlying control mechanisms. The proposed training strategy can be performed at home, is motivating and facilitates patient self-empowerment.

1. Introduction

The cerebellum and its associated tracts are essential for the coordination of movements, including in particular balance control of posture and gait [1]. Correspondingly, damage in these tracts leads to instabilities in sitting, stance and gait [2–4]. This damage is inherently progressive in patients with degenerative spinocerebellar ataxia, where effective treatments are still scarce. It has recently been shown that intensive coordinative training [5–8], e.g. via exergames (=whole-body controlled videogames) [9], can improve the control of posture and gait in degenerative ataxia, but effectiveness is still controversial [10,11]. This situation is even more complicated for degenerative ataxia subjects with high multisystemic disease load - as often present in early-onset recessive ataxias [12] - and in advanced disease stages. Here, underlying neurodegeneration has progressed to partly irreversible states and includes additional extra-cerebellar systems, making functional plasticity and therapeutic success much less likely.

We here hypothesized that exergames-training might offer a

* Corresponding author. Department of Cognitive Neurology, Hertie Institute for Clinical Brain Research, Otfried-Müller-Straße 25, 72076 Tübingen, Germany.
E-mail address: winfried.ilg@uni-tuebingen.de (W. Ilg).
[1] Authors contributed equally.

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treatment approach for improving balance control even in non-ambulatory subjects with multisystemic degenerative spinocerebellar ataxia. Using a rater-blinded, intra-individual control study design, we show that an individualized exergame training, tailored to individuals' disease stage, improves postural control and ataxia-specific control functions even in advanced disease.

2. Methods

Subjects and general training strategy. We studied 10 young patients (age: 16.0 ± 7.4 years) – including a piloting subject described before [13] - with advanced spinocerebellar disease (for details on individuals see Table 1).

All patients were recruited from the ataxia clinic of the Center of Neurology and the Children's Hospital, University of Tübingen, Germany. Patients were included based on the following criteria: (1) advanced progressive ataxia in the absence of any signs of inflammatory, vascular, malformation, or tumor CNS disease; (2) advanced impairments in gait and stance, defined as Scale for Assessment and Rating of Ataxia (SARA) [14] subscore gait ≥3 *and* stance ≥3, but still able to sit without support >10 s, as defined by SARA subscore sitting <3; (3) age between 6 and 30 years; (4) absence of visual loss, hearing disturbances, mental retardation and predominant non-ataxia movement disorders (e.g. predominant spasticity, chorea, parkinsonism). 14 consecutive patients were screened for study inclusion. 4 out of 14 patients could not be included as they were unable to sit freely (all of them SARA sitting = 4), 2 of them also showing severe mental deficits. Non-Ataxia Symptoms were documented using the INAS score (Inventory of Non-Ataxia Symptoms [15], see e-supp INAS for details). For further clinical details and subjects' individual diagnosis, see Table 1. All subjects and, if below age <18 years, their respective legal guardians gave informed consent prior to participation. The study had been ethically approved (Az. 303/2011B01) and was registered at ClinicalTrials.gov (identifier NCT02874911).

Subjects received 12 weeks of coordinative training based on commercial videogames (Nintendo Wii® and Microsoft XBOX Kinect®), specifically selected to train trunk and postural control (for details on videogames, see e-supp exergames). Depending on the individual's SARA gait and stance scores at baseline, subjects received one of three training protocols differing in the demands on coordinative abilities (Fig. 1A; e-supp protocol). Training was divided into two consecutive 6-weeks phases of exergames-training at home. Phase I was introduced by a one-week lab-training consisting of four one-hour directed sessions, supervised by a sports scientist. Phase II was started by a two-day booster session, again supervised in the lab. This allowed to introduce novel games and tailor the training challenges according to subjects' individual progress during phase I. For both home-training phases, subjects were asked to train 3 times a week, 45 min per session (analogous to previous effective training protocols, [5,9]), and to document duration of home-training.

Study design. Subjects were examined four times: two weeks before the training intervention (E1), immediately prior to the intervention (E2), after phase I (E3), and after phase II (E4). Three different comparisons were performed: 1. By comparing E1 with E2 we determined the variability in test performance not caused by intervention, but by subjects' daily condition and test practice effects. 2. By comparing E2 with E3 we assessed short-term training effects. 3. By comparing E2 with E4 we determined longer sustained effects. The comparison of the baseline period (E1/E2) with the six weeks (E2/E3) and the 12 weeks (E2/E4) intervention period, respectively, allowed taking patients as their own controls in an intra-individual control design.

2.1. Outcome measures

Primary outcome measure. Primary outcome measure was the SARA score. SARA testing was performed by a movement disorder specialist (M.S.) and was video-recorded. After all subjects had completed all examinations, videos of single examinations of individual subjects were presented in a random fashion to an ataxia specialist (Z.F.) who was blinded to the number of the specific examination (E1-E4). The SARA scores of the blinded rater were taken for analysis. For sample size calculation based on this primary outcome measure, see e-supp sample size.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.03.016.

Secondary outcome measures. As secondary outcome measure, translation of training effects into subjects' daily living and personally relevant activities was determined by the goal attainment scaling (GAS) [16], as used in previous ataxia treatment trials [5,9,13]. Before intervention, each subject selected relevant goals of his/her individual way of living which were then graded after intervention. Scores ranged from −2 to +2 (−2 worsening from initial level, −1 initial level of performance, 0 expected level of performance, +1 greater than expected outcome, +2 much greater than expected outcome) (for individual goals, see e-supp goal attainment).

As an additional secondary outcome measure changes in

Table 1
Clinical data of the participants of the study. Ataxia was clinically assessed at the four examinations E1-E4 using the scale for the assessment and rating of ataxia (SARA) as primary outcome measure. SARA covers a range from 0 (no ataxia) to 40 (most severe ataxia). GAS: scores of individual goal achievement at examination point E4. BMI: body mass index; INAS: Inventory of Non-Ataxia Symptoms [13] (see supplement 4 for details of score). FA: Friedreich Ataxia, AOA1: Ataxia with oculomotor ataxia type 1; AT, Ataxia teleangiectasia; arCA: autosomal-recessive ataxia (all tested negative for: FA, POLG, PEO1, AOA1, AOA2, Ataxia with Vitamin E Deficiency [AVED], lysosomal storage diseases). F: female. M: male.

Pat ID	Age	gen- der	BMI	diagnosis	INAS	SARA				GAS Score E4	Average training hours per week
						E1	E2	E3	E4		
C1	6	F	15.1	arCA	2	13	14	11.5	12	1	2.75
C2	13	M	15.6	FA	5	21	21	17.5	17	0	2.63
C3	11	M	17.3	FA	5	15.5	17	12	13.5	0	3
C4	29	M	21.5	FA	4	22	19.5	17	18	0	2.72
C5	24	M	29.2	FA	6	25.5	24.5	21	22.5	1	2.63
C6	10	F	15.5	AOA1	7	24.5	25	17	17	1	2.7
C7	15	M	18.4	AT	7	28	24	22	24.5	0	2.2
C8	23	F	23.8	arCA	4	17.5	17	16.5	16.5	0	0.6
C9	10	M	21.0	AT	8	29	29	26	25	1.5	3.25
C10	19	M	23.3	FA	5	13.5	12	10	11	0	2.5
Ø	16				5.3	20.9	20.3	17.1	17.8	0.45	2.49

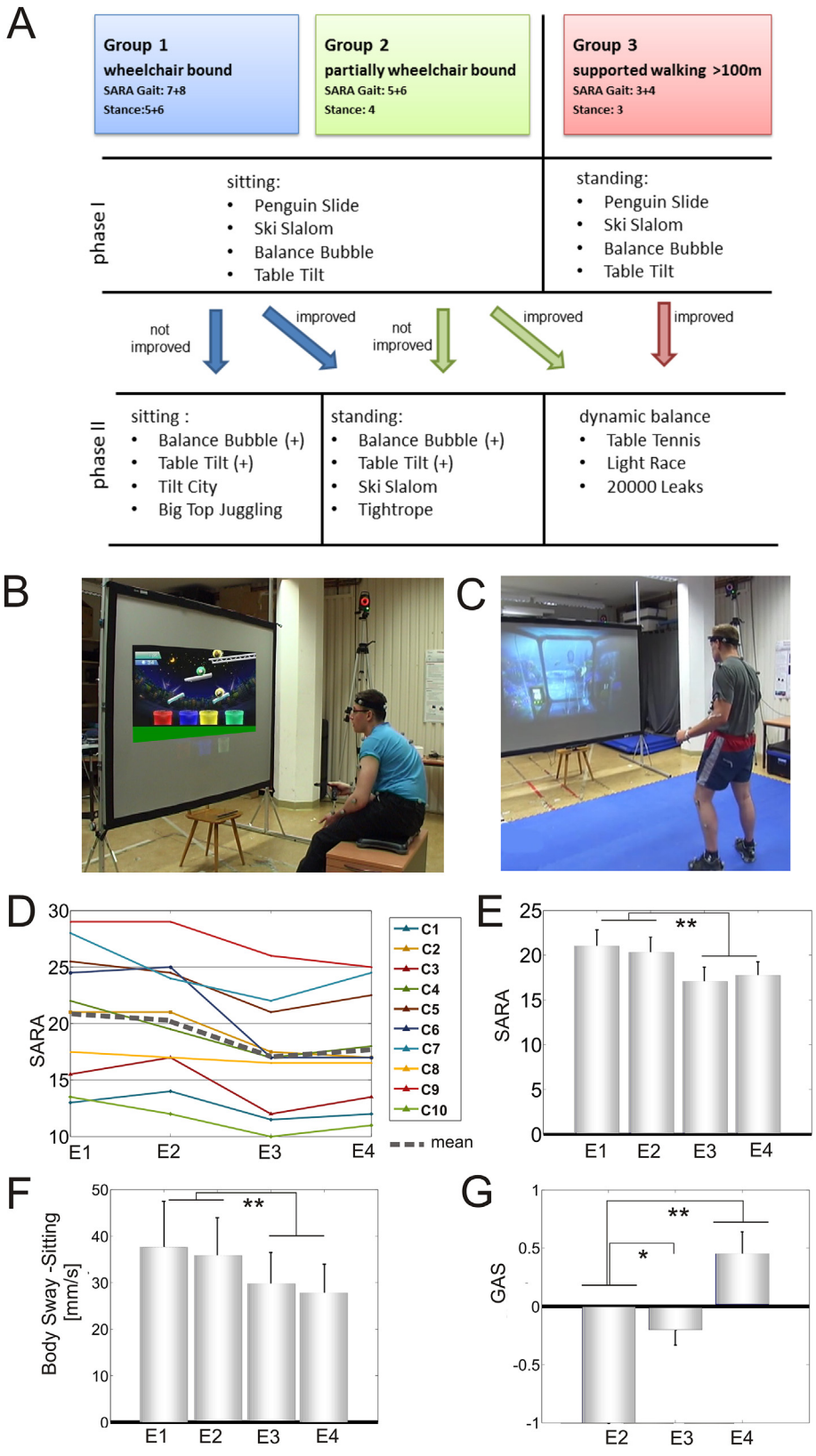

Fig. 1. (A) Overview of the individualized, adaptive training design. Training was divided into two consecutive 6-weeks phases of exergames-training at home. Subjects received one of three training protocols differing in the demands on subject's individual coordinative abilities at baseline. In the second phase, exergames and training program were adapted according to subjects' individual progress during phase I.
(B + C) Snapshots from ataxia subjects training with the games "*Tilt City*" (B) and "*20.000 Leaks*" (C) in the lab (for details of exergames see e-supp exergames).
(D–G) Changes in clinical ataxia severity, postural control, and goal-attainment scaling associated with exergame training. Scale for the Assessment and Rating of Ataxia (SARA) scores of individual patients (D) and SARA group means (E) at examinations E1-E4 at the different examinations, showing an average drop of −2.5 SARA points. (F) Body sway in sitting with closed eyes determined via quantitative movement analysis. (G) Goal attainment scaling (GAS) show improvements over the course of the training, reaching an average rating of 0.45 at E4, i.e. between expected outcome (GAS = 0) and greater than expected outcome (GAS = 1). Stars indicate significant differences between examinations (*:$p < 0.05$,**:$p < 0.01$).

postural stability were quantified by analyzing body sway while sitting. In the "Romberg sitting task" subjects had to sit freely without foot contact to the floor and with their arms stretched out to the front for 30 s. Subjects were instructed to sit as stable as possible, i.e. with as little body sway as possible. Romberg sitting was assessed with eyes open and eyes closed. Test re-test reliability of the Romberg sitting task was determined by comparing assessments E1 and E2. See details of the quantitative movement assessment in e-supp movement analysis.

2.2. Statistical methods

Analyses were performed using the non-parametric Friedman test (χ^2,p-values) to determine within group differences between examinations E1-E4. When the Friedman test yielded a significant effect ($p < 0.05$), post hoc analysis was performed using a Wilcoxon signed-rank test for pair-wise comparisons between assessments with a significance level $\alpha = 0.05$. We calculated the total SARA score and a SARA subscore posture&gait ($SARA_{p\&g}$) comprising of the items SARA gait, SARA stance, and SARA sitting. Spearman's rho was used to examine the correlation between SARA scores and movement parameters and training durations, respectively. Statistical analysis was performed using the software packages MATLAB R2012b and SPSS 22.

3. Results

At study inclusion, subjects showed an average SARA score of 20.9 ± 5.8 and INAS score of 5.3 ± 1.7, demonstrating both advanced ataxia and multisystemic disease load. The SARA score and $SARA_{p\&g}$ changed between the four assessments (SARA: $\chi^2 = 13.7$,$p = 0.003$; $SARA_{p\&g}$: $\chi^2 = 15.4$,$p = 0.001$; Friedman test). The SARA score remained unchanged before training (E1/E2), but dropped by average 2.5 points comparing pre/post intervention (E2/E3: $p < 0.002$; E2/E4:$p < 0.006$, Wilcoxon signed-rank test, Fig. 1D and E). These reductions of the SARA score correlated with the amount of individual training hours per week ($r = 0.65$; $p = 0.04$).

The change in SARA was driven by changes in the $SARA_{p\&g}$. This subscore remained unchanged before training (E1/E2), but dropped by 2.2 points at short-term (E2/E3:$p < 0.008$) and 1.8 points after 12 weeks (E2/E4:$p < 0.008$).

After training, subjects showed an improvement in individual goal attainment (E2/E4:$p < 0.002$), suggesting that training effects translate into daily living. The average GAS score of 0.45 ± 0.6 at E4 signifies that goal attainment achieved levels between expected outcome (GAS = 0) and greater than expected outcome (GAS = 1) (Fig. 1G, for individuals' goals see e-supp goal attainment).

Movement analysis revealed that postural sway remained unchanged for sitting with eyes open ($p = 0.97$, $\chi^2 = 024$; Friedman test), but improved for sitting with eyes closed ($p = 0.03$; $\chi^2 = 8.5$; Friedman test, E2/E3:$p = 0.13$; E2/E4:$p = 0.01$, Fig. 1F). These improvements correlated with the benefits in $SARA_{p\&g}$ ($r = 0.4$; $p = 0.005$).

4. Discussion

We here aimed to examine the effectiveness of individualized home-based exergame training on improving posture control mechanisms in non-ambulatory patients with advanced degenerative ataxia. Key results were improvements on different outcome levels: (1) Posture and gait ataxia severity improved clinically, correlating with (2) improvements in body sway (quantitative movement analysis) as well as with (3) the amount of training, and (4) translating into goal attainment in daily living. This is in particular remarkable given that 80% of the patients had an at least additional afferent ataxia component due to the nature of their ataxia (FRDA) – a subject group which has been shown to benefit less from coordinative training [5].

4.1. Training-induced improvements in clinical ataxia severity

The training improvement of 2.5 SARA points (Fig. 1) indicates a meaningful improvement, given that a reduction of one SARA point is generally considered as clinically relevant [17]. It represents a treatment effect equivalent to gaining back functional performance of 1.5 years of natural disease progression (e.g. progression in Friedreich's Ataxia: 1.4 point SARA increase/year [18]). Interestingly, the 2.5 SARA point training improvement is in the same range as training via exergames [9] or via physiotherapy [5,6] in mild-to-moderate degenerative ataxia. Thus, even largely non-ambulatory subjects with advanced degenerative ataxia are still capable of training-induced improvements, despite far more progressed and multisystemic neurodegeneration.

4.2. Improvements of posture control mechanisms

The overall effect in the SARA score was driven by the $SARA_{p\&g}$ subscore (rather than by other SARA items), indicating that the observed training effects reflect an improvement of particularly those capacities targeted by the training, namely balance control of sitting, stance and gait. This notion is further supported by the finding that gains in the $SARA_{p\&g}$ correlated with improvements in body sway while sitting determined via quantitative movement analysis. This correlation indicates that observed effects in the SARA score were not driven by unspecific improvements in e.g. cardiovascular endurance, but by improvements of posture control mechanisms.

Although we can only speculate about the specific underlying posture control mechanisms, the improvements in body sway in the closed-eyes condition indicate an improvement of sensor integration of non-visual cues. In this condition without visual feedback, control of one's own sitting performance relies solely on non-visual information, namely proprioceptive and vestibular information [19] and motor efference signals. Improvements in such an active proprioception, known to be impaired in cerebellar patients [20], could explain the observed improvements in postural control.

4.3. Improvements correlate with amount of training

Benefits of training seemed to depend on the amount of training, as suggested by the correlation between averaged hours of training and improvements in clinical ataxia severity ($r = 0.65$; $p = 0.04$). These results are consistent with earlier studies on physiotherapy [5] and exergames [9] in mild-to-moderate ataxia, thus demonstrating that continuous, frequent training may serve as a key principle for efficacy in ataxia neurorehabilitation.

4.4. Limitations

Limitations of this study include heterogeneity of the included early-onset ataxia subjects, small sample size, lack of sham training, and lack of assessment of long-term effects. Future studies specifically tackling these limitations are warranted to confirm the effects observed here.

5. Conclusions

Our findings provide first evidence for the effectiveness of a home-based inexpensive rehabilitation strategy to improve

dynamic balance in advanced multisystemic neurodegenerative disease.

Conflicts of interest

Conny Schatton reports no disclosures.
Matthis Synofzik received grants and honoraria from Actelion Pharmaceuticals.
Zofia Fleszar received a travel grant from Actelion Pharmaceuticals.
Martin A. Giese reports no disclosures.
Ludger Schöls reports no disclosures.
Winfried Ilg reports no disclosures
'The Authors declare that there is no conflict of interest'

Author contributions

CS: conceptualization of the study, acquisition and analysis of data, revising the manuscript
MS: design and conceptualization of the study, analysis and interpretation of the data
ZF: conceptualization of the study, acquisition and analysis of data, revising the manuscript
MG: interpretation of the data, revising the manuscript
LS: conceptualization of the study, interpretation of the data, revising the manuscript
WI: design and conceptualization of the study, analysis and interpretation of the data, drafting the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.03.016.

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