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Research Paper

Novel interdisciplinary intervention, GAIN, vs. enhanced usual care to reduce high levels of post-concussion symptoms in adolescents and young adults 2–6 months post-injury: A randomised trial

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ABSTRACT

Background: Evidence for effective interventions to prevent long-term sequelae after concussion is sparse. This study aimed to test the efficacy of Get going After concussIoN (GAIN), an interdisciplinary, individually-tailored intervention of 8 weeks duration based on gradual return to activities and principles from cognitive behavioural therapy.

Methods: We conducted an open-label, parallel-group randomised trial in a hospital setting in Central Denmark Region. Participants were 15–30-year-old patients with high levels of post-concussion symptoms (PCS) 2–6 months post-concussion (i.e., a score ≥20 on the Rivermead Post-concussion Symptoms Questionnaire (RPQ)). They were randomly assigned (1:1) to either enhanced usual care (EUC) or GAIN+EUC. Masking of participants and therapists was not possible. The primary outcome was change in RPQ-score from baseline to 3-month FU. All analyses were done on an intention-to-treat basis using linear mixed-effects models. This trial is registered with ClinicalTrials.gov, number NCT02337101.

Findings: Between March 1, 2015, and September 1, 2017, we included 112 patients. Patients allocated to GAIN+EUC (n=57) reported a significantly larger reduction of PCS than patients allocated to EUC (n=55) with a mean adjusted difference in improvement of 7·6 points (95% confidence interval (CI) 2·0–13·1, p=0·008), Cohen's d=0·5 (95% CI 0·1–0·9). Number needed to treat for prevention of one additional patient with RPQ ≥20 at 3-month FU was 3·6 (95% CI 2·2–11·3). No adverse events were observed.

Interpretation: Compared with EUC, GAIN+EUC was associated with a larger reduction of post-concussion symptoms at 3-month FU.

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1. Introduction

Patients with concussion, also termed mild traumatic brain injury (mTBI), are common in the hospital setting. One of the highest incidence rates of 150-200 per 100 000 years is found among adolescents and young adults [1]. However, as many patients are not seen in hospital, the population rate may be much higher [2]. Although the majority recovers within the first weeks, it is typically estimated that 10–15% continues to suffer from post-concussion symptoms (PCS) such as headache, dizziness, fatigue, concentration problems, sadness, and irritability [3]. However, recent studies suggest that the prevalence of persistent symptoms may even be as high as 40% [4]. Patients reporting high levels of PCS 2–3 months after concussion are at risk of prolonged disability and reduced health-related quality of life [5–7]. These are particularly serious and problematic prospects in relation to adolescents and young adults both in terms of personal suffering and socioeconomic implications [3]. Nevertheless, according to recent systematic reviews there is a striking lack of methodologically rigorous clinical trials investigating treatment for these patients. Thus, there is an urgent need for trials developing and investigating interventions for persistent PCS [8].

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Research in context

Evidence before this study

Management of persistent post-concussion symptoms (PCS) is commonly regarded as difficult by both cliniciancs and researchers across disciplines, and evidence for specific treatments is limited. There is general agreement in literature that development of persistent PCS is determined by not only pathophysiological factors, but also psychological and behavioural factors which may be amenable to treatment. Therefore, we performed a broad literature search on psychological and behavioural interventions for persistent PCS. We searched PubMed, PsycINFO and Cochrane Library Databases for original research and review articles published before March 1, 2014, without language restriction. We repeated the search on January 21, 2019. Keywords were "brain concussion", or "mild traumatic brain injury", or "mTBI" or "minor head injury" in combination with "rehabilitation", or "therapy", or "cognitive therapy" or "randomised trial". We applied the filters "humans" and "age>13 years". In addition, we hand-searched the reference list of relevant studies.

However, randomised controlled trials (RCTs) of interventions were limited and suffered from methodological weaknesses. Furthermore, there was considerable heterogeneity in intervention and outcome measures which limited comparison between studies.

According to systematic reviews, simple education, information and reassurance provided early after concussion might prevent persistent PCS in some, but not all, patients. There was promising evidence from three smaller trials ($n<50$) that cognitive behavioural interventions focusing on modifying symptom-perpetuating illness-related cognitions and illness behaviours might be effective in reducing persistent PCS. However, there was a general lack of larger, high-quality trials investigating the efficacy of cognitive behavioural interventions.

Added value of this study

We developed an 8-week, interdisciplinary intervention, "Get going After concussIoN" (GAIN), for young patients with persistent PCS 2–6 months after concussion, focusing on modifying specific illness-related cognitions and behaviours associated with persistent PCS. We tested the efficacy of GAIN added to enhanced usual care (EUC) in a randomised trial. Our data showed that GAIN+EUC was associated with significantly larger reduction in PCS compared with EUC alone (i.e., early education, information and reassurance) at 3-month follow-up (corresponding to a median of 11 months after concussion), and that patient satisfaction with GAIN was high. On the basis of our results we suggest that GAIN is a feasible intervention that may prevent long-lasting PCS in young patients.

Implications of all available evidence

The findings from the present study add to the previously limited evidence that cognitive behavioural interventions may be effective in reducing persistent PCS. Future research should address the generalisability of our results, explore the mechanisms of change, and explore the effect of GAIN on objective long-term outcomes such as health-care costs, sick-leave and work ability. In addition, more research is needed to enable early identification of patients at risk of developing persistent PCS, and to determine the optimal timing of intervention.

Knowledge about modifiable prognostic factors is essential to identify viable targets for intervention. Recent studies suggest that prognostic factors are best understood in terms of a bio-psycho-social model [6,9]. According to current understanding, the acute and subacute pathophysiological processes following a concussion (with no findings on standard neuroimaging) may induce a temporary disturbance of neurometabolism and thereby brain function, which seems to normalise within a few weeks [10]. Findings regarding permanent microstructural changes that may explain persistent PCS are inconclusive [10,11]. There is general agreement that other factors than pathophysiological processes seem to be involved in the development of persistent PCS, some of which may be modifiable.

One such factor may be patients' illness perceptions, which seem to be significantly associated with outcome after concussion [6,12]. Illness perceptions contain a number of dimensions that can be psychometrically measured and followed over time [13]. A new understanding of illness perceptions and persistent somatic symptoms is emerging based on an updated model of the working brain [14]. According to this model, unconscious expectations of symptom experience are crucial in the understanding of the conscious experience of symptoms [14,15]. The unconscious expectations are mirrored in patients' illness perceptions. Importantly, such expectations can be modified not only in the laboratory, but also in real-world settings [15,16].

Illness perceptions lead to subjectively meaningful strategies that patients use to manage their symptoms in everyday life, often referred to as illness behaviours. Illness behaviours that have been associated with poor outcomes after concussion are avoiding activities because of fear that they may provoke or reinforce PCS, excessive rest, and so-called "all-or-nothing behaviour", i.e., oscillations between periods with very low and very high levels of physical and mental activity [6,17].

In line with the considerations above, treatments for persistent PCS that aim to modify illness perceptions and related behaviours seem promising [7,18,19].

Owing to Danish governmental budget funds allocated to strengthen the treatment options for adolescents and young adults (15–30 years) with concussion the opportunity arose for developing an intervention for this high-risk group. We developed "Get going After concussIoN" (GAIN), for young people with high levels of PCS 2–6 months after concussion. In an uncontrolled study, we found GAIN to be feasible with the potential to reduce the risk of still having high levels of PCS 3 months after end of intervention (EOI) corresponding to a median of 11 months post-concussion [20].

The primary aim of this randomised trial was to evaluate the efficacy of GAIN added to Enhanced Usual Care (EUC) in reducing PCS. We hypothesised that GAIN + EUC would lead to significantly larger reductions in PCS at 3-month follow-up (FU) (i.e., 3 months after EOI) than EUC.

2. Methods

2.1. Study design

This open-label, parallel-group randomised trial was carried out in two university hospitals in Central Denmark Region. The trial was approved by the Danish Data Protection Agency (no. 1-16-02-23-15) and the Committee of Health Research Ethics of Central Denmark Region (no. 1-10-72-79-14). The full study protocol can be accessed at http://www.hospitalsenhedmidt.dk/regionshospitalet-hammel/research-unit/research-projects.

2.2. Participants

From March 1, 2015, to September 1, 2017, patients were recruited from a cohort study on concussion or referred by general practitioners (GPs). The trial was stopped due to limitations in financial resources, because it was primarily financed through the governmental budget funds which ended in September 2017. Patients were recruited based on the following inclusion criteria: (1) concussion within 2–6 months according to the diagnostic criteria recommended by the WHO Task Force [21]; from March 1, 2015, to October 22, 2015, the criterion was concussion within 2–4 months; then a single protocol change was performed to the trial due to slow recruitment; (2) a direct contact between the head and an object in order to rule out acceleration-deceleration traumas; (3) age 15–30 years at the time of concussion (defined by the funding source); and (4) high levels of PCS defined as a score of ≥20 points on the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) [22]. Patients were excluded in case of (1) objective neurological findings indicating more severe brain injury; (2) previous concussion within the last 2 years leading to previous or ongoing PCS lasting ≥3 months; (3) current substance abuse; (4) severe psychiatric, neurological, or other medical disease that would impede participation in the intervention; and (5) inability to speak and read Danish. Patients were included after oral and written informed consent. They received no financial reimbursement for participation. The criterion on no previous concussion within 2 years was pragmatically defined because we were able to extract data on previous diagnosis from the electronic patient journal for this time frame only.

2.3. Procedures

Consecutive patients were assessed for eligibility by a team of two physicians (six physicians were involved during the recruitment period) based on (1) a baseline questionnaire (filled out before randomisation), (2) a neurological examination (performed by a neurologist or trainee in neurology), and (3) a standardised psychiatric interview (performed by a trainee in psychiatry or social medicine). Further details regarding the assessment have been reported elsewhere [20]. Non-eligible patients were advised to contact their GP. Included patients were randomised to either GAIN+EUC or EUC.

2.3.1. Enhanced usual care (EUC)

EUC was provided to all patients by the physician performing the psychiatric interview. The physician was not involved in providing GAIN. The patients were reassured that a good outcome was expected. They received individual psychoeducation about the bio-psycho-social understanding of persistent PCS, including advice on adaptive illness behaviours, such as gradually resuming premorbid activities and avoiding excessive rest and "all-or-nothing behaviour". For further details see Panel A1 (appendix). The duration of EUC was flexible; approximately 10 min for patients allocated to GAIN+EUC and approximately 30 min for patients allocated to EUC. The patient's GP was informed about the result of the clinical assessment including any indication for further assessment or other treatment.

2.3.2. "Get going After concussIoN" (GAIN)

GAIN was an individually-tailored, 8-week, interdisciplinary intervention programme based on principles from cognitive behavioural therapy (CBT) and gradual return to activities [20]. In short, the programme covered three structured group sessions (performed jointly by a neuropsychologist (MMT, the first author, an authorized psychologist with specialization in neuropsychology), an occupational therapist, and a physiotherapist), up to five semi-structured individual sessions with an allocated therapist (the occupational therapist or the physiotherapist) either in person or by telephone/video, and homework between each session. The number of individual sessions was flexible, and adjusted according to the patient's wishes.

The primary objective of the intervention was to reduce PCS. The hypothesised mechanisms of change were modification of symptom-perpetuating illness beliefs and illness behaviours, and improvement of participation in daily activities. The principle of gradual return to activities was applied to all daily activities. Daily activities were broadly defined and included both social, cognitive, and physical activities such as reading, working by the computer, house cleaning, exercising, and going out with friends. Patients were as part of their homework advised to gradually increase intensity and duration of daily activities that provoked symptoms (e.g., begin with 5 min of walking in week 1 and gradually increase the duration and intensity up to 15 min of jogging in week 8). All treatment providers had several years of clinical experience within neurorehabilitation, and they had received 5 days education in the management of persistent somatic symptoms and CBT principles. They all received regular group supervision from psychiatrists specialised in CBT (CUR and AS). All group sessions were video recorded in three GAIN groups. A research assistant, who was not involved in the study, watched one random first, second, and last group session to confirm therapists' adherence to the manual. To monitor application of the treatment principles in individual sessions, a self-report check-list was completed by the therapists after each session.

3. Outcomes

Data collection took place by electronic questionnaires distributed at three time points: at baseline, EOI, and at 3-month FU.

3.1. Primary outcome

Post-concussion symptoms as measured by the RPQ at 3-month FU were a priori chosen as primary outcome [22]. Respondents were asked to rate the degree to which 16 common PCS were more of a problem within the last 24 h compared with pre-injury levels on a 5-point rating scale ranging from 0 "not experienced at all" to 4 "a severe problem". A total symptom score was calculated (range 0–64) with higher scores indicating more severe PCS. In accordance with the standard scoring method, a score of 1 corresponding to "no more of a problem" was assigned the value 0 [22]. The RPQ is a valid and reliable measure of PCS severity both 7–10 days and 3–6 months post-concussion [22]. In addition to the total score, somatic (9 items, range 0–36), cognitive (3 items, range 0–12), and emotional (4 items, range 0–16) subscores were calculated [23]. There is no standardised method for classifying severity of symptoms. In the present study, we defined high levels of PCS as a score of ≥20 on the RPQ based on data from the first 108 participants in the cohort study and before randomisation of the first patient.

3.2. Treatment targets

Illness behaviours were measured by two subscales from The Behavioural Responses to Illness Questionnaire, i.e. "limiting behaviour" corresponding to excessive rest (7 items) and "all-or-nothing behaviour" (6 items). *Illness perceptions* were measured by 7 items from The Brief Illness Perception Questionnaire. The sum scores of both measures were transformed into scales ranging from 0 (worst) to 100 (best).

3.3. Secondary outcomes

Secondary outcomes were *illness-specific health-related quality of life* measured by The Quality of Life after Brain Injury – Overall Scale, where the sum score was transformed into a 0 (worst) to 100 (best) scale; *illness worry* measured by Whiteley-7, where the sum score

was divided by 7 to yield a mean item-score ranging from 0 (best) to 4 (worst) [24]; *psychological distress* measured by Symptom Checklist-8, an 8-item subscale measuring the risk of suffering from anxiety/depression derived from the Symptom Checklist-90-Revised, where the sum score likewise was divided by 8 to yield a mean item-score from 0 (best) to 4 (worst) [25]; *physical and mental health* measured by the Physical and Mental Component Summaries from the Short Form 36 Health Survey (2nd version), which were converted to T-scores based on US normative data; *perceived stress* measured by the Danish consensus version of the 10-item Perceived Stress Scale ranging from 0 (best) to 40 (worst); and *executive function* measured in participants ≥18 years by means of the Behaviour Rating Inventory of Executive Function – Adult Version (self-report). It includes 9 subscales which combine to form a global score for executive function, the Global Executive Composite, and two index scores, the Metacognitive Index and the Behavioural Regulation Index. Raw scores were converted to T-scores based on U.S. normative data retrieved from the manual.

3.3.1. Supplementary outcomes

Subjective improvement was measured by Patient Global Impression of Change. The 7 response categories were dichotomised into either "not improved" (i.e. 1 = "no change or worse" to 3 = "a little better") or "improved" (i.e. 4 = "somewhat better" to 7 = "a great deal better"). *Patient satisfaction* was measured at EOI in patients allocated to GAIN+EUC by 10 items from The Experience of Service Questionnaire to which we added 7 items to evaluate satisfaction with the applied methods and materials. *Adverse events* were not proactively monitored, but treatment providers were aware of whether any adverse events were volunteered by participants.

3.3.2. Additional treatment

Information on additional treatment was collected at 3-month FU by asking patients if they had sought additional help for PCS since inclusion and if yes, which help they had received.

3.4. Randomisation and masking

Participants were randomised (1:1) using randomly permuted block sizes of 8 to 15 participants to ensure allocation concealment (initially 11–15 participants, but from February 8, 2016, it was reduced to 8 to 10 participants to facilitate earlier treatment) by means of a computer algorithm. Sealed, opaque envelopes containing the randomisation codes were prepared in advance. The procedure was managed by an independent statistician. After the clinical assessment, the physician performing the psychiatric interview enrolled eligible participants into the study, opened the randomisation envelope in the presence of the patient, and assigned the participant to either GAIN+EUC or EUC. Due to the nature of the intervention, masking of patients and therapists regarding treatment allocation was not feasible. However, treatment allocation was blinded during data analysis, interpretation of results and decisions for post-hoc analyses for all authors, except for the statistician (JSJ).

3.5. Statistical analysis

The sample size calculation was based on the RPQ [22]. The natural decrease of RPQ scores from 3 to 9 months after concussion was estimated from previous studies [19,22]. We would need 60 patients in each intervention arm, to reach a power of 0·93, based on an expected drop out of 10%, a standard deviation (SD) in RPQ score of 11, reductions in RPQ scores of 15 and 8 points in GAIN+EUC and EUC, respectively, and an alpha of 0·05.

All analyses were done on an intention-to-treat (ITT) basis, including all patients for whom data was available. The primary outcome, RPQ, was analysed by using both unadjusted and adjusted linear mixed-effects models with a random intercept and a cluster effect for treatment group for those allocated to GAIN+EUC. Both models included RPQ as the dependent variable and intervention arm, time (baseline, EOI, 3-month FU), and intervention arm x time interactions as independent variables. In the adjusted model, we added predefined prognostically important baseline characteristics, i.e. age, sex, previous mental health issues (no/yes), and recruitment (GP/cohort). To assess clinical significance, we calculated the relative risk (RR) in each intervention arm of having an RPQ ≥20 at 3-month FU as well as the number needed to treat (NNT) for prevention of one additional patient with RPQ ≥20.

The treatment target measures and the secondary outcomes were analysed using unadjusted and adjusted linear mixed models similar to those described for the primary outcome. Based on the mixed models, the mean score of each outcome measure at each time point was calculated for GAIN+EUC and EUC as well as the adjusted difference in mean change between GAIN+EUC and EUC from baseline to 3-month FU. All models were checked by graphical inspection of the random intercepts and residuals and by testing the equality of covariance matrices between GAIN+EUC and EUC. If the covariance matrices differed between the intervention arms, different SDs and correlations between GAIN+EUC and EUC were allowed in the models. The residuals and random intercepts for Whiteley-7 were right-skewed. We therefore performed a sensitivity analysis using bootstrapped confidence intervals CIs. This did not change the CIs.

A post-hoc analysis was performed to explore the effect of GAIN+EUC on the somatic, cognitive, and emotional subscales of the RPQ using an unadjusted linear mixed model similar to the one described above. The unadjusted between-group effect size at 3-month FU was calculated for all primary and secondary outcomes, treatment targets and RPQ subscales using Cohen's *d*.

Furthermore, for descriptive purposes we calculated the mean score at baseline, EOI, and 3-month FU for each of the 16 RPQ items in GAIN+EUC and EUC, respectively. In addition, we calculated the mean T-score at baseline and 3-month FU on each of the 9 subscales and the 3 index scales on the Behaviour Rating Inventory of Executive Function in GAIN+EUC and EUC, respectively. Regarding Patient Global Impression of Change we calculated a RR comparing the proportion of patients in each group who reported improvement. Data from the Experience of Service Questionnaire on patient satisfaction was analysed descriptively. Differences between groups regarding additional treatment were analysed using chi-squared test.

Stata version 15·1 for Windows was used. This trial is registered with ClinicalTrials.gov, number NCT02337101.

3.6. Role of the funding source

The present study was partly financed by governmental budget funds allocated to a larger project in Central Denmark Region, and earmarked for strengthening the treatment options for 15–30-year-old patients with concussion or acquired brain injury, and partly by the foundation "Public Health in Central Denmark Region - a collaboration between municipalities and the region". The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (MMT) and the last author (AS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4. Results

Between March 1, 2015, and September 1, 2017, we randomly assigned 112 patients to treatment: 57 patients to GAIN+EUC (12 treatment groups) and 55 patients to EUC. Thus, data from 57 patients allocated to GAIN+EUC and 55 patients allocated to EUC

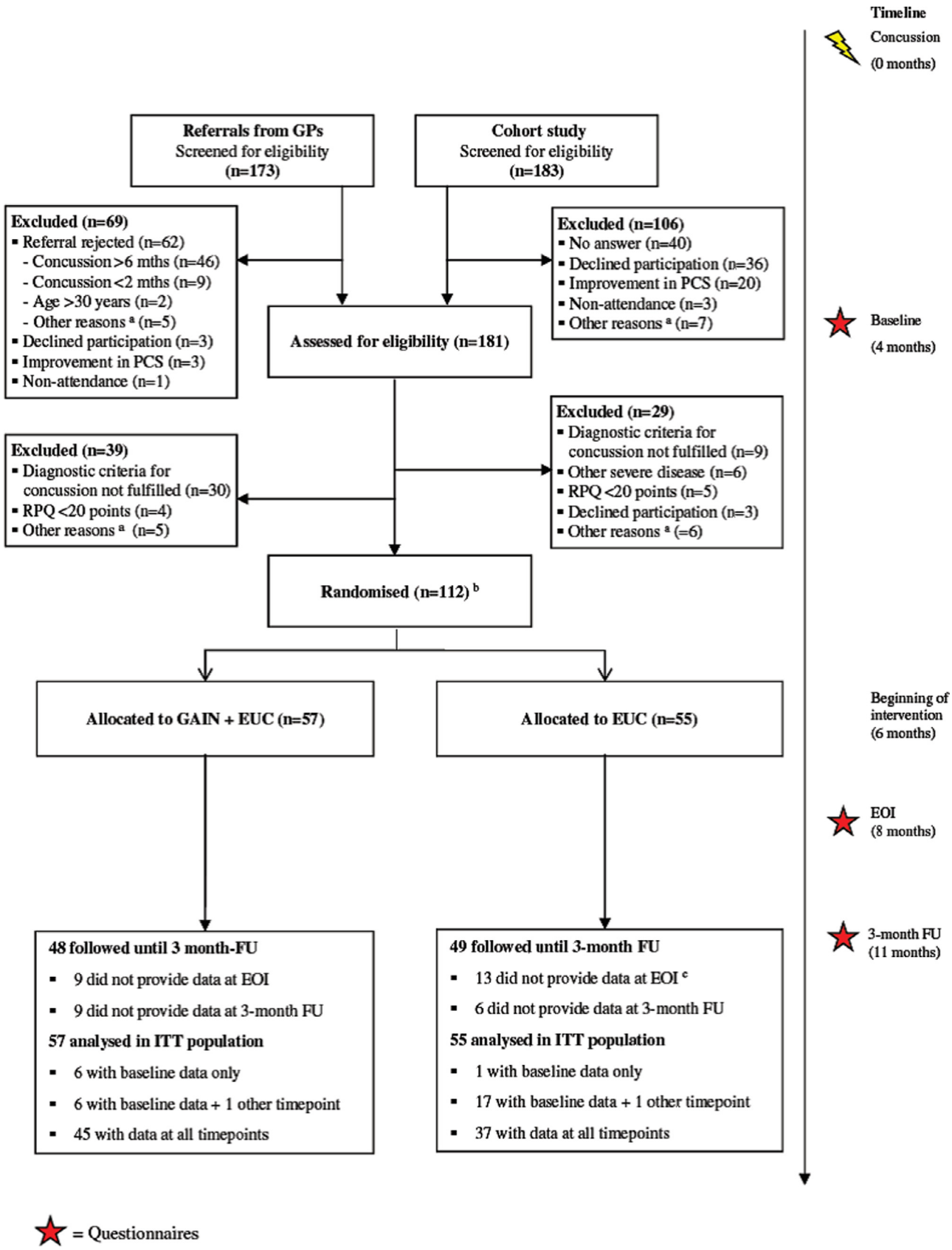

Fig. 1. CONSORT flowchart and timeline of assessments.

The timeline represents median time in months after concussion at the three assessment points, with 0 being the time of injury.

Baseline: 3·7 months (range 2·1–7·1 / IQR 3·1–4·6); EOI: 7·5 months (range 4·1–12·1 / IQR 6·5–8·8); 3-month FU: 10·6 months (range 6·9–15·6 / IQR 9·5–11·9).

[a]Other reasons" includes: not from Central Denmark Region; previous concussion within 2 years leading to previous or ongoing post-concussion symptoms lasting ≥3 months; signs of more severe brain injury; time since injury >6 months; other severe psychiatric or somatic disease; going abroad; unable to communicate in Danish.

[b] Due to a protocol violation one patient diagnosed with bipolar disorder was erroneously randomised to EUC and excluded after inclusion (i.e., 113 patients were randomised).

were analysed in the ITT population. Fig. 1 shows the flowchart and the timeline of assessments. 3-month FU data from the last participant was collected on June, 20, 2017. Data from at least two time points were available for 105 patients (94%). Loss to FU was similar for GAIN+EUC and EUC. No adverse events were volunteered by participants during treatment.

Table 1 shows characteristics of the included patients according to intervention arm. Patients allocated to GAIN+EUC and EUC were demographically and clinically similar at baseline except that the EUC group had a higher frequency of previous mental health issues (n = 27, 49%) than GAIN+EUC (n = 19, 33%).

Two patients allocated to GAIN+EUC never attended; one had recovered and one gave no reason. The median number of sessions in total (group + individual) was 8 (inter quartile range (IQR) 7-8).

Therapist adherence to the written manual for the group sessions was confirmed by the independent research assistant after inspection of the video recordings. The therapists' application of the different treatment principles in the individual sessions are presented in Table A1.

4.1. Primary outcome

Table 2 shows unadjusted and adjusted mean differences in improvement between GAIN+EUC and EUC on the RPQ total score (primary outcome) and for the RPQ subscales (post-hoc analysis). The results are displayed in Fig. 2. Fig. 2(A) displays the improvement in RPQ in GAIN+EUC and EUC. There were different developments over time in favour of GAIN+EUC as indicated by a significant interaction effect between intervention arm and time (p= 0·024). From baseline to 3-month FU, patients allocated to GAIN+EUC had a mean improvement of 17·4 points (95% CI 13·0–21·9), whereas patients allocated to EUC had a mean improvement of 9·9 points (95% CI 6·6–13·2). This corresponds to an unadjusted mean difference in improvement of 7·5 points (95% CI 2·0–13·1, p= 0·007) in favour of GAIN+EUC. The adjusted difference in improvement was likewise 7·5 points (95% CI 2·0–13·1, p= 0·008).

The effect of GAIN was clinically meaningful. Thus, at 3-month FU 22/49 patients (46%) in GAIN+EUC vs 36/48 patients (73%) in EUC still had an RPQ ≥20 (unadjusted relative risk 0·6 (95% CI 0·4–0·9), p = 0·008). In addition, the NNT for prevention of one additional case of RPQ ≥20 at 3-month FU was 3·6 (95% CI 2·2–11·3). Fig. 2(B)–(D) displays post-hoc analyses of the improvement of the RPQ subscales in GAIN+EUC and EUC. GAIN+EUC made significantly larger improvements than EUC in somatic symptoms and emotional symptoms, but not significantly larger improvements in cognitive symptoms. Fig. A1 presents the mean score at baseline, EOI, and 3-month FU on each of the 16 RPQ items in GAIN+EUC and EUC.

4.2. Treatment targets and secondary outcomes

Table 3 shows unadjusted and adjusted mean differences in improvement between GAIN+EUC and EUC for treatment targets and all secondary outcomes. Fig. 3(A)–(H) displays the change in treatment targets and five secondary outcomes from baseline to 3-month FU. Compared with EUC, patients allocated to GAIN+EUC made larger improvements in symptom-perpetuating illness perceptions (p = 0·004) and "limiting behaviour" (p = 0·032). Furthermore, GAIN+EUC made significantly larger improvements in illness worry (p= 0·024) and physical health (p= 0·005) compared with EUC. Although scores on "all-or-nothing behaviour", illness-specific health-related quality of life, psychological distress, mental

Table 1
Baseline characteristics of the intention-to-treat population (n = 112).

	GAIN+EUC (n = 57)	EUC (n = 55)
Age (years)	22·9 (4·2)	22·9 (4·3)
Sex (female)	45 (79%)	44 (80%)
Educational status		
Basic school (7–10 years)	19 (33%)	20 (36%)
Upper secondary education (13 years)	25 (44%)	16 (29%)
Further education	13 (23%)	14 (26%)
Missing	0 (0%)	5 (9%)
Work status		
Employed or student full time	19 (33%)	18 (33%)
Part-time sick leave	16 (28%)	16 (29%)
Full-time sick leave	16 (28%)	17 (31%)
Other	5 (9%)	1 (2%)
Missing	1 (2%)	3 (5%)
Cohabitant status		
Living with parents	18 (32%)	18 (33%)
Living with partner or friends	22 (38%)	20 (36%)
Living alone	7 (12%)	3 (5%)
Missing	10 (18%)	14 (25%)
Recruitment		
Cohort study	23 (40%)	25 (45%)
Referred from general practitioners	34 (60%)	30 (55%)
Mechanism of injury		
Traffic accident	18 (32%)	14 (25%)
Fall	15 (26%)	11 (20%)
Direct blow to the head	9 (16%)	14 (25%)
Sports-related concussion	12 (21%)	15 (28%)
Other [a]		
Time since injury, months (median/IQR)	3·8 (1·7)	3·8 (1·6)
Mental health		
Previous mental health issues [b]	19 (33%)	27 (49%)
Current mental health issues		
- according to psychiatric assessment [c]	3 (5%)	0 (0%)
- according to SCL-8 [d]	20 (35%)	21 (38%)
- SF-36 mental health, T-score [e]	36·7 (11·1)	38·5 (11·3)
Physical health		
Previous concussion diagnosis within 2 years before inclusion with PCS lasting <3 months	4 (7%)	8 (15%)
Chronic medical condition diagnosed prior to injury [f]	9 (16%)	9 (16%)
SF-36 physical health, T-score [e]	40·7 (7·7)	39·3 (7·4)
Post-concussion symptoms and quality of life		
RPQ (0–64) [g]	38·5 (9·1)	37·4 (7·4)
RPQ somatic factor (0–36)	19·7 (5·9)	19·9 (5·0)
RPQ cognitive factor (0–12)	8·7 (2·8)	8·9 (2·0)
RPQ emotional factor (0–16)	10·1 (3·6)	8·5 (3·8)
QOLIBRI-OS (0–100) [e]	32·5 (15·4)	31·0 (16·4)
Illness perceptions and illness behaviours [g]		
BRIQ "all-or-nothing" behaviour (0–100)	51·2 (16·4)	53·6 (17·0)
BRIQ "limiting behaviour" (0–100)	66·8 (18·7)	66·0 (19·2)
B-IPQ (0–100)	62·4 (9·5)	62·7 (8·9)

Data are n (%), mean (SD), if not stated otherwise.
Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; BRIQ = Behavioural Response to Illness Questionnaire; GAIN = Get going After concussIoN; IQR = interquartile range; PCS = post-concussion symptoms; QOLIBRI-OS = Quality of Life after Brain Injury – Overall Scale; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; SCL-8 = Symptom Checklist-8; SD = standard deviation; SF-36 = Short Form 36 Health Survey.
[a] "Other" comprises four participants who had a concussion by an assault.
[b] Includes previous psychiatric treatment and previous treatment by a psychologist.
[c] Mild depression or anxiety diagnosed at the psychiatric assessment.
[d] Number of participants with a dichotomised score ≥5 on SCL-8 corresponding to ≥60% risk of suffering from anxiety or depression. [25].
[e] Higher scores indicate better mental health / higher physical functioning / higher health-related quality of life.
[f] Medical conditions include both chronic well-defined somatic disorders such as diabetes and metabolic disorder, and symptom-defined conditions such as chronic musculoskeletal pain.
[g] Higher scores indicate more PCS / more symptom-perpetuating illness perceptions and behaviours.

[c] Violation of procedure: seven patients from EUC did not receive questionnaires at EOI on December 18, 2017, as planned due to an error in the database. This was not realised until 3-month FU.

Abbreviations: EOI = end of intervention; EUC = enhanced usual care; FU = follow-up; GAIN = Get going After concussIoN; GP = general practitioner; ITT = intention-to-treat; IQR = interquartile range.

Table 2
Change in RPQ total score and RPQ subscales in GAIN+EUC and EUC.

	Improvement from baseline to 3-months FU				Unadj. difference in improvement			Adj. difference in improvement		
	GAIN+EUC (n = 57)		EUC (n = 55)		"GAIN+EUC" − EUC			"GAIN+EUC" − EUC		
Outcome	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**p**	**Mean**	**95% CI**	**p**
RPQ total	−17·4	(−21·9; −13·0)	−9·9	(−13·2; −6·6)	−7·5	(−13·1; −2·0)	0·007	−7·5	(−13·1; −2·0)	0·008
RPQ somatic subscale	−9·1	(−11·3; −6·8)	−5·2	(−6·9; −3·4)	−3·9	(−6·7; −1·1)	0·007	−3·9	(−6·8; −1·0)	0·007
RPQ cognitive subscale	−3·5	(−4·6; −2·5)	−2·3	(−3·3; −1·4)	−1·2	(−2·6; 0·3)	0·106	−1·2	(−2·6; 0·3)	0·116
RPQ emotional subscale	−4·9	(−6·5; −3·2)	−2·4	(−3·6; −1·1)	−2·5	(−4·6; −0·4)	0·019	−2·5	(−4·6; −0·4)	0·020

Change in RPQ total score (primary outcome) and RPQ subscales (post-hoc analysis) based on an unadjusted and adjusted linear mixed model. Higher scores indicate more symptoms.
Abbreviations: RPQ = Rivermead Post-concussion Symptoms Questionnaire; EUC = Enhanced Usual Care; GAIN = Get going After concussIoN.

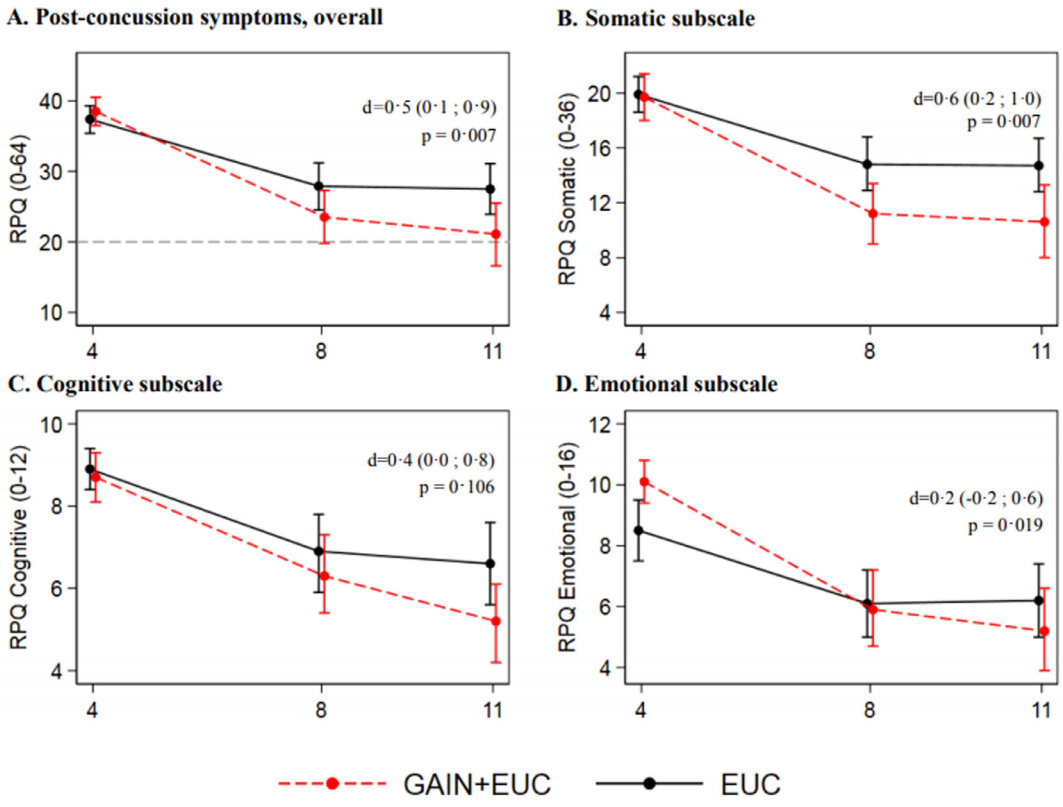

Fig. 2. Change in RPQ total score and RPQ subscales (unadjusted mean, 95% CI), (n = 112).
The x-axis represents median time in months after concussion at the three assessment points (baseline; end of intervention; 3-month follow-up). The reference line on (A) indicates the a priori defined cut-off for a high level of post-concussion symptoms (RPQ ≥20), i.e., the cut off for inclusion in the study. RPQ total score = primary outcome. RPQ subscales = post-hoc analysis. *P*-values are based on an unadjusted linear mixed model. *d* = Cohen's d (95% CI) at 3-month FU.
Abbreviations: EUC = enhanced usual care; GAIN = Get going After concussIoN; RPQ = Rivermead Post-Concussion Symptoms Questionnaire.

health, perceived stress and executive function improved from baseline to 3-month FU in GAIN+EUC and EUC, no significant between-group differences were found (Table 3). Fig. A2 displays patients' ratings on the Behaviour Rating Inventory of Executive Function at baseline and 3-month FU in GAIN+EUC and EUC, respectively.

At 3-month FU, 38/57 (67%, 9 missings) of the patients in GAIN+EUC reported on the Patient Global Impression of Change that they had improved since inclusion compared to 21/55 (38%, 9 missings) of the patients in EUC. The difference was statistically significant (RR 1·7 (95% CI 1·2–2·5), p = 0·002). Furthermore, patient satisfaction with GAIN+EUC was high (Fig. A3). Compared with patients receiving GAIN+EUC, a higher number of patients allocated to EUC had more than one visit to their GP (16 vs. 6, p = 0·012), the hospital (10 vs. 1, p = 0·003), and medical specialists or psychologists (15 vs. 7, p = 0·004). We found no differences regarding use of physiotherapy (22 vs. 19, p = 0·472) or alternative therapies (14 vs. 10, p = 0·313).

5. Discussion

According to a recent review, psychological treatment represents a promising approach to the treatment of persistent PCS, but there is an urgent need for methodologically sound clinical trials to inform clinical practice [8]. Data from this randomised trial of GAIN, a novel intervention for high levels of PCS in young patients, showed that GAIN+EUC led to significantly larger reductions in PCS at 3-month FU than EUC alone as measured by the RPQ. The relative risk of having an RPQ score ≥20 at 3-month FU was 0·6 (95% CI 0·4–0·9) in favour of GAIN+EUC, and the NNT for prevention of one additional patient with RPQ ≥20 was 3·6 (95% CI 2·2–11.3). Additionally, GAIN+EUC was associated with significantly larger reductions in symptom-

Table 3
Change in treatment targets and all secondary outcome measures in GAIN+EUC and EUC (n = 112).

	Improvement from baseline to 3-months FU				Unadjusted difference in improvement			Adjusted difference in improvement		
	GAIN+EUC (n = 57)		EUC (n = 55)		"GAIN+EUC" - EUC			"GAIN+EUC" - EUC		
Outcome	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**p**	**Mean**	**95% CI**	**p**
QOLIBRI-OS[a]	23·5	(16·5; 30·6)	16·8	(10·1; 23·4)	6·8	(−2·9; 16·5)	0·172	6·8	(−2·8;16·5)	0·165
B-IPQ[a]	−18·3	(−13·2; −23·5)	−8·5	(−4·2; −12·8)	−9·8	(−3·1; 16·5)	0·004	−9·8	(−16·6; −3·1)	0·004
BRIQ-lim[a]	−31·4	(−22·4; −40·2)	−19·9	(−14·6; 25·2)	−11·3	(−1·0; −21·7)	0·032	−11·4	(−2·0; −0·1)	0·033
BRIQ-all[a]	−14·8	(−8·3; −21·3)	−6·4	(−0·7; −12·0)	−8·4	(−17·0; 0·2)	0·055	−8·4	(−17·1; 0·3)	0·058
SCL-8	−0·7	(−0·9; −0·4)	−0·4	(−0·6; −0·1)	−0·3	(−0·7; 0·0)	0·086	−0·3	(−0·7; 0·1)	0·090
Whiteley-7	−0·8	(−1·0; −0·5)	−0·4	(−0·6; −0·1)	−0·4	(−0·7; −0·1)	0·024	−0·4	(−0·7; 0·0)	0·025
PSS	−5·7	(−3·1; −8·4)	−3·0	(−0·9; −5·0)	−2·8	(−6·1; 0·6)	0·106	−2·8	(−6·1; 0·6)	0·104
SF-36 pcs[b]	9·3	(7·2; 11·3)	4·7	(2·4; 7·1)	4·5	(1·4; 7·6)	0·005	4·6	(1·4; 7·7)	0·004
SF-36 mcs[b]	6·6	(2·9; 10·3)	3·0	(−0·6; 6·7)	3·6	(−1·6; 8·8)	0·179	3·5	(−1·7; 8·7)	0·189
BRIEF-A MI[b,c]	−4·2	(−8·6; 0·3)	−4·3	(−7·4; - 1·2)	0·2	(−5·3; 5·6)	0·958	0·1	(−5·2; 5·5)	0·961
BRIEF-A BRI[b,c]	−3·7	(0·72; 6·6)	−2·0	(−5·0; 1·0)	−1·7	(−5·8; 2·5)	0·439	−1·8	(−6·0; 2·3)	0·386
BRIEF-A GEC[b,c]	−4·2	(−8·0; −0·5)	−3·5	(−6·4; 0·6)	−0·7	(−5·5; 4·0)	0·768	−0·8	(−5·5; 3·8)	0·736

Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; BRIEF-*A* = Behaviour Rating Inventory of Executive Function - Adult Version; BRIQ-all = Behavioural Response to Illness Questionnaire, subscale "All-or-nothing behaviour"; BRIQ-lim = Behavioural Response to Illness Questionnaire, subscale "limiting behaviour"; EUC = enhanced usual care; GAIN = Get going After concussIoN; PSS = Perceived Stress Scale; QOLIBRI-OS = Quality of Life after Brain Injury – Overall Scale; SCL-8 = Symptom Checklist-8; SF-36 = Short Form 36 Health Survey (pcs = physical component summary, mcs = mental component summary).

[a] The sum of all items was transformed into a 0–100 scale to enable comparison between scales.

[b] The sum scores on SF-36 and BRIEF-A were converted to T-scores based on US normative data.

[c] BRIEF-A results are for participants ≥18 years only. Higher scores on the following questionnaires indicate less symptoms / better function: QOLIBRI-OS, SF-36 pcs and mcs. Higher scores on the following questionnaires indicate more symptoms / worse function: B-IPQ, BRIQ, SCL-8, Whiteley-7 and PSS.

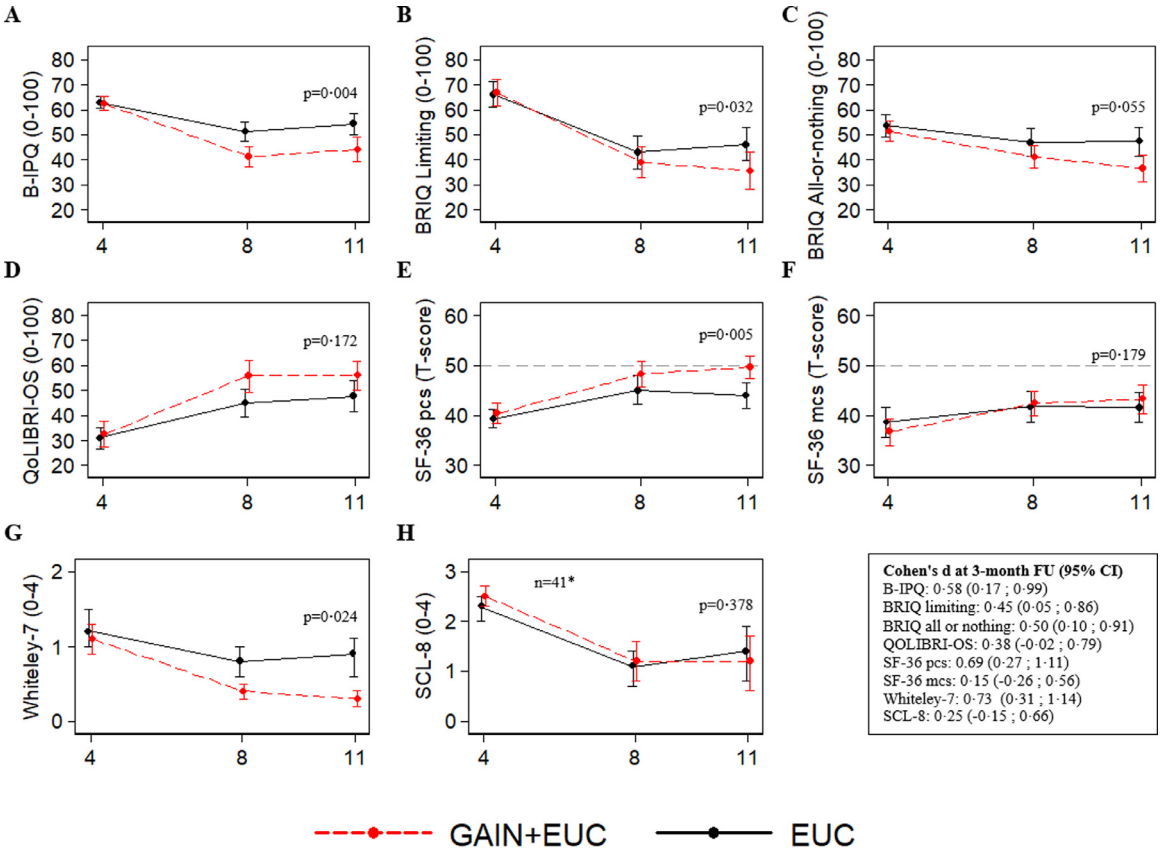

Fig. 3. Change in treatment target measures and secondary outcomes (unadjusted mean, 95% CI), (n = 112).

The *x*-axis represents median time in months after concussion at the three assessment points (baseline; end of intervention; 3-month follow-up). *P*-values are based on an unadjusted mixed model and pertain to change between baseline and 3-month follow-up.

(A), (B), (C), (G), and (H): higher scores indicate more symptoms/worse function.

(D), (E), and (F): higher scores indicate less symptoms/better function.

(A)–(D): the sum was transformed into a 0–100 scale according to the questionnaire manuals.

(E) and (F): SF-36 subscales were converted to T-scores based on US normative data. The reference line at *T*= 50 shows the US population mean.

* The SCL-8 analysis was performed on the subgroup of patients with an SCL-8 dichotomised score ≥5 at baseline (n = 41) [25].

Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; BRIQ = Behavioural Response to Illness Questionnaire; EUC = enhanced usual care; GAIN = Get going After concussIoN; QOLIBRI-OS = Quality of Life after Brain Injury – Overall Scale; SCL-8 = Symptom Checklist-8; SF-36 = Short Form 36 Health Survey (pcs = physical component summary, mcs = mental component summary).

perpetuating illness perceptions and illness behaviours and with larger improvements in overall physical health than EUC. Patient satisfaction with GAIN+EUC was high. The present study adds important evidence that treatment focusing on psychological factors may effectively reduce PCS.

Our results are consistent with findings from two previous randomised controlled trials (RCTs) investigating the effect of CBT for PCS [19,26]. In a pilot RCT, at-risk patients (n = 28) were recruited within 6 weeks post-concussion based on a prediction model including symptom severity and illness perceptions [19]. Compared to treatment as usual, patients allocated to 6 weekly individual 50-minute CBT sessions had less PCS, less depression, and less symptom-perpetuating illness perceptions at 3-month FU suggesting that the intervention could prevent persistent PCS [19]. In another small RCT (n = 46), 12 weekly, individual 1-hour CBT sessions were shown to improve quality of life for patients with PCS lasting ≥6 months after traumatic brain injury (52% suffered from concussion) compared to a waiting list [26]. In contrast, a recent RCT found that 5 highly structured group-sessions of CBT provided to patients with high levels of PCS 2 weeks after concussion were inferior to 5 sessions of telephone counselling in reducing PCS and in improving functional outcome at 12 months [27]. Reasons for this unexpected result may be, amongst others, the timing and/or the content of the intervention. Regarding the timing, most patients experience further symptom reduction after 2 weeks without specific treatment, and offering psychological treatment at such an early time point may in fact increase symptom awareness and foster negative expectations for outcome [12,27]. Regarding content, highly structured CBT group sessions may impede sufficient individualisation of the treatment as recommended by systematic reviews on treatment of PCS [28]. The positive trials referred above as well as the present study applied an individualised, semi-structured treatment protocol in recognition of the heterogeneity of patients with persistent PCS suggesting that such individualisation is crucial [19,26].

In contrast to the present study, 3 previous studies found no effect of interdisciplinary rehabilitation [29–31]. Again, this may be due to their timing of the interventions (1 week, 2–8 weeks, and 2 months post-injury, respectively). In addition, none of these interventions specifically targeted symptom-perpetuating illness perceptions. In contrast, a recent Danish study, which included CBT techniques to modify symptom-perpetuating illness perceptions, showed positive effects of an interdisciplinary intervention provided to patients suffering from PCS for more than 6 months [32]. Together, these findings suggest that focusing on changing negative illness perceptions may be crucial for the effective treatment of high levels of PCS regardless of the profession of the health care provider.

Our trial has a number of strengths. We benefitted from a randomised design with a reasonable number of participants. We recruited young people with high levels of PCS, both diagnosed at the hospital and referred from GPs without excluding patients with mild psychiatric disorders or benign somatic disease, thereby increasing the generalisability of the results. All patients went through a thorough assessment before inclusion using recommended, standardised criteria for verifying the concussion diagnosis. We developed an intervention based on a flexible treatment manual, using occupational therapists and physiotherapists as treatment providers and adding the possibility of video or telephone consultations. The latter ensured that GAIN was easily accessible, interfered less with daily life, and that patients were less dependent of geographical distance to the hospital. The intervention and the treatment dose were tailored according to individual needs. Altogether, this flexibility in the content and delivery of GAIN may be crucial for the positive findings.

Our trial had some limitations. Though the concussion diagnosis was sought verified at inclusion, objective information on PTA, GCS, and other clinical signs and symptoms of concussion at the time of injury was often lacking and obtained by self-report only. Due to the nature of the intervention, masking of patients and therapists regarding treatment allocation was not feasible. Since the outcomes had to be measured by self-report, there is a risk that placebo effects in GAIN+EUC and nocebo effects in EUC inflated the effectiveness of GAIN. However, the fact that the patients in EUC also received a systematic intervention (i.e. psychiatric and neurological assessment, reassurance, and advice) is likely to have improved their outcome, which could have led to a smaller effect of GAIN+EUC. Therapist adherence to the manual in the group sessions and to the treatment methods in the individual sessions could have been more systematically evaluated by multiple and trained evaluators. Adverse events could have been more carefully monitored. The intervention was carried out by only three different therapists, and it cannot be ruled out that the efficacy of GAIN+EUC might partly be owing to their special skills. Thus, our findings require replication. In addition, GAIN is a complex intervention with multiple components, and the design of the study does not allow us to determine if one component was more important than others in achieving a change. Mediation analyses will be applied to elucidate mechanism(s) of change. From a trial design perspective, it is a potential limitation that the individual treatment sessions were tailored to patients' needs and wishes rather than adhering to a fixed manual, since this may make it more difficult to replicate our study. A similar point applies to the fact that we included patients aged 15–30 years. While it is encouraging that GAIN+EUC effectively reduced PCS in this high-risk age group, we do not know whether GAIN+EUC will be feasible and effective in older age groups. Finally, although post-hoc analysis indicated that GAIN +EUC had a general effect on all types of post-concussion symptoms (which is in line with our treatment rationale), we could not document a clear effect on cognitive symptoms. This finding needs further exploration.

In conclusion, GAIN+EUC was safe, feasible, and associated with high patient satisfaction. Compared with EUC, GAIN+EUC was associated with larger reduction of PCS at 3-month FU (corresponding to a median of 11 months post-concussion). Additional data are needed to explore the long-term effects of GAIN+EUC on work ability and health care use. Replications in other health care settings and in larger multicentre trials as well as across countries are needed.

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Declaration of Competing Interest

None.

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Appendix

Panel A1: Enhanced usual care

As part of enhanced usual care, all patients received reassurance and psychoeducation about the bio-psycho-social understanding of persistent PCS, including advice on adaptive illness behaviours, such as gradually resuming premorbid activities and avoiding excessive rest and "all-or-nothing behaviour". They were advised to exercise regularly, and they were told that they could exercise above the symptom threshold as long as it did not lead to prolonged exacerbation of symptoms (i.e. >24 h). In that case they were recommended to lower the level and only gradually increase exercise intensity and duration. Furthermore, they were advised to use non-prescription painkillers with caution and for a maximum of 10 days per month in total to avoid medication-overuse headache. In addition, patients received individual advice according to their needs such as to seek help from a student counsellor or to consult their GP in case of psychological distress.

Table A1
Therapists application of treatment principles in Get going After concussIoN (GAIN).

Intervention target	Intervention strategy	Frequency (% of sessions)
Negative illness perceptions:		
Beliefs that symptoms	Education on	
• cannot be controlled.	• concussion and transient PCS as part of the normal recovery process.	
• are exclusively caused by the concussion.	• persistent PCS in terms of the bio-psycho-social disease model.	60
• are a sign of brain damage and will persist.	Techniques derived from newer waves of cognitive behavioural therapy such as	
	• creating a distance to ones thoughts.	
	• exploring the relationship between thoughts and behaviour.	
	• identifying individually important goals.	
	• refocusing on individually important goals instead of focusing on symptoms.	38
Maladaptive illness behaviour:		
• Excessive rest	Education on:	
• Continuous physical or mental exertion	• the negative effects of excessive rest, exertion and “all-or-nothing” behaviour.	
• “All-or-nothing” behaviour	• the negative effects of fear-avoidance behaviour.	
	• the negative effects of "pushing through symptoms" and how it may exacerbate PCS.	
	• the health-related benefits of exercise.	71
	• stress after concussion (lower threshold, self-perpetuating circle of stress)	48
	Balancing activity and rest at home, school, and / or work by:	
	• increasing or reducing daily activities.[1]	
	• managing and prioritizing energy and resources, also including pleasurable activities.	
	• scheduling daily activities[1] and evening out activity level.	56
	Gradual return to activities by:	
	• gradually increasing daily activities[1] and physical exercise in duration and intensity.	General principle,
	• using a “pyramid of objectives” to work stepwise towards individually important goals.	applied in all sessions
	Relaxation training.	
	• Deep-breathing exercise.	14
	• Guided relaxation training (using a CD).	26
Specific techniques to facilitate	Counselling on:	
more adaptive symptom-management	• sleep habits and sleep hygiene.	22
	• ergonomics and work habits.	6
	• individually tailored neck exercises to reduce headache and/or neck pain.	10
	• exposure exercises to reduce fear-avoidance behaviour.	26
	• cognitive difficulties	
	- education about cognitive dysfunctions and compensation strategies	13
	- computer-based cognitive remediation training	3
	• pain medication.	6

The table shows the different treatment elements in GAIN as presented previously [20]. The number in the right column indicates the percentage of the total number of individual treatment sessions provided in the study period ($n = 245$) where the treatment element was applied according to therapists' self-report check-lists.

[1] Daily activities are broadly defined as everything normally done in daily living including both physical and cognitive activities in work and education, leisure-time, and personal care. Patients were supported in adjusting intensity and duration of daily activities to the appropriate level.

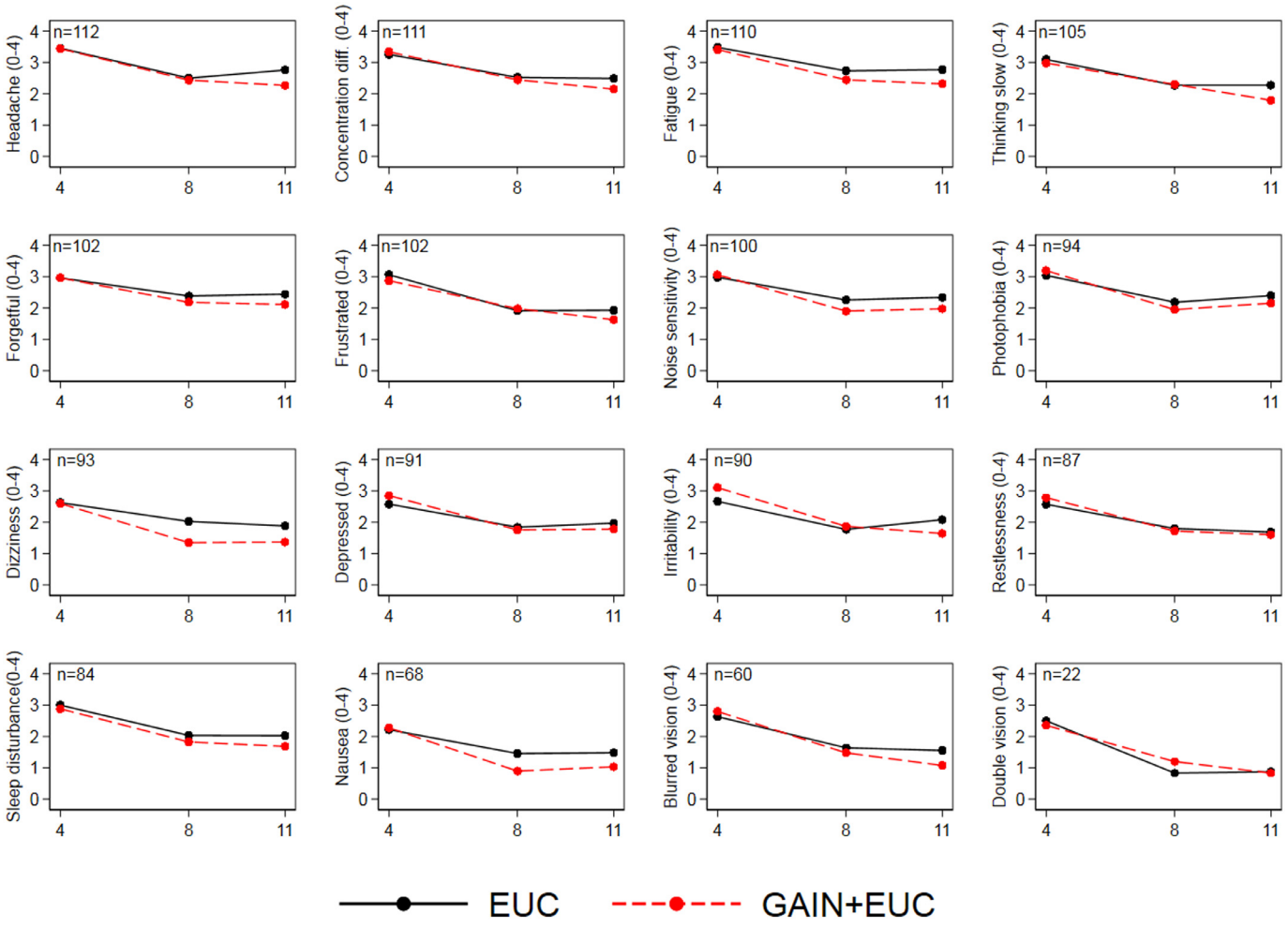

Fig. A1. Post-concussion symptoms: change in single RPQ items.

The graphs show the mean score on each RPQ item at each assessment point in GAIN+EUC and EUC for those patients, who reported a score ≥2 on the respective RPQ item at baseline (= *n* displayed on each graph). Patients are asked how much they suffer from each symptom now compared with before the injury. Response categories: 0 = not experienced at all; 1 = no more of a problem; 2 = *a* mild problem; 3 = *a* moderate problem; 4 = *a* severe problem. Response category 1 is scored 0.

The x-axis represents median time in months after concussion at the three assessment points (baseline; end of intervention; 3-month follow-up).

Abbreviations: EUC = enhanced usual care; GAIN = Get going After concussIoN; RPQ = Rivermead Post-concussion Symptoms Questionnaire.

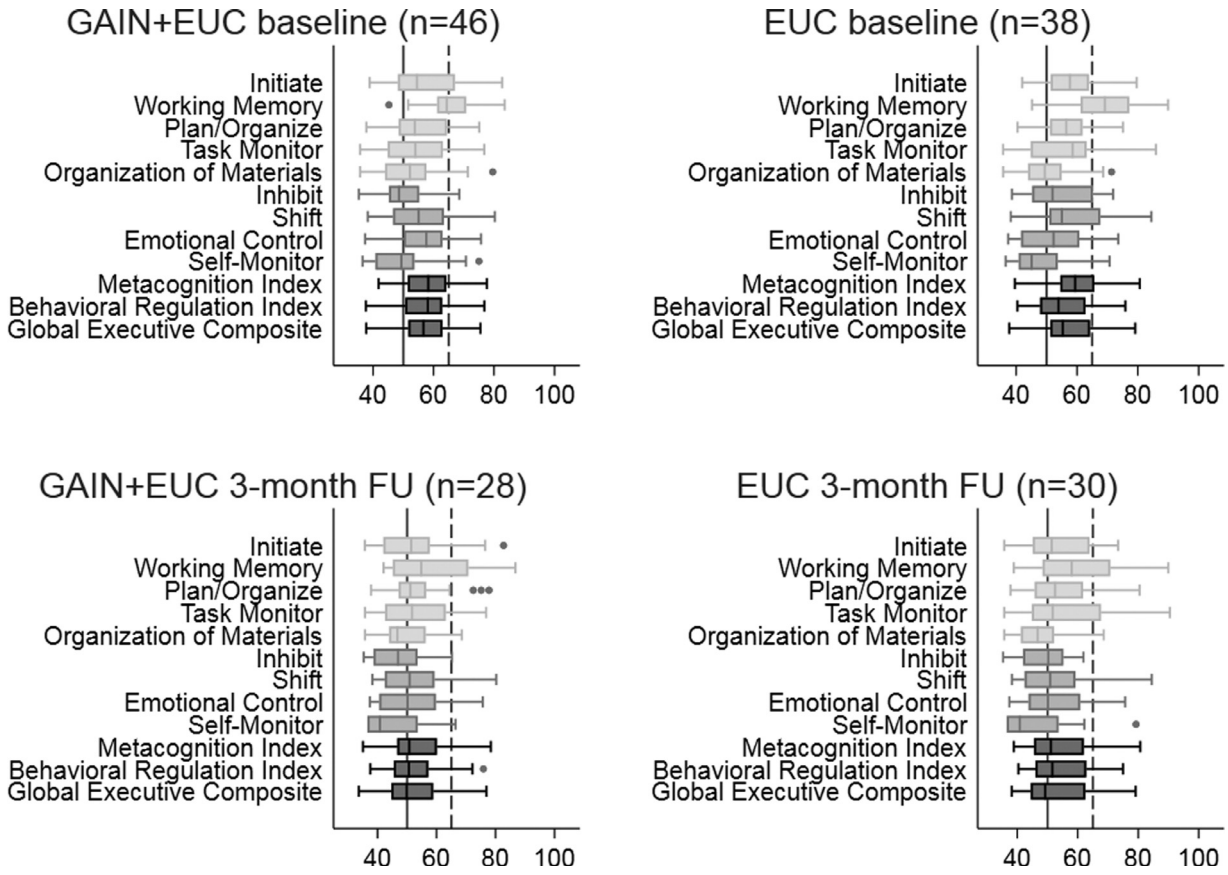

Fig. A2. BRIEF-A subscale and composite T-scores for participants ≥18 years at baseline (n = 84) and 3-month FU (n = 58).

The x-axis represents T-scores. BRIEF-A raw scores were converted to T-scores based on US normative data. The reference line at T= 50 shows the US population mean. The dotted reference line at T = 65 indicates the recommended threshold for interpreting a score as elevated according to the manual (i.e. 1·5 SD above the population mean).

Metacognition Index (MI) subscales: Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials.

Behavioural Regulation Index (BRI) subscales: Inhibit, Shift, Emotional Control, and Self-Monitor.

Global Executive Composite = MI + BRI.

Abbriviations: BRIEF-A = Behaviour Rating Inventory of Executive Function - Adult Version; EUC = enhanced usual care; GAIN = "Get going After concussIoN".

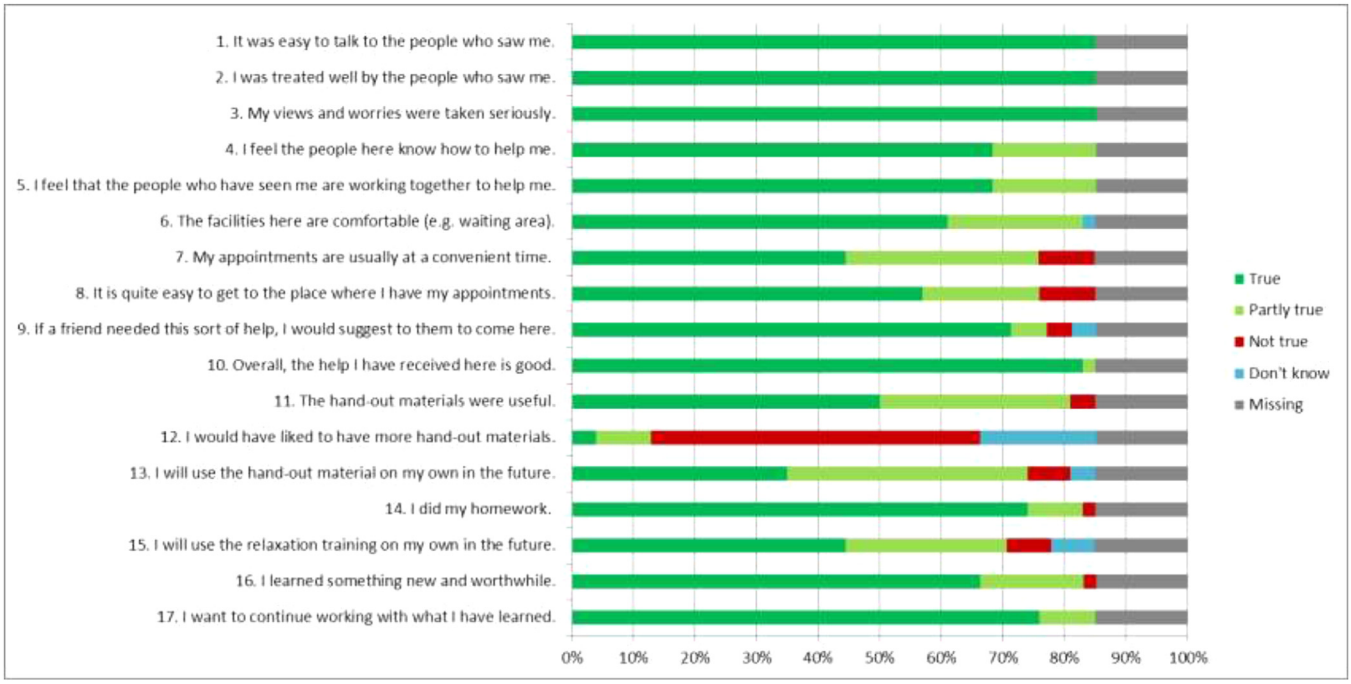

Fig. A3. Experience of Service Questionnaire modified (applied to patients allocated to GAIN+EUC, *n* = 54*).
Item 1 – 10: from Experience of Service Questionnaire.
Item 11 – 17 were added in order to evaluate the methods and materials.
* Excluded from dataset (*n*= 3): Two patients allocated to GAIN (Get going After concussIoN) who never received the intervention and one patient who withdrew after 2 sessions and declined to receive any further questionnaires. Missing: *n* = 8.

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