Effects of internet-based exercise (e-training) on fatigue and other patient reported behavioural outcomes (PRO) in patients with relapsing-remitting multiple sclerosis (RRMS)

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Objective

To evaluate the impact of structured, internet-guided exercise (e-training) on the profile/expression of fatigue and other behavioural PROs.

Methods

Prospective, multicenter study across ~~of~~ **12 months** with assessments at baseline (BL) and after 3, 6, 9 and 12 months (T3/T6/T9/T12) (Fig.1).
83 fatigued RRMS patients (Mc Donald, EDSS 0-3.5, FSMC total scale > 43, stable on INFbeta-1b at study onset, aged 18-60 yrs, mean: 36.6) cared at ambulant MS centers were randomized to an **instant training group (TG1)** that trained for a period of 3 months from baseline onward (BL-T3), and a **delayed training group (TG2)** that, after a 3 month waiting period, trained for 6 months (T3-T9).
Primary Outcome: fatigue (FSMC total, motor and cognitive subscores).
Secondary Outcome: MS-specific QoL/FAMS, clinical outcomes (neurostatus, relapses, EDSS); depression/ADS; daytime sleepiness/ESS; self-assessed deficits of attention/FEDA with subscores "reduced drive "/FEDA-AM "fatigue and slowdown in practical activities"/FEDA-EV, "distractibility and slowdown in mental processes"/FEDA-AV; BICAMS cognition battery (processing speed/SDMT, verbal learning and memory/AVLT, non-verbal memory/BVMT), and mobility (two-minute walk test/TMWT, timed up and go test/TUG).
E-training : Internet-guided strength and endurance training at home, 2-3 times/week, duration 10-60 min

Results

At Baseline homogeneous distribution of age, sex and EDSS was observed between TG1 and TG2 (Table 1). Despite randomization, TG1 shows significant lower total-fatigue level ($p < 0.001$) compared to TG2 (Fig.4).

After 3 months of exercise (BL-T3), TG1 showed highly significant less fatigue (FSMC total decreasing by -5.98 pts.; **p=0.001, effect size/ES -0,56); this effect was observed in motor fatigue (FSMCmot: -3.46 pts.; *p< 0.01, ES -0.61), and, albeit to a lesser extent, in cognitive fatigue (FSMCcog *p< 0.01, ES-0.42). In TG2, staying without training during BL-T3, all fatigue scores remained relatively stable on higher levels, nevertheless declining slightly. Comparing TG1 vs. TG2, there was a statistical trend (p=0.09) towards higher improvement of motor fatigue in TG1.

Adherence to e-training (Fig. 8) was comparable in both groups in the first 3 months of the training period. In the following 3 month training frequency is decreasing in TG2.

TG1 shows significant improvement in all investigated parameters (Table 2). Compared to TG2 significant (p=0.05) superior improvement has only been observed in quality of life (FAMS-total). A statistical trend to higher improvement in TG1 has been observed in mood/depression (ADS) (p=0.1) and self-assessed deficits of attention/FEDA including subscores drive and motivation /FEDA-AM .

At T12, TG1 still exhibits significant less (7.73pts. p=0.007) fatigue compared to BL (Fig. 9). This seems to indicate a positive long term effect of eTraining on fatigue.

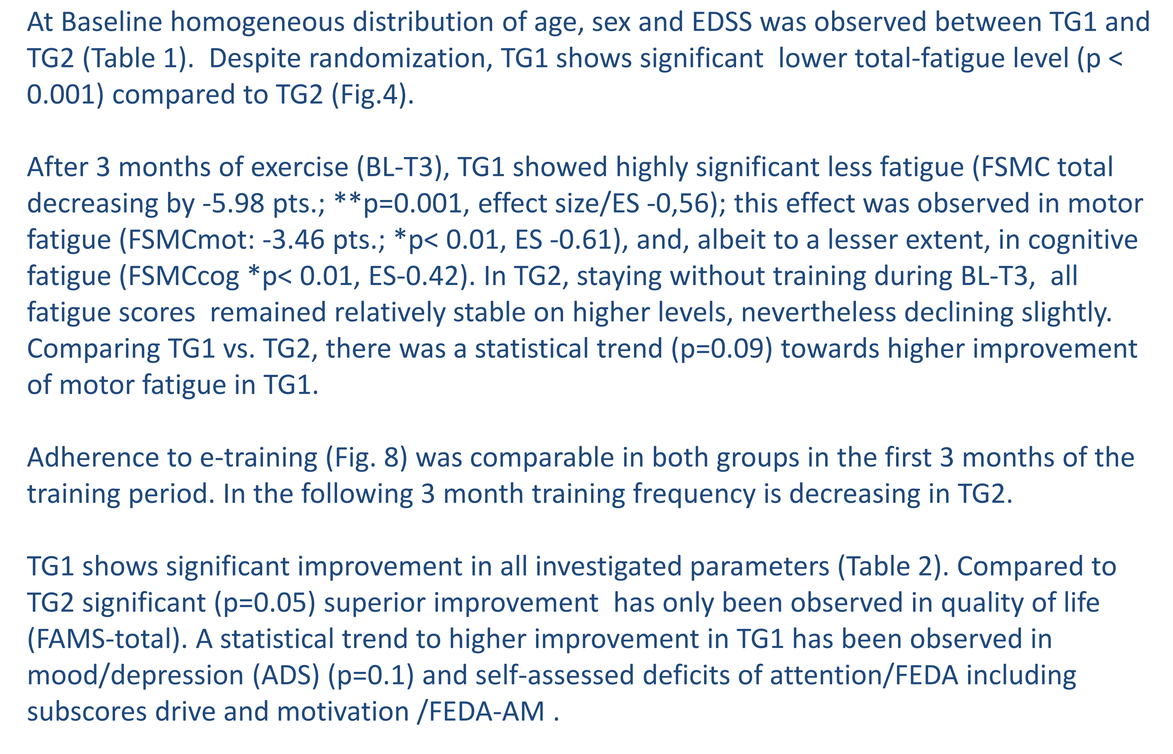

Fig. 1: Study design with groups (TG1 in red and TG2in blue), timepoints from baseline to Assessment at 12 month (T12). Mean observation period (M3)

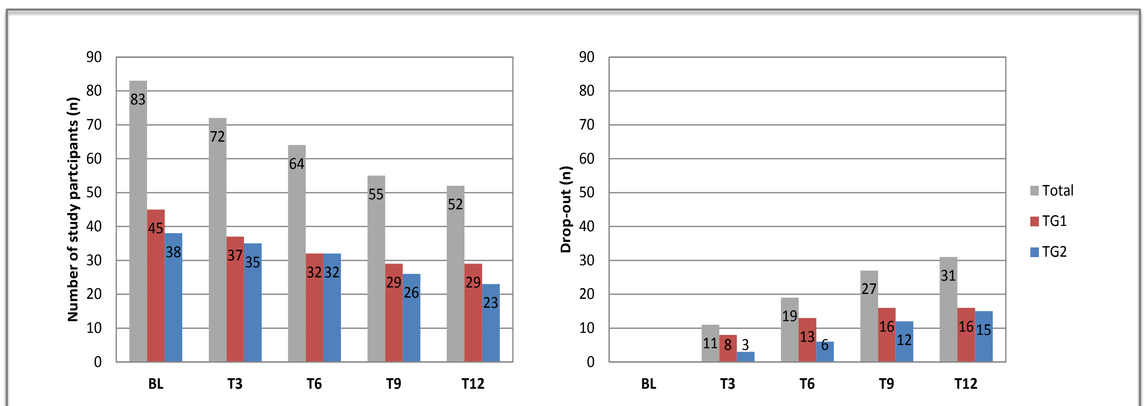

Fig. 2: Number of study participants across time (Total; instant training grp. /TG1; delayed training grp/TG2 .)

Fig. 3: Number of Drop-outs across time

	Total (n=83)	TG1 (n=45)	TG2 (n=38)
Age	36.67 ± 9.35	36.47 ± 9.47	36.92 ± 9.32
Sex			
female	60 (72.29%)	29 (64.44%)	31 (81.58%)
male	23 (27.71%)	16 (35.56%)	7 (18.42%)
FSMC	63.68 ± 14.84	58.91 ± 13.70	69.34 ± 14.29
EDSS	1.39 ± 0.49	1.38 ± 0.49	1.39 ± 0.50
BMI	25.92 ± 5,34	24.97 ± 4.98	27.05 ± 5.59
MS Duration (month)	58.66 ± 68.23	50.41 ± 64.27	68.21 ± 72.23
Relapses (n)	2.67 ± 3.39	2.18 ± 1.77	3.26 ± 4.60

Table 1: Demographic data at baseline (BL)

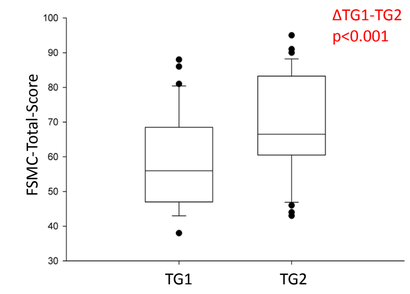

Fig. 4: Total-Fatigue level at BL comparing TG1 and TG2

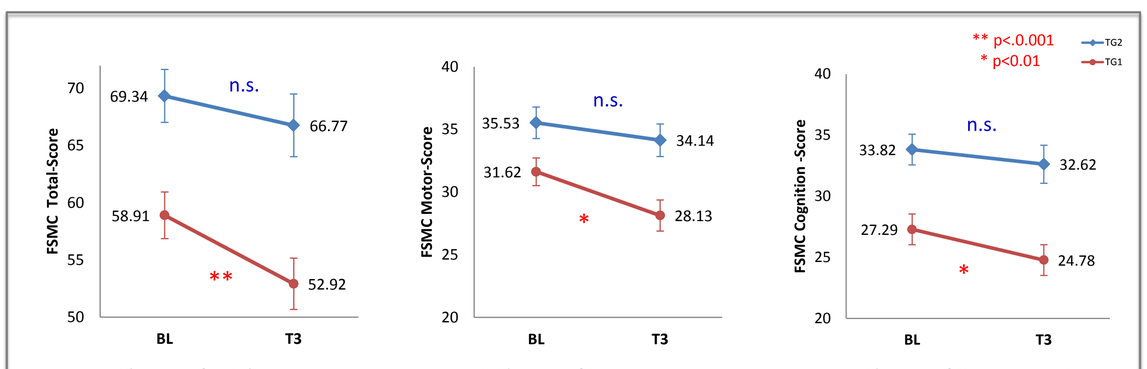

Fig. 5 Change of Total-Fatigue

Fig. 6 Change of Motor-Fatigue

Fig. 7 Change of Cognitive-Fatigue

	TG1 M3			TG2 M3			Δ(TG1-TG2) M3		
	Mean	ES	p-value	Mean	ES	p-value	Mean	ES	p-value
FSMC Total	-5.99	-0.62	< 0.001	-2.57	-0.26	-	-3.41	-0.18	-
FAMS Total	-7.21	0.47	0.01	0.11	0.01	0.97	-7.31	-0.24	0.05
TMWT	13.63	0.46	0.01	4.72	0.16	-	8.91	0.15	-
SDMT	2.13	0.32	0.06	0.82	0.12	-	1.31	0.10	-
ADS	-3.71	-0.47	0.01	-0.61	-0.08	-	-3.10	-0.20	(0.10)
ESS	-0.96	-0.33	0.06	-0.34	-0.12	-	-0.61	-0.10	-
FEDA AV	7.29	0.47	0.01	3.40	0.22	-	3.89	0.13	-
FEDA EV	3.23	0.45	0.01	1.20	0.17	-	2.02	0.14	-
FEDA AM	9.67	0.49	0.01	2.01	0.10	-	7.65	0.19	(0.10)
BVMT Total	5.82	0.49	0.01	6.32	0.52	<0.001	-0.50	-0.02	-

Table 2: Change of Outcomes in the mean observation period M3 (T0-T3) in TG1, TG2 and TG1 compared to TG2(ΔTG1-TG2). Means (black), effect size (blue) and p-value (red).

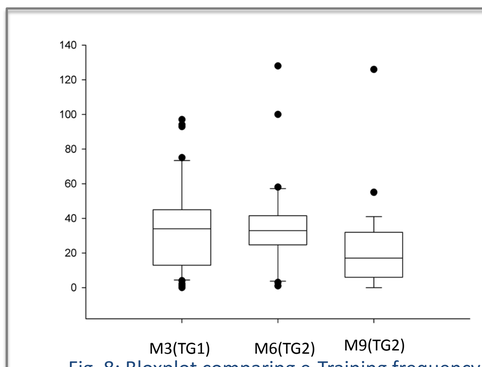

Fig. 8: Bloxplot comparing e-Training frequency in the observation periods M3, M6 and M9

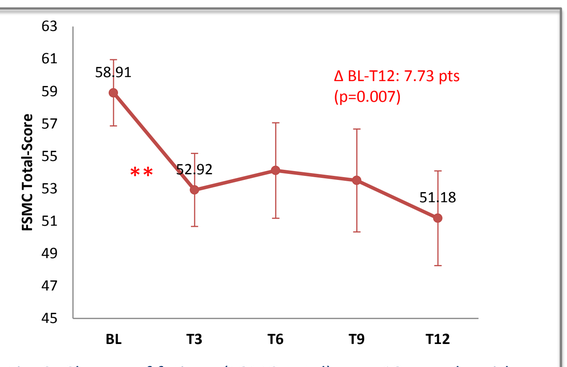

Fig. 9: Change of fatigue (FSMC-total) over 12 month, with a significant positive long-term effect

Conclusion

- **After 3 months of eTraining, a highly significant decrease (p<0.001) of fatigue can be validated in actively training RRMS patients (TG1)**
- **Compared to a delayed training group(TG2), only a statistical trend towards less motor-fatigue is present in TG1, possibly due to concomitant positive psychological effects on fatigue in TG2**
- **The significant positive long-term effect of eTraining on fatigue persists until 9 months thereafter**
- **Adherence to e-training decreases after 3 months of training. No additional benefit of eTraining longer than 3 months can be substantiated**

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