Understanding effects of cognitive rehabilitation under a knowledge discovery approach

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ARTICLE INFO

Keywords:
Cognitive rehabilitation
Traumatic brain injury
Knowledge discovery
Motifs
Clustering-based on rules
Post-processing

ABSTRACT

Traumatic brain injury (TBI) is the leading cause of death and disability in children and young adults worldwide. Cognitive rehabilitation (CR) plans consist of a sequence of CR tasks targeting main cognitive functions. There is not enough on-field experience yet regarding which specific intervention (tasks or exercise assignment) is more appropriate to help therapists to design plans with significant effectiveness on patient improvement. The selection of specific tasks to be prescribed to the patient and the order in which they might be executed is currently decided by the therapists based on their experience.

In this paper a new data mining methodology is proposed, combining several tools from Artificial Intelligence, clustering and post-processing analysis to identify regularities in the sequences of tasks in such a way that treatment profiles (classes) can be discovered. Due to the cumulative effect of rehabilitation tasks, small variations within the sequence of tasks performed by the patient do not significantly change the final outcomes in rehabilitation and makes it difficult to find discriminant rules by using the traditional machine learning inductive methods. However, by relaxing the formalization of the problem to find patterns that might include small variations, and introducing motif discovery techniques in the proposed methodology, the complexity of the neurorehabilitation phenomenon can be better captured and a global structure of successful treatment task sequences can be devised.

Following this, the relationship between the discovered patterns and the CR treatment response are analyzed, offering a richer perspective than that provided by the single task focus traditionally used in the CR field.

The paper provides a definition of the whole methodological approach proposed from a formal point of view, and its application to a real dataset. Comparisons with traditional AI approaches are also presented and the contribution of the proposed methodology to the AI field discussed.

1. Introduction

According to the World Health Organization (WHO), traumatic brain injury (TBI) is the leading cause of death and disability in children and young adults worldwide and it is involved in nearly half of all trauma deaths (Schroeter et al., 2011). In Europe, brain injuries from trauma are responsible for more years of disability than any other cause (Maas et al., 2009). The incidence is increasing in lower income countries; the WHO predicts that TBI and road traffic accidents will be the third cause of disease and injury worldwide by 2020. Cognitive impairments due to TBI are substantial sources of morbidity for affected individuals, their family members, and society. Disturbances of attention, memory, and executive functioning are the most common consequences of TBI.

Neurorehabilitation is the process that exploits the cerebral plasticity to reduce brain deficit. Cognitive rehabilitation (CR) aims to reduce the impact of disabling conditions and tries to improve the cognitive deficits caused by TBI. From Luria's theory back in 1978, there is a common believe that direct retraining of damaged cognitive processes through repeated stimulation and activation of the targeted brain areas can help patient recovery. For maximum activation to occur, the patient must face tasks *just barely too difficult* for him (Green and Bavelier, 2005). Designing a CR treatment for a given patient therefore means determining the correct sequence of CR tasks to be asked of the patient in a quite precise trade-off between *enough stimulating* and *sufficiently achievable* tasks, which is far from intuition, and still is both an empirical and theoretical open problem in the area. It has been seen that similar patients respond differently to similar CR treatments. Literature reports single task approaches to this purpose, analysing the

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associations between the performance of a certain task and the response to the CR treatment. However, although there is some empirical knowledge, traditional approaches do not seem to provide sufficient scientific evidence about the factors determining a favourable outcome, and there is still a limited scientific base to support the effectiveness of CR (Cicerone et al., 2011). In fact, most of the work found in this field adopts traditional pre-post analysis with intervention studies where a specific treatment is applied to a sample of patients and contrasted with a control group. But none of this analysis includes detailed characteristics of different CR programs in the model. They only use assessment of the patient before and after the treatment and characteristics of the lesion and of the patient to predict improvement. These works, although useful to prove the effectiveness of CR, do not contribute to a better design of CR programs for a specific patient.

In this work, the underlying structure of the CR phenomenon has been analyzed in depth and it has been seen that the CR field has some specific characteristics that make a successful application of traditional methods difficult:

- Patients following a CR program are not performing a single task, neither a single type of task, but a certain complex combination of them that are likely to be interrelated or synergistics. A single task approach cannot take into account the complex interactions among tasks.
- Cognitive tasks, even when specifically designed to target a particular cognitive function, might also have side-effects on other cognitive functions (Cicerone et al., 2011). This makes it difficult to examine the isolated effect of a single task in a specific cognitive function, and no clear evidence appear when all tasks are integrated into a traditional model.
- The additional effect of a single task might be affected by the cumulative effect of the sequence of previous tasks executed under the treatment, and this might determine that the order of execution is relevant in the treatment.
- The effect of a single task may be too subtle to be detected, whereas the effects of the whole CR treatment may be sufficient to be detectable, taking into account the cumulative effect of rehabilitation already mentioned.

From a structural point of view, these characteristics resemble those in nutritional epidemiology, where a global approach has been adopted in recent years, and all nutrients are analyzed together due to the high degree of interaction (Hu, 2002). This points to analyzing the overall CR treatment, by considering all kinds of interactions among tasks together, instead of using the traditional single task approach. Therefore, CR treatment in this work will be considered as a sequence of cognitive tasks and data mining methods will be used to determine the multivariate associations between a CR treatment (or relevant subsequences) and the degree of response of the patient, under this new perspective. Analyzing CR tasks as *treatment patterns* offers an innovative perspective in neurorehabilitation, and describing their relationship with their clinical outcome provides a practical approach to evaluate the effects of rehabilitation treatments. It can also enhance our conceptual understanding of CR treatments practice, and might be useful to provide guidance for cognitive treatment interventions.

To this end, an innovative data mining methodology is proposed to analyze the underlying structure of CR processes and to better determine the most suitable CR treatment for a given patient. In a first approach, one would be tempted to identify the task sequences associated with the improvement of different patients, by using a traditional classifier to find patterns associated with the different treatment responses found in different patients. However, this approach has shown serious limitations in this field, providing extremely weak patterns that do not really help in clinical practice, as will be discussed later.

In this particular field, because of the cumulative effect of the tasks mentioned above, it is reasonable to think that the effect of a certain sequence of CR tasks can behave robustly to slight variations of the sequence. Thus, small variations of the sequence of tasks performed might keep the global effect of the treatment unaltered. This means that the model to be built should admit a certain level of variation around every relevant pattern. However, working with a task's global profile for treatments is neither useful, as the order of executions becomes relevant in CR. These characteristics have already been encountered in the bioinformatics fields, particularly in *transcription factor binding sites* (TFBS) field, where slightly different sequences of DNA are associated with a certain biological function. *Motif discovery or motif finding* methods are used in this field, to represent those weak patterns. Similarly, motif discovery methods will be introduced in our proposed methodology to identify patterns of CR treatments, where slight variations in the treatment program might be packed into a single CR motif with a similar therapeutic effect, and might be associated with a certain response level.

This paper introduces the new Sequence of Activities Improving Multi-Area Performance (SAIMAP) methodology, as an innovative combination of pre-processing tools, clustering, AI methods, motif discovery and post-processing techniques. SAIMAP is a hybrid methodological frame where useful patterns can be found from data. SAIMAP works for domains with high order interactions among variables and sequential information along time that involves cummulative effects. This provides a complex structure, for which most of the classical data mining approaches do not perform very well. The proposed methodology is general for problems with the structure described before, although in the paper it is applied to the particular field of finding design guidelines for CR treatments. SAIMAP first finds groups of similar treatments, then makes a local characterization of each group by using motif discovery methods, and finally analyzes the relationships between those typical treatments and the evaluation of patients' improvement after treatment. Statistical tests and multiple boxplots are used to relate the discovered groups with patient' characteristics, level of impairment and associated with specific treatment patterns.

The structure of the paper is the following: Section 2 introduces the state of the art, organized in sections related to the different research areas involved in this multidisciplinar research, from both the application and methodological point of view. In Section 3 methodological issues are provided: first, the formalization of the general problem addressed is defined, with a clear presentation of the structural components of the problem (our methodological proposal addresses scenarios where individuals perform sequences of predefined set of activities with high order interactions among them and cumulative effects). The main goal is to identify a reduced set of characteristic sequences of activities profiling groups of individuals who behave similarly. The second part of Section 3 introduces the SAIMAP methodology as our proposal to address this problem. SAIMAP is composed by 13 formal steps, where sequential patterns are induced from data fitting the structure defined in Section 3.1. In Section 4 our methodology is applied to a specific real case, regarding cognitive rehabilitation treatments of traumatic brain injury patients; the inputs are sequences of cognitive rehabilitation tasks performed by the patients along the CR treatment; preprocessing activities are detailed and sequential patterns of CR tasks are obtained following the SAIMAP steps. The discovered patterns, are interpreted through motif discovery tools and associated with several criteria measuring improvement in a predefined set of impact areas that might be targeted in parallel by a single task (in the particular case

of application, memory, attention and executive function impact areas). Section 5 compares the patterns obtained under SAIMAP approach with traditional data mining methods, like classifiers (decision trees, neural networks, …) and sequential pattern mining. Finally, Section 6 provides conclusions and future work.

2. State of the art

2.1. Cognitive rehabilitation

Neurorehabilitation is the process of identifying the residual deficit and exploiting the cerebral plasticity to reduce it. This is achieved by elaborating therapeutic plans to favor the establishment of new and appropriate neurological connections, observing patient responses to the plan and guiding them to the proper responses (Taly et al., 1998). Cognitive rehabilitation (CR), as part of neurorehabilitation, aims to reduce the impact of disabling conditions and tries to improve the cognitive deficits caused by TBI. It aims to reduce functional limitations and increase the individual's ability in their daily activities. The modern era of CR dates to Gianutsos's seminal article, *What is cognitive rehabilitation?* (Gianutsos, 1980), which laid out an approach based on Alexander Luria's theory of *cognitive processes* (Luria, 1978), based on the assumption that direct retraining of specific cognitive processes through multiple repeated trials of stimulation and activation of the targeted cognitive process can lead to the reorganization of higher level neurologic and cognitive processes. There is a common belief that CR is effective for persons with TBI, based on a large number of studies and extensive clinical experience (Rohling et al., 2009). However, current knowledge about the factors determining a favourable outcome is mainly empirical, and there is still a limited scientific basis to support the effectiveness of such interventions (Cicerone et al., 2011).

According to Gianutsos it is possible to isolate and measure foundational aspects of cognition—attention, perception, and memory, among others— to treat them directly with the use of specifically designed activities, either on tabletops or personal computers. Repetition is perhaps the hallmark of this approach. A typical CR program mainly provides specialized tasks, which require repetitive use of the impaired cognitive subsystem in a progressively more demanding sequence (Sohlberg, 2001). Each task targets a principal cognitive function (attention, memory, reasoning/problem solving, or executive functions) and can be proposed to the subject at different levels of difficulty. As soon as a patient has mastered a particular exercise or group of exercises, higher-level treatment tasks targeting the same cognitive component need to be available so that the continued stimulation and activation of the objective cognitive process can occur.

This paradigm, known as *process-specific or skill-specific* (Sohlberg, 2005), spread quickly, and can impact differentially on neurocognitive deficits, provided that the proper sequence of tasks is delivered to the patient. For maximum activation to occur, the patient must face tasks *just barely too difficult* for him (Green and Bavelier, 2005). Thus, finding the correct training schedule for a given patient requires a quite precise trade-off between *enough stimulating* and *sufficiently achievable* tasks, which is far from intuition, and still is both an empirical and theoretical open problem. In our previous research (García-Rudolph and Gibert, 2014) the *neurorehabilitation range* has been introduced as an objective criterion to determine the proper level of difficulty to be proposed for a task, but it is still insufficient in terms of managing CR treatment globally, since cognitive tasks interact among them.

The design of a CR program has become an essential issue. However, in clinical practice, therapists mainly design CR plans from scratch, determining clinical settings for specific patients mainly based on the therapist's expertise (Jagaroo, 2009; Cicerone et al., 2011). Each specific plan evolves according to each therapist's own criteria and evaluation on the patient's follow-up. There is not enough on-field experience yet regarding which specific intervention (task or exercise assignment) is more appropriate to help CR therapists to design their CR plans (Cicerone et al., 2011). Therefore finding patterns of cognitive task sequences that produce significant improvement on affected cognitive functions can definitely contribute in this area.

Traditionally, neurorehabilitation efforts have been focused on modelling and quantifying the effect of a single cognitive task on a patient. These types of analyses have been quite valuable (Cicerone et al., 2011). They have shown, for instance, that the effect of a task mainly depends on the ratio between the skills of the treated patient and the challenges (difficulty) involved by the task (IOM, 2011; Whyte and Hart, 2003). However, the *single task* approach may be inadequate for finding global models for the rehabilitation process in clinical practice. Limitations of single factor approaches have also been found in other research areas, such as nutritional epidemiology (Hu, 2002) where research topics recently moved towards the *overall dietary patterns* by considering how foods and nutrients are consumed in combinations towards global nutritional models (Millen et al., 1996). This seems to indicate that the multivariate approach will be much more convenient in our case too.

In addition and on account of the cumulative effect of the tasks mentioned above, it is reasonable to think that the rehabilitative power of a certain sequence of tasks could remain unaltered, even when the patient executes other tasks at intermediate points of the sequence. In fact, improvement in attention of two patients performing two sequences of tasks (for example *Circles-Matching-DiffDirection-StraightLine*) and (*Circles-Matching-Categorizing-Discrimination-DiffDirection-Planif-StraightLine*) is expected to be the same, since *Categorizing, Discrimination* and *Planif* are tasks oriented mostly to work executive functions and do not mainly interact with attentional skills.

This means that the model to be built should admit a certain level of variation around every relevant pattern. These characteristics have already been encountered in bioinformatics, related to *transcription factor binding sites* (TFBS), in which regulatory elements in nucleotide sequences are searched. Certain segments of the DNA are transcribed into another molecule (RNA), which serves as a template to make the basic building blocks of cellular life: proteins (Zambelli et al., 2012). This first step of gene expression, *transcription*, is regulated by different factors, among which *transcription factors* (TFs) play a key role binding DNA *near* the transcription start site of genes. Even though some TFs bind to DNA in a very unspecific way, most of them bind by recognizing specific sequence elements (the TFBS) (D'Haeseleer, 2006). Typically, a TF recognizes not just one particular sequence but a number of similar sequences that can include small variations within it. This collection of slightly different sequences and its diverse set of representations are collectively known as *binding motifs*. TF bind the DNA in a specific way forming sequences that are similar but not necessarily identical, differing among them in a few nucleotides, but accomplishing the same biological function. Binding motifs are found using *motif discovery or motif finding* methods. These techniques enable us to find short similar sequence elements (building the motif) shared by a set of nucleotide or protein sequences with a common biological function.

Structural similarities involving binding motifs and the properties of CR treatments are proposed to be exploited in our approach. The main contact point is that the effect of a certain sequence of CR tasks can behave robustly to slight variations of the sequence, those of introducing other cognitive tasks within the sequence. A typical CR program targets a limited group of CR

functions (e.g. attention, memory, executive functions). The hypothesis of the cumulative effect of rehabilitation tasks makes it suitable to model the problem by using motif discovery techniques over CR task sequences. This way, slight variations in the treatment program might be packed in a single CR motif with a similar therapeutic effect, in the same way as small variations of nucleotide sequences are packed in a single binding motif if they regulate in the same way a certain protein. Searching for motifs over CR treatment programs (sequences of cognitive functions) is expected to identify basic sequences of CR tasks that produce a certain response to treatment pattern, even if they are performed with small variations.

2.2. Classification

A classification technique (e.g. decision trees, k-nearest neighbors, neural networks, support vector machines, naive bayes) is a systematic AI approach to build classification models from input data sets (Tan et al., 2006). The input data of a classification task is a collection of examples, describing objects by a set of attributes and a class label. Classification is the task of learning a target function f that maps each attribute set $\mathbf{x}$ to one of the predefined class labels y. The target function is also known as classification model and depending on the classification method used, it might be implicit or explicit and can take the form of a knowledge base, or a decision tree, or even a black-box, as in the case of neural networks. In order to evaluate the performance of the specific classification technique, k-fold cross-validation is used for estimating how accurately a predictive model will perform in practice (Hall et al., 2009).

A number of studies employ traditional classification techniques for the automatic prognosis of TBI patients, i.e. anticipating treatment outcome from the usual course of the disease and/or the peculiarities of each individual case. There is no consensus yet on an optimal method. Different approaches have therefore been explored (Garcia et al., 2013). Decision trees are the most common choice, (Brown et al., 2005); (Rovlias and Kotsou, 2004), but neural networks (Pang et al., 2007); (Segal et al., 2006) or different regression models (Andrews, 2002) are also used. These studies focus on determining survival, predicting gross outcome, and/or identifying predictive factors of a patient's condition after TBI (usually acute TBI). Recent studies (Pignolo Pignolo and Lagani, 2011) compare different machine learning classifiers (C4.5, Support Vector Machine, Naive Bayes, K-NN) in the early prediction of outcome of the subjects in vegetative state due to TBI. As previously mentioned, neural networks have also been applied e.g. to predict in-hospital survival following TBI (Rughani et al., 2010). When given the same limited clinical information, the ANN significantly outperformed regression models and clinicians on multiple performance measures. Particularly, three layered back-propagation neural network with an input layer of 10 nodes whose output provides the inputs to a hidden layer was used. Thirty-two TBI patients of different age and gender were taken in the study, a significant relationship between system outputs and neurologists' decisions was found (Güler et al., 2009).

To the best of our knowledge, no work has been found using classifiers to learn CR task patterns to determine the degree of improvement of a patient after a CR treatment.

2.3. Sequential pattern mining

Since the structure of the dataset that we intend to analyze contains sequences of CR tasks performed by a patient along a CR treatment, sequential pattern mining (SPM) is also considered. A sequential pattern is a sequence. Given a sequence of itemsets $S_A = X_1, X_2, \ldots X_k$, the sequence $S_B = Y_1, Y_2, \ldots Y_m$, $m \leq k$ occurs in S_A if all elements in S_B belong to S_A and precedences of S_B elements are conserved in S_A. The support of an SP is the proportion of sequences where the pattern occurs in the database. Frequent SP has a support greater than a certain threshold provided by the user; subsequences are also considered.

SPM plays an important role in data mining and is essential to a wide range of applications such as the analysis of web click-streams, program executions, healthcare data, biological data and e-learning data (Mabroukeh and Ezeife, 2010). Patterns in the healthcare domain include the common patterns in paths followed by patients in hospitals, patterns observed in symptoms of a particular disease, patterns in daily activity, and health data (Gupta and Taly, 2012). A recent example of mining in a medical context is the application of the sequential pattern mining algorithms on a database known as the RSU Dr. Soetomo medical database to find disease SP (Yuliana et al., 2009). However, age and gender were not included in the sequential rules and the author only displayed a selection of rules. Other existing work aims to detect medical SP intended to focus on time series data (Pradhan and Prabhakaran, 2009) or specific illnesses, such as patterns predicting the onset of thrombosis and identifying traits leading to atherosclerosis in a database of approximately 1400 middle aged men (Klema et al., 2008).

To the best of our knowledge the identification of SP where a TBI rehabilitation treatment is considered as a sequence of CR tasks has not yet been addressed. And the methodologies used in related works previously mentioned do not resist sets of variables with cumulative effects and high-degree interactions, as stated in the introduction.

Several efficient algorithms have been proposed for SPM such as ClaSP (Gomariz et al., 2013), CloSpan (Yan et al., 2003) GSP (Srikant and Agrawal, 1996), PrefixSpan (Pei et al., 2004), SPADE (Zaki, 2001). and SPAM (Ayres et al., 2002). SPM algorithms can use a horizontal database format (e.g. CloSpan, GSP and PrefixSpan) or a vertical database format (e.g. ClaSP, SPADE, SPAM). Using the vertical format provides the advantage of generating patterns and computing their supports without performing costly database scans. This allows vertical algorithms (CM_SPADE, CM-SPAM) to perform better on datasets having dense or long sequences than algorithms using the horizontal format, and to have excellent overall performance (Fournier-Viger et al., 2014).

Although SPM methods are suitable for our problem, we will see that they do not provide useful results from a clinical point of view. Indeed, SPM methods can provide most frequent subsequences in a dataset, and subsequences do not require contiguity of elements to occur. So, this seems to be a suitable framework to model the slight variations of the patterns required in our problem. However, the complexity of the solutions space provided by this kind of method seems to be higher than the one in the original dataset and this seems to increase complexity instead of providing a better understanding of the underlying structure of the problem as it will be seen in the application below.

2.4. Motif discovery in sequential data

A motif is a short distinctive sequence pattern shared by a number of related sequences. The distinctiveness of a motif is mainly reflected in the over representation of the motif pattern at certain locations in the related sequences and the under representation elsewhere.

One of the early origins of motif discovery in the context of DNA analysis is the Korn algorithm (Korn et al., 1977). Especially relevant to gene activities are regulatory elements bound by proteins such as TFs identification (D'Haeseleer, 2006). Because a single protein often recognizes a variety of similar sequences, motifs are subject to some degree of sequence variation at each motif position without losing their function.

More than a hundred methods (Klepper and Drabløs, 2010) have been proposed for motif discovery in recent years, representing a large variation with respect to both algorithmic approaches as well as the underlying models of regulatory regions. Among them, MEME (Multiple Expectation-Maximization for Motif Elicitation) is one of the best established motif finding tools, quick and accurate enough and with suitable implementations available (Das and Dai, 2007; Bailey and Elkan, 1995). MEME searches motifs by performing Expectation Maximization (EM) on a motif model of a fixed width and using an initial estimate of the number of sites.

Few applications are found with motif discovery for relevant patterns in non genetic sequences. They have been recently applied to acoustic analysis (Burred, 2012), where sounds are first transformed into a sequence of discrete states, and these subjected to the MEME algorithm for motif discovery, searching for repetitive patterns The relationship between biological sequences and mobility mining has also been explored (Jawad et al., 2011), searching for patterns in traffic sequence data. Specifically in the medical field, motifs search have been applied to find precursors of acute clinical events regarding electrocardiographic activity (Syed et al., 2010).

However, to the best of our knowledge, no work applying motifs to the identification of patterns in CR treatments has been conducted. In this work, a novel application of motif discovery techniques is proposed to find patterns of CR in a context quite far from genomic datasets and search of DNA sequences that are conserved across genomes, for which motif discovery techniques were originally designed. As already stated, our proposal is based on the fact that cognitive rehabilitation shares some structural components with the gene behavior, which makes motifs useful in genetics. Motif discovery methods are also introduced as a piece of particularly complex methodology that combines with other AI tools as presented in the next section.

3. Methodology

In this section, the formulation of the problem and the methodological proposal are presented. Section 3.1 provides a generic formulation of the problem which is not restricted to the particular application presented in this work.

3.1. 3.1. Problem formulation

Given

- $I = \{ i_1 \ldots i_n \}$ a set of individuals
- $T = \{T_s \; s = 1{:}T \}$ a set of activities (or tasks) that can be executed by any individuals.
- $\mathcal{A} = \{A_1, A_2, \ldots, A_a\}$ set of areas impacted by each task from T.
- $f : T \rightarrow \mathcal{A}$ a function that relates an activity with its area of impact: $f(T_s) = A_j$,

$s = 1{:}\mathcal{T}$, $j = 1{:}a$, being A_j the area of impact of activity T_s.

Given a scenario in which each individual i executes a sequence of t_{f_i} activities, one at a time $t = 1 \ldots t_{f_i}$.

Given i, the matrix R_i provides the list of all his executions (runs): $R_i = [\, i, T, t \,]_{(t_{f_i}, 3)}$.

Matrix R represents the total set of activities executed by all individuals

$$R = \begin{bmatrix} [R_1] \\ [R_2] \\ \vdots \\ [R_i] \\ \vdots \\ [R_n] \end{bmatrix}_{(\rho,\, 3)}$$

being $\rho = \sum_{i=1}^{n} t_{f_i}$ the total number of activities' executions performed by all individuals.

On the other hand, the sequence of activities executed by an individual i on time $t = 1 \ldots t_{f_i}$ is $s_i = (T_{i1}, \ldots, T_{it}, \ldots, T_{if_i})$. In fact, s_i is $s_i = R_i[2]^T$. The longest sequence having length $M_t = max_{i=1..n} t_{f_i}$.

$\chi = [\, T_{it} \,]_{(n, M_t)}$ with $i = \{1 \ldots n\}, t = \{1 \ldots t_{f_i}\}$, is a matrix where each row indicates the sequence of activities performed by individual i. Note that this might not be a rectangular table, as each row has length $t_{f_i} \leq M_t$, $\forall\, i = 1 \ldots n$.

$A_{it} = f(T_{it})$ is the area of impact of activity T_{it} executed by individual i in time t.

$s_i^a = (A_{i1}, \ldots, A_{it}, \ldots, A_{tf_i})$ is the sequence of areas impacted by the activities executed by individual i in the period $[1, t_{f_i}]$, being $A_{it} \in \mathcal{A}$ $\forall\, t = 1 \ldots t_{f_i}$.

$\chi^a = [\, A_{it} \,]_{(n, M_t)}$ with $i = \{1 \ldots n\}, t = \{1 \ldots t_{f_i}\}$, is a matrix where each row indicates the areas of impact of the sequence of activities performed by individual i.

$Y_{1t} \ldots Y_{at}$ a set of numerical indicators of performance for individuals in each area of impact.

Y_{jt} measures the global performance obtained from individual i in the Area of impact.

$A_j \in \mathcal{A}$ $j = 1 \ldots a$ at a certain time point t.

$E_0 = (Y_{10} \ldots Y_{a0})$ evaluates the performance levels of individuals in the different areas of impact before executing their sequence of activities.

$E_f = (Y_{1f} \ldots Y_{af})$ evaluates the performance levels of individuals in I, in the areas of impact in $\mathcal{A}$ after executing their corresponding sequence of activities described in χ.

$D_j = Y_{j0} - Y_{jf}$ evaluates the effect of χ in the performance levels of activity A_j. Note that a global effect of the whole sequence is measured, taking into account that several activities in the sequence might impact on the same area. Ideally Y_{jf} will be an implicit or explicit function of all those activities impacting A_j independently of their position in the particular sequence, due to the cumulative effect of activities discussed above. Assuming that 0 indicates best performance, $D_j > 0$ indicates improvement, $D_j \leq 0$ indicates non-improvement. Depending on the particular application, other semantics might also be assigned to the values of the performance indicators as well, and this will require reinterpretation of values of the D_j variables accordingly.

$\Delta = (D_1 \ldots\ldots D_a)$ provides the effect of χ on each area of impact.

$X = (X_1 \ldots X_K)$ additional information about individuals X_K might be either numerical or qualitative.

Being $\mathcal{B}$: Boolean expression build over χ^a, $\mathcal{L}$: Label; $KB = \{r: \mathcal{B} \rightarrow \mathcal{L}\}$ is a Knowledge base composed of a set of rules partially expressing the a priori knowledge in the domain. It is important to note here that no assumption of completeness is imposed over KB.

Eventually, a binary variable Z might be available for model assessment, indicating the success of an individual performing their sequence of activities under a certain criterion of performance,

$$Z = \begin{cases} YES, \textit{successful performance} \\ NO, \textit{unsuccessful performance} \end{cases}$$

Eventually Z might be a multidimensional vector and each component might be a function of some Δ component.

Under all these premises, it is desirable to find:

- a set of patterns $\mathcal{M}$ describing the behavior of the individuals when executing activities $\mathcal{M}=\{\mu_1, \mu_2, \ldots \mu_m\}$; $\forall\ \mu\in\mathcal{M}$ μ is a sequence of impact areas of variable length (always lower than Mt). Thus, each pattern μ is expressed as:

  $\mu = (a_1, a_2,\ldots,a_{n_\mu})$ with $a_l\in\ \mathcal{A}\ l$: 1. n_μ.
  Such that

1. $\forall\ \mu, \mu'\in\mathcal{M} : \mu \neq \mu'$
2. $\forall\ i \in$ I, $\exists\ \mu\in\mathcal{M}$: $\mu$is a subsequence of s_i
3. $\forall\ \mu'\in\ \mathcal{M}$, $\mu'\neq\mu$,$\mu$is a not subsequence of s_i
4. Thus, $\mathcal{M}$ inducing a partition P over I. Being P$=\{I_{\mu_1}\ldots I_{\mu_m}\}$,

   $I_\mu=\{i$:$\mu$is a subsequence of $s_i\}$

- The relationship among the patterns in $\mathcal{M}$ and the improvements in global and/or individual areas of impact in $\mathcal{A}$ due to execution of activities in T and the characteristics of individuals associated with the pattern (associations between $\mathcal{M}$ and X) This means finding associations between $\mathcal{M}$ and Z. In particular, given a threshold γ the subset $\mathcal{N}\ \subseteq\ \mathcal{M}$: $\forall\ \mu\in$N $Prob\left(Z|I_{\mu_1}=YES\right)\geq\gamma$ is searched.

3.2. The SAIMAP methodology

The SAIMAP (Sequence of Activities Improving Multi-Area Performance) methodology is our proposal to solve the problem described in the previous section.

Given the R matrix, SAIMAP consists of the following steps:

1. Preprocessing

1. Build s_i $\forall\ i=\{1, \ldots, n\}$ as $s_i=(R_i[2])^t$; s_i contains the sequences of tasks done by i

2. Build $\chi=\begin{bmatrix} s_1 \\ \vdots \\ s_n \end{bmatrix}$ as the matrix of the sequence of tasks performed by each individual

3. Identify the frequency threshold f to retain a task

4. Recategorize T by using a new category OTHERS grouping all infrequent tasks

5. Determine l the threshold task length to be considered (percentile -95 of length of treatments distribution).

Use only first l columns of χ for the whole study and complete shorter sequences by "NULL" values

6. Build

$\Delta=(D_1\ldots\ldots D_a)$ effect of χ over each area of impact

Z as a function of a subset of Δ

2. Descriptive analysis

1.Build frequency plot of first l columns and f tasks of χ

2.Build heatmap of first l columns and f tasks of χ

3.Build heatmap of first l columns and f tasks of χ^a

3. Prior expert knowledge acquisition: Knowledge is represented by means of lf-Then rules in order to provide maximum flexibility and expressiveness to the expert. Only available knowledge is collected even if it is a partial description of the domain.

Build $KB=\{r: \mathcal{B}\ \rightarrow\ \mathcal{L}\}$ from a priori expert knowledge in target domain

4. Clustering of matrix χ: The idea is to obtain standard patterns of sequences in terms of the areas impacted by the tasks performed by the users. The methodology might accept any clustering method, but in our approach *Clustering based on rules* (Gibert and Zonicki, 1999) is strongly recommended, as it will be justified in the section below.

Let P$=\left\{C_1..C_\xi\right\}$ be the set of classes found, P being a partition of I ($\forall\ C\in P$, $C\subseteq$ I)

5. Split of χ per class: Divide the data matrix into submatrices according to the different classes found in previous step.

$\forall\ C\in$ P build $\chi^a_C=\chi^a|C=\left[A_{it}\right]_{n_cM_t}$, with i$\in${i| i={1,...,n} and i $\in$ C}, i={i:i:1.n and i $\in$ C}, n_c =card{C}.

χ^a_C contains only the rows corresponding to individuals in class C.

6. Visualization of classes: $\forall\ C\in P$build a heatmap of χ^a_C

7. Find motifs per class

1. Define an alphabet ζ of a single letters associated with the areas of impact in $\mathcal{A}$ such that $\forall\ A\in\mathcal{A}$ is represented by $w\in\zeta$

2. $\forall\ C\in$ P build χ^ζ_C by replacing the activities in χ^a_C by their corresponding initial in ζ

3. $\forall\ C\in$ P find motifs of χ^ζ_C of length l (other methods can be used as well but MEME method is recommended)

Let $e^l=\left\{e^l_{C1}\ldots e^l_{cM}\right\}$ be the vector with the E-values for all motifs found

$\forall$motif m^l_C, C $\in$ P, $l\in\left[l_{min}, l_{max}\right]$

Let π^l_C be the *letter probability matrix* indicating the presence of the letter of alphabet in the position of the motif.

Eventually l might range in a certain interval $\left[l_{min}, l_{max}\right]$

8. Determine a level of minimum quality for motifs (α)

Usually $\alpha=0.05$ is considered but other values can be considered as well

9. Pruning motifs: retain the more frequent motifs for interpretation

1. $\forall\ C\in$ P build $M^*_C=\left\{m\ in M_C\ |\ e_{c_m}\leq\alpha\right\}$

10. Visualize motifs

1. $\forall\ C$ **visualize $\mathbf{M_C}$** on the basis of π^l_C using the Seq_{Logo} representation, and interpret the motifs.

2. The characteristics of the sequences associated with each class might be easily identified via the motifs visualization.

3. Describe which areas of impact are addressed at which points of the sequences in each class

11. Analyze the effect of executing activities over the different areas of impact

1.Build multiple boxplot of D_j vs P, $\forall\ D_j\in\ \Delta$

2. Kruskal-Wallis between D_j and P

Identify which areas improve the most in which classes.

12. Project all other illustrative variables over the clusters:

1.$\forall\ X_k$ in X

If X_k is numerical

Build the multiple boxplot X_k vs P;

Perform Kruskal-Wallis test

If X_k is qualitative

Build the Stacked Barchart of X_k vs P;

Perform χ^2 test

2. Retain all significant variables in X and build the description of additional characteristics of each cluster

13. Build final interpretation: Associate the descriptions of motifs with the profile of performance and the characteristics of the individuals in each class, and constitute the final characterization of P.

Although SAIMAP is available for any clustering or motif discovery method, this work proposes a particular implementation using Clustering Based on Rules (ClBR) and MEME method. A brief description of this method is provided below, together with the specific approach proposed for pattern interpretation.

3.2.1. Clustering phase ***(ClBR)***

Clustering Based on Rules (*ClBR*) combines inductive learning elements with statistical methods to enhance clustering results (Gibert et al., 1998). In our previous research *ClBR* was applied for knowledge discovery on the response to neurorehabilitation

treatment of TBI patients where CR tasks have not been considered (Gibert et al., 2008). The main idea of *ClBR* is to allow the user to introduce semantic constraints on the formation of clusters (classes), providing them in a declarative way. This condition imposed by experts formalizes the apriori domain knowledge and induces a sort of *super-structure* on the domain; clustering is performed within this structure and providing clusters is easier to be interpreted than traditional algorithms. In the present analysis *ClBR* is applied to sequential data to identify meaningful classes. Prior domain knowledge is considered, like the length of the prescribed treatment.

3.2.2. Motif discovery (MEME)

The resulting clusters are then treated with the MEME algorithm for motif discovery. MEME takes as input a group of sequences and the length of the searched motif and outputs as many motifs for the group as requested by the user. MEME then calculates the E-values of the motifs and ranks them by decreasing E-values (estimate of the number of motifs, with the same width and number of occurrences, having equal or higher log-likelihood ratio; accepted threshold is 0.005 (Bailey and Elkan, 1995). The position-specific probability matrix (PSPM) is also provided, representing the importance of each letter in each position of the motif. The PSPM matrix is input into the sequence logos (Schneider and Stephens, 1990) (*SEQ_LOGOS tool)*, providing the graphical representation for the discovered motif. The most representative motif for each of the classes is obtained together with its logo by using different motif lengths.

3.2.3. Pattern interpretation

The logos summarizes the characteristics of treatments followed in each class and are used to understand regularities in the treatments of different classes. Then the relationships between those typical treatments and evaluations of patient performance might be analyzed. In our application, performance is evaluated through standardized neuropsychological assessment battery (NAB) and effect of treatment might be computed as pre-post differences over these batteries.

Statistical tests and multiple boxplots (Tukey, 1977) are used to relate the discovered groups with patient characteristics, level of impairment and associated with specific treatment patterns. The proposal includes ANOVA or Kruskal-Wallis test (denoted as K_W in the proposed algorithm) for numerical variables depending on the characteristics of the variable itself and $\chi 2$ independence test (Tukey, 1977) or two-tailored exact Fisher test (Agresti and Franklin, 2012).

4. Application to a real case

4.1. Effects of cognitive rehabilitation on traumatic brain injury patients

This section presents the clinical context of application: The Neuropsychology Department of the Acquired Brain Injury Unit at Institut Guttmann Neurorehabilitation hospital (IG) where TBI patients undergo CR treatments.

The Information Technology framework for CR treatments in this clinical setting is the PREVIRNEC© platform (Tormos et al., 2009). A J2EE client-server architecture specifically designed and developed to manage CR plans assigned by therapists to patients, as well as follow-up information about the process (i.e. CR session dates, task executions in each session, performance, involved therapists, patients, task results, task time, detailed in Section 2.1.1).

There are three main cognitive functions to be rehabilitated in a CR program (Sohlberg and Mateer, 2001): *attention, memory and executive functions;* all of them can profoundly affect an individual's daily functioning. Even mild changes in the ability to attend, process, recall and act upon information can have significant effects in the quality of life of the patient. Consider the cognitive skills required for successful meal preparation as an example: the individual must *plan* a menu, identify required ingredients, develop a shopping list for required items and schedule sufficient time for shopping and preparing the meal; then the individual must *sequence* many food preparation activities in an organized way so that everything is ready at dinner time. Even a mild attention or executive function deficit can render this difficult, ineffective or even impossible.

The main hypothesis framing our proposal is:

1) Some CR rehabilitation tasks are designed to improve particular cognitive functions, although attention, memory and executive functions are related and interdependent (Sohlberg and Mateer, 2001). Their close interdependence stems from both a functional association and their shared neurocircuitry. This means that performing a task targeting memory can also have collateral effects on other cognitive functions like attention or executive functions.
2) The additional effect of a single task might be affected by the cumulated effect of the sequence of previous tasks executed under the treatment, this might determine that order of execution is relevant in the treatment outcome.

4.2. Cognitive rehabilitation tasks

For each patient the therapist creates a specific CR treatment i.e. an ordered sequence of tasks. At IG a typical CR program in the PREVIRNEC© platform ranges from 2–4 sessions/weeks for 2–5 months, with no constraints on task order, therefore leading to different task sequences in a different order from patient to patient.

At the time of this analysis the PREVIRNEC© platform supports 96 different CR tasks targeting the three main cognitive functions mentioned above (17 concern attention, 59 memory, and 20 executive functions). Each task is defined by some parameters that determine its level of difficulty. The therapist creates a CR treatment as a set of sessions in the PREVIRNEC© platform, each one consisting of a certain sequence of computerized tasks for a certain day. For each task, the therapist configures the suitable combination of input parameters, including the one for the automatic adjustment of the difficulty level introduced above. This dynamic adjustment of the difficulty level is performed (if necessary) twice for each task, meaning that if the patient experiences a task that is too difficult or too easy in the first execution, PREVIRNEC© automatically re-generates the task with an adjusted difficulty level. The therapist designs the sequences for every patient based on the therapist's expertise and the sequence of tasks assigned to every patient may have variable length. This work aims to generate some guidelines that can help the therapist in this design.

4.3. Assessment of the effect of the treatment

Before starting the CR program every patient undergoes a Neuropsychological Assessment Battery (NAB). This battery includes 28 items covering the major cognitive domains (attention, memory and executive functions) measured using standardized cognitive tests. NAB consists of a selection of some items from seven assessment instruments, associated with the different cognitive functions, which in turn are evaluated under some specific sub-functions. Being aware that conventional neuropsychological instruments are notorious for amalgamating cognitive operations (Jagaroo, 2009; Sabb et al., 2009), a subset

of NAB items with highest levels of specificity has been selected in collaboration with domain experts for the proposed approach. The final items considered in this work are the following 14 non redundant items:

- Memory:

  - Visual and Verbal Memory: The Rey Auditory Verbal Learning Test] (Rey,1964) (RAV075, RAV015 and RAV015R items)

- Attention:

  - Sustained Attention: *Continuous Performance Task Test (Conners, 2002) (OMI, COMI and CPT items) and *Trail Making Test-A (Reitan and Wolfson, 1993) (TMTA item)
  - Selective Attention: the WAIS-III Selective Attention (Wechsler, 1999) (VWAIS item)
  - Divided Attention: the Trail Making Test-B (Reitan and Wolfson, 1993) (TMTB item).

- Executive Functions:

  - Planification: the WAIS-III Visuo Construction (Wechsler, 1999) (CUBES item)
  - Inhibition: the Stroop Test (Golden, 1994) (INTER item)
  - Flexibility : * the Wisconsin Card Sorting Test (Heaton et al., 1997) (TERR item) and * the Letter Fluency Test (Artiola i Fortuny et al., 1999) (PMR item)
  - Categorization: The Wisconsin Card Sorting Test (Heaton et al., 1997) (CAT item)

All NAB items are normalized to a 0 to 4 scale (where 0=No affectation, 1=mild affectation, 2=moderate affectation, 3=severe affectation and 4=acute affectation).

After this initial evaluation patients start PREVIRNEC© sessions (for 2 to 5 months, depending on the patient) and after treatment every patient undergoes the same NAB to evaluate the cognitive outcome status.

Information obtained in the NAB before and after treatment is the source to understand patient improvement, and, in consequence, the response level to the treatment itself. Measuring global improvement in a specific cognitive function (e.g. Attention) implies studying response to treatment in each of the NAB tests' subfunctions (e.g. Sustained, Selective, Divided Attention). Different criteria can be adopted (subfunctions' average, maximum difference, etc). To the best of our knowledge no standardized approach is universally accepted in the clinical CR therapists community to determine the improvement of the patient from a systematic point of view.

This work tries to contribute to this issue by breaking the problem down into several steps. As a first approach we will initially focus on the identification of CR patterns (through clustering and motif discovery), flexible enough to catch the most effective sequences of tasks, even if interrupted by others. Once the patterns have been identified, the dominant effect of the treatment associated with each pattern will be analyzed. With this information, well-founded improvement criteria will be defined at a later stage (Fig. 1).

4.4. The dataset

One hundred and twenty-three TBI adults following a 3–5 months CR treatment at IG Neuropsychological Rehabilitation Unit are analyzed in this study. For every patient the demographic and clinical variables considered are: age, gender, educational level, Glasgow Comma Scale (GCS) and Post Traumatic Amnesia (PTA) duration. Table 1 shows the basic statistics for numerical variables while frequency distribution of qualitative ones are shown in Table 2.

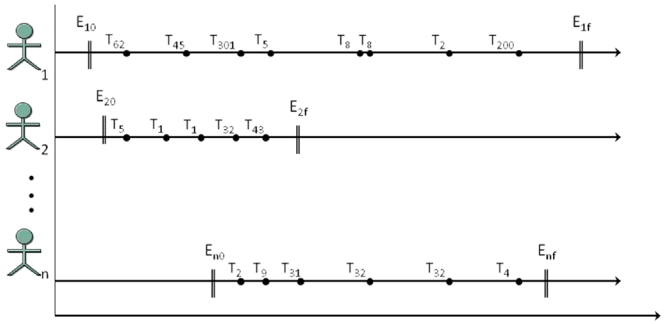

Fig. 1. Representation of individuals executing sequences of tasks impacting areas that are evaluated before and after the period of executions.

Table 1
Basic descriptive statistics for numerical variables.

Variable	N	N*	Mean	Std Dev	Min	Q1	Median	Q3	Max
AGE	123	0	36.56	6.50	18	25	32	40	68
GCS	89	34	6.45	3.15	0	4	6.5	40	14
PTA	40	83	131.6	140.5	34	79	103	136	947

Table 2
Basic descriptive statistics for gender and educational level.

GENDER	Count	Percentage	EDU	Count	Percentage
Female	32	26.02	**Elementary**	60	48.78
Male	91	73.98	**Intermediate**	40	32.52
			High	23	18.70

Initial assessment of the TBI severity is reported according to GCS levels. A GCS score of eight or less after resuscitation from the initial injury is classified as a *severe* brain injury. The GCS score for *a moderate* brain injury ranges between 9 and 13 and a score of 13 or greater indicates a *mild* brain injury, or concussion. As detailed in Fig. 2 most GCS scores (86,17%) show *severe* brain injury level (mean value $6{,}45 \pm 3.15$). It is known that those whose length of PTA is less than two months have a very good chance of at least being able to live on their own (even if they are unable to return to work or school). On the other hand, patients whose length of PTA is longer than three months are unlikely to be able to return to work or school (although they might be able to live on their own). As N* shows in Table 1, PTA measures were not available for 67% of the participants; considered values show very severe conditions as indicated by the median (103), which is more reliable than the mean because of the outlier visualized in Fig. 2 (right).

Demographic qualitative (Table 2) indicates 91 men (73.98%) and 32 women (26.02%) participating in the analysis. Each participant's educational background is categorized in three groups, with Elementary school predominant.

All participants signed informed consent to the neuropsychological procedure, which was approved by IG's Ethical Committee. All met criteria to initiate IG neuropsychological rehabilitation treatment.

After NAB initial evaluation all patients initiated a three to five months' program (November 2007 to November 2009) based on personalized interventions in the PREVIRNEC© platform where patients worked in each of the specific cognitive domains, considering the degree of the deficit and the residual functional capacity. All patients were administered the same NAB neuropsychological assessment at the end of the rehabilitation

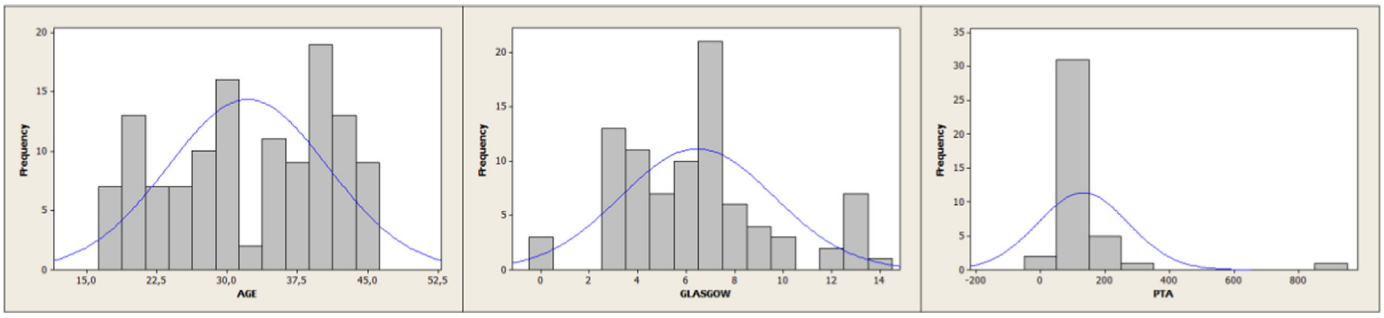

Fig. 2. Numerical variables histograms: Age (left), Glasgow Comma Scale scores (center) and Post Traumatic Amnesia days (right).

program. A total of 39412 task executions were initially included in this analysis, involving the 96 different CR tasks included in the PREVIRNEC© platform.

4.5. Structure of database

Originally, the system records the execution of every task as a single row in a log file, which additionally records the following information:

Date is the date of the execution of the T_s task (date *yyyymmdd*)
TaskName is a descriptive name assigned to identify the task T_s
Score is the result obtained in that execution (0 to 100 real number)
NumTask is the automatic task generation number assigned to the task (0,1,2)
Difficulty is the difficulty level of the task (0,1,2,3,4)
Function: cognitive function addressed by the task: Attention, Memory, Executive func.
Subfunction is the specific cognitive subfunction addressed by the task (as described below, for the Attention function the addressed subfunctions are visual attention, sustained attention, selective attention, etc).
Original data structure (*S1*):

$$\begin{bmatrix} i & T & Date & TaskName & Score & NumTask & Dificulty & Function & Subfunction \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{bmatrix}$$

4.6. Instantiation of the formal problem

The presented dataset approaches the formal problem presented in Section 2 as a particular case where a CR treatment is the scenario in which each patient i executes a sequence of activities, one at a time

- I is the set of TBI patients undergoing CR treatment at IG
- $T=\{T_s\ s=1:\mathcal{T}\ \}$ is a set of 96 CR tasks that patients execute during treatment:
  T={GlobalLocal, MathMazeComp, MathMazeExer, ConcOps, Submarine, Matching,BagOfCoins, Differences, Figures,PuzzComp, PuzzExer, LetterSoup,Bingo, DiffDirection,StraightLine, SameDirection, GroupWords, CategorizationTwo, CategorizationThree, SameCatWords, Circle, Platforms, Zigurat, GoNoGoEst, GoNoGoGame, GoNoGoPos, Hanging, SinkFleet, Maze, FourInRow, Fourth, JigSaw, BuildSentence, Fragments, Serie, CyclicSerie, SameCat, TempOrder, Position, Sequential, Simoultaneous, WordSeqDec, WordSeqSel, WordSeqDifCat, WordSeqSameCat, WordSimDec, WordSimSel, WordSimDifCat, WordSimSameCat, WordTempOrder, PairsSeqDec, PairsSeqRel, PairsSeqSel, PairsSeqSameOrder, PairsSeqRandOrder, PairsSimDec, PairsSimRel, PairsSimSel, PairsSimSameOrder, PairsSimRandOrder, SentSecOrder, SentSecTest, SentSecWrite, SentSecQuestion, SentSecTrueFalse, SentSimOrder, SentSimTest, SentSimWrite, SentSimQuestion, SentSimTrueFalse, RecSeqNumbers, RecSimNumbers, RemSecNumbers, RemSimNumbers, TextSort, TextQuestion, TextWrite, TextTrueFalse, ImgWordTempOrder, ImgWordSeqDecide, ImgWordSeqRel, ImgWordSeqSel, ImgWordSeqSameOrder, ImgWordSeqRandOrder, ImgWordSimDecide, ImgWordSimRel, ImgWordSimSel, ImgWordSimSameOrder, ImgWordSimRandOrder, DrawTemporalOrder, DrawRecognition, SceneRecognition, SceneRecall, VisualMemory, VisualSimon}
- $\mathcal{A}$ is the set of areas of impact. In this particular case it matches with the family of cognitive functions targeted by the CR tasks. $\mathcal{A}$={Attention, Memory, Executive functions} are the main cognitive functions involved in daily activities (Sohlberg and Mateer, 2001); these are therefore treated in PREVIRNEC too.
- $f(T)$=a provides the main cognitive function a, (a $\in\mathcal{A}$) targeted by task T.
- Given a patient i, the matrix R_i provides the list of all tasks executed by the patient i with its corresponding execution times throughout his CR treatment.
- Row i of matrix χ gives the sequence of CR tasks done by i during treatment.
- The set Y_{jt}, t=1.14 of numerical indicators of performance is, in this work, the selection of 14 relevant and non redundant items from NAB, used in IG for evaluating the degree of impairment of each cognitive function.
- D_j, is the difference between the scores obtained by the patient before and after the prescribed CR treatment in the corresponding NAB item.
- $\Delta=$ (D_1..... D_a) represents the effect of CR treatment in all cognitive functions.
- $X=(X_1 \ldots X_K)$ additional information about patients. X_K might be either numerical (like age or GCS) or qualitative (like Sex or Educational level).
- Z indicates a global improvement of the patient after treatment.

The execution of each task by a patient occurs at different periodicities for every patient; the length of treatment is variable in both number of task executions and total treatment time for the different patients; the sequence of task executions changes from one patient to another; the result obtained in an execution determines both the task and difficulty of the next task proposed by the system; the effect of a task in terms of cognitive functions of the patient is accumulative and the effect of a certain sequence of tasks might not be affected by small variations of the sequence itself, i.e. the introduction of small additional tasks in intermediate positions of the sequence. For these reasons, our problem may be treated under SAIMAP methodology.

4.7. The Sequence of Activities Improving Multi-Area Performance (SAIMAP) methodology

4.7.1. Preprocessing

As a first hypothesis it is assumed (after consulting with experts) that the time interval (delay) between the execution of two consecutive tasks is irrelevant for rehabilitation purposes, since

the cognitive functions of each patient is sensitive to the task execution and not so much to the time period between consecutive tasks. Thus, the *sequence* of tasks followed by each patient is the main target, independently of the time interval in which the tasks have been performed. This enables a simplification of the problem into a new structure in which the order of tasks is maintained, but dates are omitted.First step of preprocessing is building the s_i sequence of tasks performed by each patient.

$i = \{1,\ldots 123\}$ on the basis of R matrix by building $s_i=(R_i[2])^t$

R being a matrix that for every task executed by the patient provides the

$\langle patientid, Name\ of\ task, Time\ stamp\ of\ execution\rangle$

All tasks performed by patient i are collected in R_i

$$R_1 = \begin{bmatrix} 1 & TemporalOrder & 1 \\ 1 & StraightLine & 2 \\ 1 & DiffDirection & 3 \\ & \vdots & \\ 1 & NumMaze & 632 \\ 1 & MatchMaking & 633 \\ 1 & FourInRow & 634 \end{bmatrix} \ldots\ldots R_{123} = \begin{bmatrix} 123 & PositionalStimuli & 1 \\ 123 & FourInRow & 2 \\ 123 & MatchMaking & 3 \\ & \vdots & \\ 123 & GoNoGo & 621 \\ 123 & GoNoGo & 622 \\ 123 & Platforms & 623 \end{bmatrix}$$

Thus:

$$s_1=\begin{pmatrix} TemporalOrder & StraightLine & DiffDirection & \ldots & NumMaze & MatchMaking & FourInRow \end{pmatrix}$$

$$s_{123}=\begin{pmatrix} PositonalStimuli & FourInRow & MatchMaking & \ldots & GoNoGoPlatforms \end{pmatrix}$$

The lengths are also variable: $t_{f_1} = 634$; $t_{f_{123}} = 623$.

Next, χ matrix is built by combining all s_i in the rows. Eventually the tasks are identified by shorter alias, for simplicity

$$\chi = \begin{bmatrix} T127 & T145 & T034 & \ldots & T256 & T045 & T145 \\ & & \ldots & \ldots & \ldots & & \\ T123 & T065 & T134 & \ldots & T011 & T032 & T035 \end{bmatrix}$$

Next step is to determine the minimum f to retain a task. Regarding the number of task executions, as shown in Fig. 3, a pack of 12 tasks is shown from left to right as idTask 151 to IdTask 210, which are executed more frequently than the rest and there is a high number of available tasks, only exceptionally included in CR treatment programs.

For our purposes the subset of most frequently executed tasks will be the focus and all remaining tasks will be recorded into an OTHERS category.

Table 3 details the percentage of the total number of executed tasks for each idTask showing that the 12 more frequently occurring tasks exceed 70% of the total activity in the considered period. Thus taking $f=1000$ means to retain only tasks executed more than 1000 times, and this points to the 12 more frequently occurring tasks identified above. We will therefore focus on this pack of tasks since this percentage is close to the Pareto Principle.

Patients also exceptionally perform very large sequences of tasks. It is often possible to identify a threshold length *l*.,which can be considered as most usual. Patterns of sequences are searched for only in the first l task executions of the patient's sequences to avoid dealing with the sparseness of the final part of the data matrix. According to the Pareto principle, l threshold is determined in such a way that no more than 20% of patients perform larger tasks. Those data rows are completed with a special idTask label (e.g. "NULL"). As each patient's activities are different, each sequence of tasks shows a different length, with the shortest one being length 9 and the longest one length 1391.

As shown in Fig. 4, most of the execution lengths are less than 600. Longer sequences represent less than 17% of the patients. 83%

Table 3
Number of executions for the 12 most frequent Tasks.

IdTask	Task name	Number of executions	Percentatge (tot)	Percentatge (selection)
151	Memory	3369	8.20	11.51
146	StraightLine	3329	8.10	11.37
153	TemporalOrder	3226	7.85	11.02
148	FourInRow	3170	7.71	10.83
161	Matching	2978	7.25	10.17
145	Exercise	2951	7.18	10.08
149	Competition	2589	6.30	8.84
144	Cercles	1780	4.33	6.08
147	Serie	1671	4.06	5.71
150	DiffDirection	1531	3.72	5.23
182	GoNoGoGame	1411	3.43	4.82
210	Platforms	1251	3.04	4.27
		29256	**71.17**	**99.99**

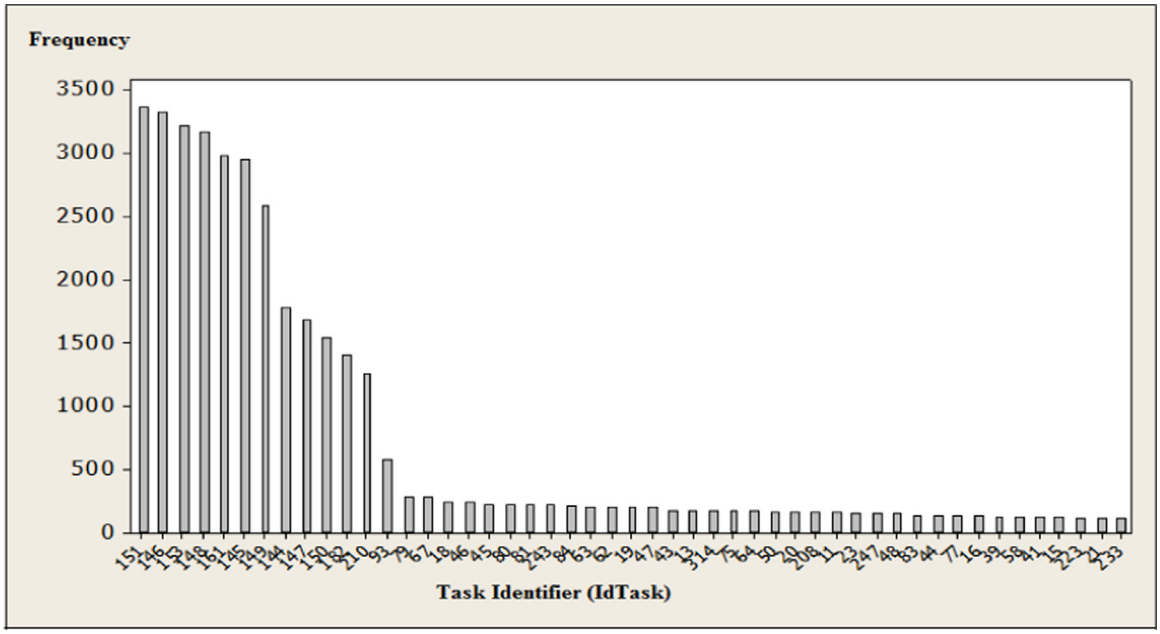

Fig. 3. Frequencies of task executions. X axis shows the identifier of the task. Y axis shows number of executions. Only tasks with more than 100 executions are shown.

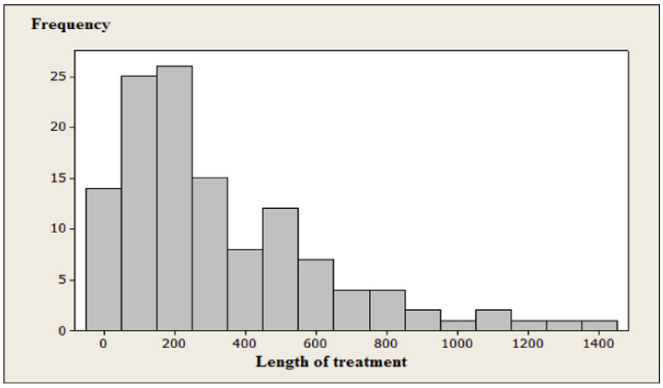

Fig. 4. Histogram of the treatment length. X axis shows the lengths of the treatments. Y axis shows the observed frequency of treatments for a certain range.

Table 4
Selected tests and items targeting specific cognitive functions.

Test	Item	Cognitive Function
Continuous performance test	OMI	A
	COMI	
	CPT	
Trial making test	TMTA	
WAIS-III selective	VWAIS	
Trial making test	TMTB	
Rey auditory verbal learning test	RAV075	M
	RAV015	
	RAV015R	
WAIS-III-Visuo-spatial	CUBES	EF
Stroop test	INTER	
Wisconsin card sorting test	TERR	
Letter fluency test	PMR	
Wisconsin card sorting test	CAT	

of patients have followed CR treatment programs shorter than 600 task executions per patient. This includes 103 patients from the 123 initial ones. Therefore in our model we propose an equally sized rectangular data matrix considering $l=600$ executions, 83% of those patients followed shorter sequences of CR treatments. This transforms our originally variable length matrix into a rectangular matrix χ, which is easier to process.

Next the matrices to evaluate the effect of the treatment are built:

In our particular application, $\Delta=(\Delta_A, \Delta_M, \Delta_{EF})$ is composed of three normalized effect indexes, evaluating improvement in each cognitive function. As already stated, the IG uses the NAB battery to assess improvement. Together with the experts, the main cognitive function targeted by each of the 14 selected items from NAB is shown in Table 4.

As all items evaluate in the interval [0,4], simple mean is used as a measure of the cognitive function performance of the patient either before or after the treatment. Thus the Δ components are built as the post – pre difference, using those indicators. As all items indicate higher impairment with higher values and as it is expected that patients improve during treatment, differences between scoring after and before the treatment are expected to be positive. For this reason the components of Δ are defined as:

$$\Delta_A = \frac{OMI_f + COMI_f + CPT_f + TMTA_f + VWAIS_f + TMTB_f}{6} - \frac{(OMI_0 + COMI_0 + CPT_0 + TMTA_0 + VWAIS_0 + TMTB_0)}{6}$$

$$\Delta_M = \frac{RAV075_f + RAV015_f + RAV015R_f}{3} - \frac{(RAV075_0 + RAV015_0 + RAV15R_0)}{3}$$

$$\Delta_{EF} = \frac{CUBES_f + INTER_f + TERR_f + PMR_f + CAT_f}{5} - \frac{(CUBES_0 + INTER_0 + TERR_0 + PMR_0 + CAT_0)}{5}$$

4.7.2. Descriptive analysis

As a first step in this phase, the construction of the frequency plot of the first l columns and f frequency of tasks for χ is performed. In Fig. 5 it can be noticed that less frequent tasks (shown in grey and labelled as OTHER) are more frequently executed at the beginning of the treatments, but as the treatment progresses their frequency decreases.

Next, the construction of the heatmap of the first l columns and f frequency of tasks for χ is performed. Fig. 6 suggests the need for a method to group tasks to allow identification of execution patterns. Each task is represented with the colour gradient as in Fig. 5 but no structure can be identified, neither in the Figure nor permuting patients on the vertical axis.

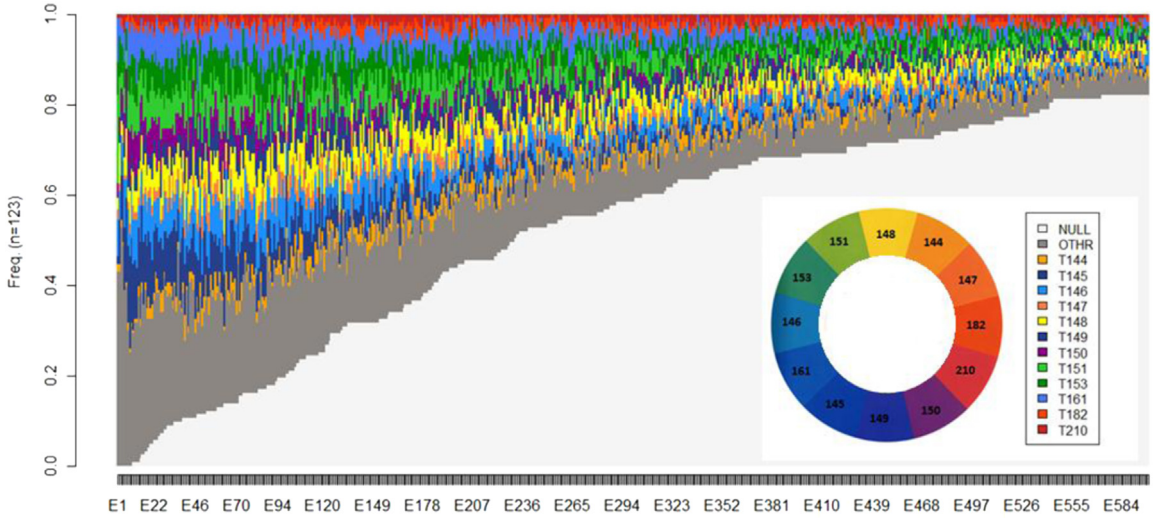

Fig. 5. Frequency of the 12 selected tasks during the treatments. X axis provides the time in the CR program where the task was executed. The tasks are identified by colors according to legend and circular pantone.

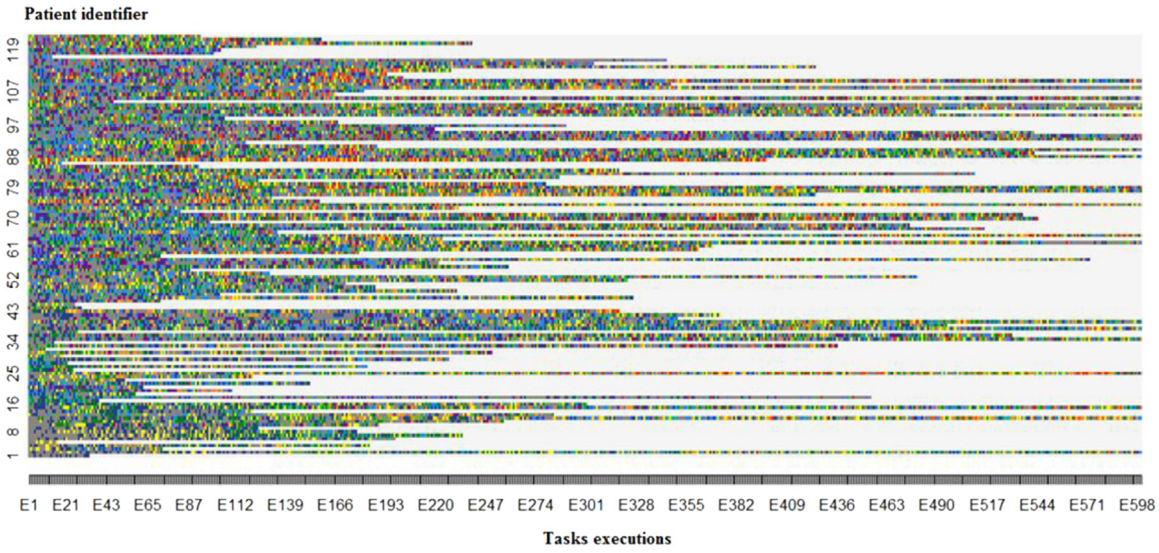

Fig. 6. Heatmap for individual treatments representing the 12 selected frequent tasks. Y axis represents patients (identified 1 to 123) and X axis shows position of the task during the treatment. First 600 tasks are represented. Task colors are the same as in Fig. 5. Treatment lengths are variable. Apparent lack of any recognizable structure or pattern in the tasks.

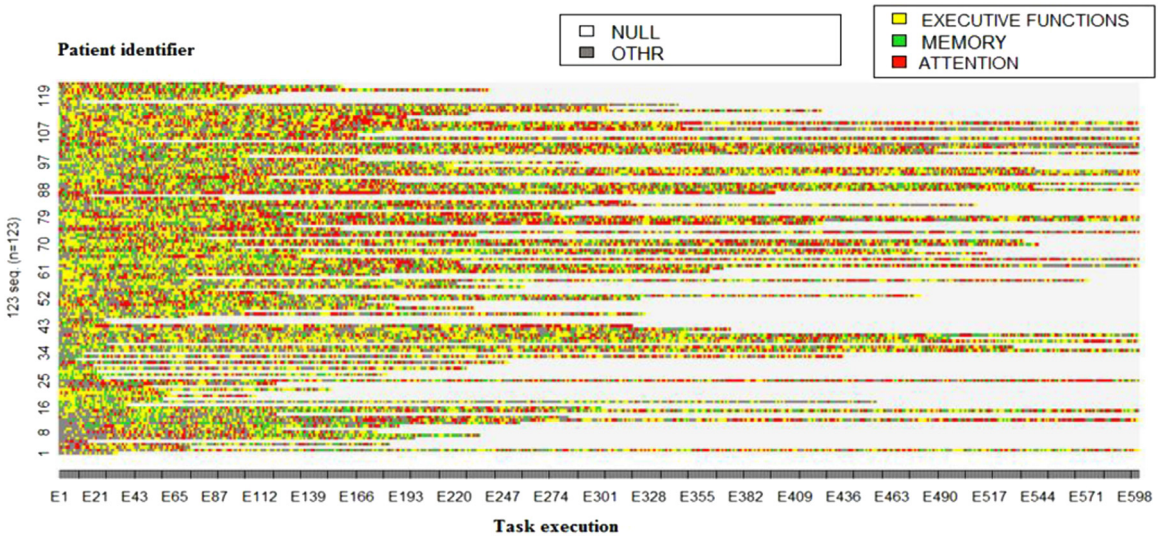

Fig. 7. Heatmap of individual treatments representing the cognitive function addressed by each executed task. X axis represents the position of the task along the treatment sequence. Y axis represents the individual patients.

Next, the construction of the heatmap of the first l columns and f frequency of tasks for χ^a is performed. Fig. 7 provides a heatmap with a lower granularity level of information. Tasks are grouped per cognitive function and a color is assigned to every group (green is used for memory tasks, red for attention tasks, and yellow for executive function tasks, grey points to other non-frequent tasks, which are not considered at this stage of the analysis). As in Fig. 5 even grouping by targeted functions, execution patterns cannot be identified from this figure.

4.7.3. Prior expert knowledge acquisition

Domain knowledge is represented by means of IF-THEN rules. Experts expressed knowledge regarding what is considered a long or short treatment in terms of the number of tasks it comprises.

KB = { r1: *if* SeqLength $<$ 450 *then* SHORT,
r2: *if* SeqLength $>$ 480 *then* LONG}

4.7.4. Clustering phase

The software **KLASS v86** was the data mining platform for the ***ClBR*** algorithm executions (Gibert et al., 1998). ***ClBR*** was run with Ward's method, Gibert's mixed distance (Gibert et al., 1998), and KB as referred knowledge base. Resulting dendrogram is shown in Fig. 8.

Calisnki-Harabasz criterion (Calinski and Harabasz, 1974) suggests a cut in 29 classes for which 26 are singleton and 3 main groups are conformed. One contains most of the patients satisfying r2 and the other 2 subdivide patients satisfying r1 in 2 subgroups. Obtained classes are shown in Table 5.

4.7.5. Split into classes

According to experts, singletons were disregarded as exceptional cases to be carefully analyzed one by one. Data matrix is then divided into 3 submatrices according to the three identified classes: SHORT70, SHORT86 and LONG6

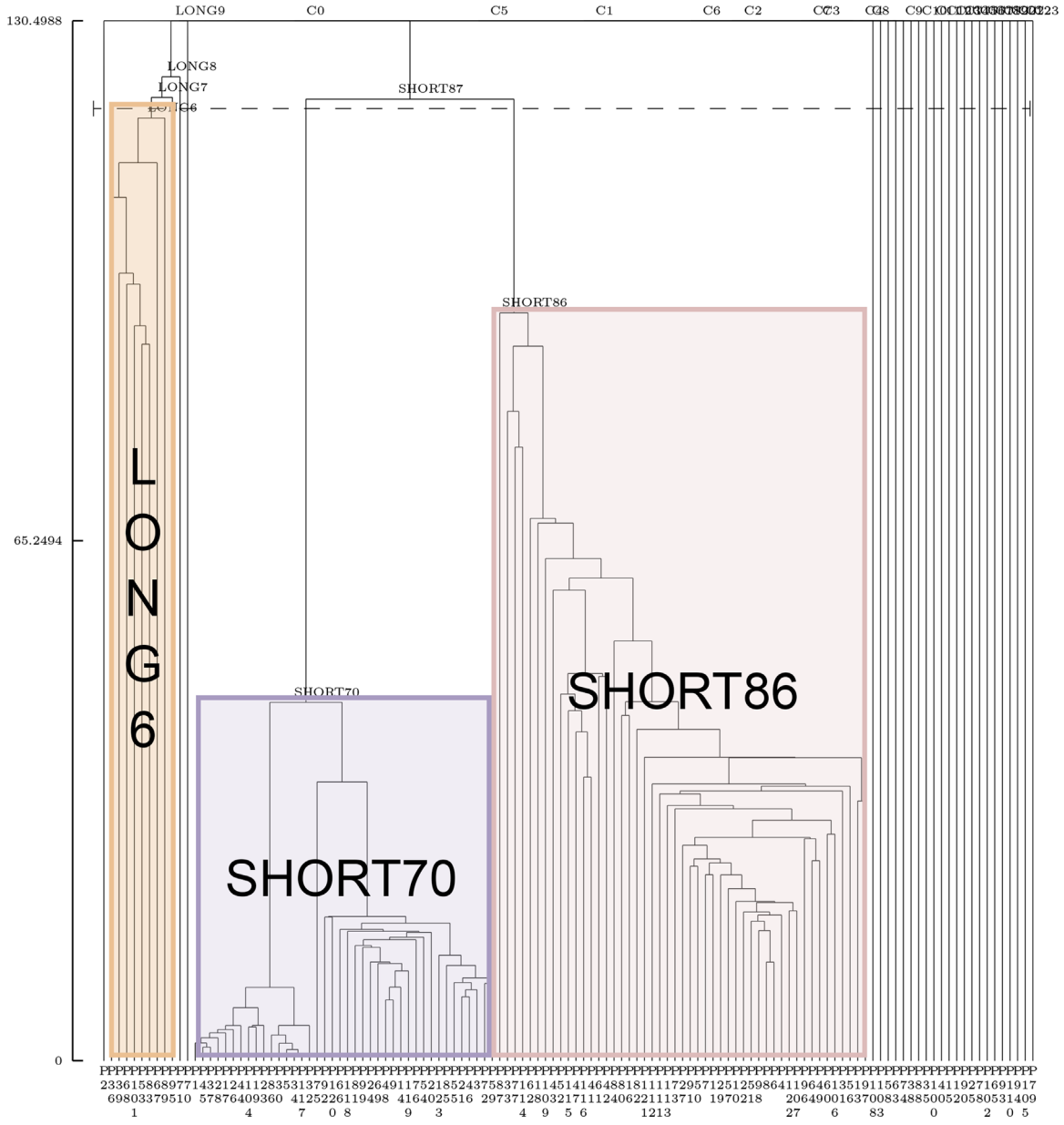

Fig. 8. Dendrogram from the *ClBR*. Leaves represent patients; internal nodes represent the intermediate clusters; the height of nodes is proportional to the homogeneity of the class. The dashed line shows a partition of the dataset in a set of classes (highlighted in different colors). Singletons at the right are patients that remain isolated.

4.7.6. *Visualization per classes*

Local heatmaps are built for every class and shown in Figs. 9 to 11. SHORT70 (Fig. 9) class contains patients with shorter treatments, less than 150 tasks; SHORT86 class (Fig. 10) contains patients with intermediate length treatments, between 150 and 460 tasks; and LONG6 catches patients following treatments longer than 460 tasks.

4.7.7. *Find motifs per class*

Toolbox for Motif Discovery (TMOD) version 1.1.1 is the framework for motif discovery (Hanchang et al., 2010) run on a 3.4 GHz Pentium IV computer with 2 GB of RAM.

MEME (Bailey and Elkan, 1995) implementation was executed in TMOD with the following input parameters:

- *Sequences* (in FASTA format) of cognitive functions targeting the different task executions, therefore input data to MEME is the same as for sequential pattern mining.

Table 5
Number of patients in each identified class.

Class label	Nc
SHORT70	40
SHOT86	49
LONG6	8

- *Alphabet*: Run with DNA sequences, which must contain only ACGT letters: A is used for attention tasks, C for memory, and T for executive functions.
- *Distribution:* how the occurrences of motifs are distributed in the input sequences. Run with Any Number of Repetitions (ANR): in this case MEME assumes each sequence may contain any number of non-overlapping occurrences of each motif. This

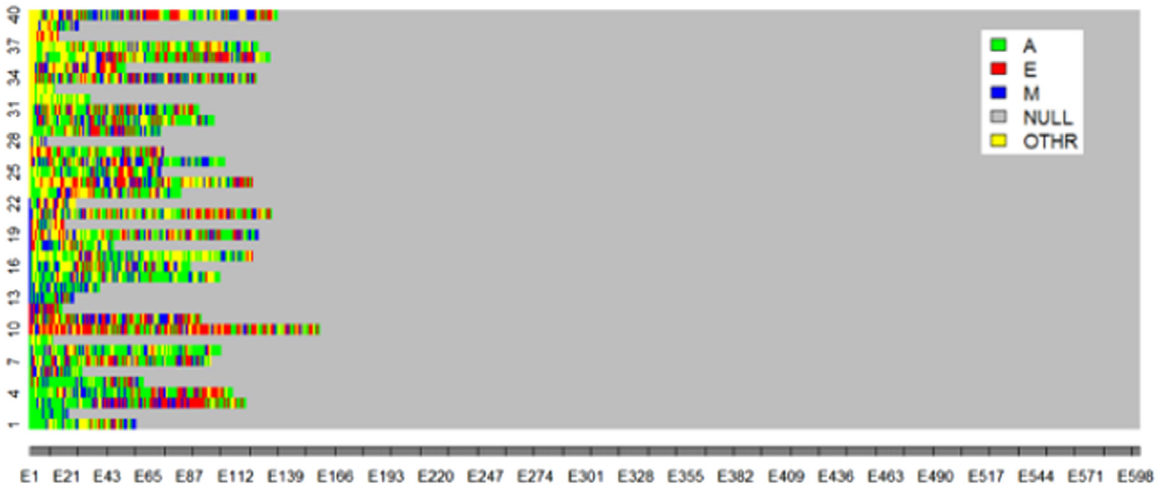

Fig. 9. Heatmap representing SHORT70 class executions.

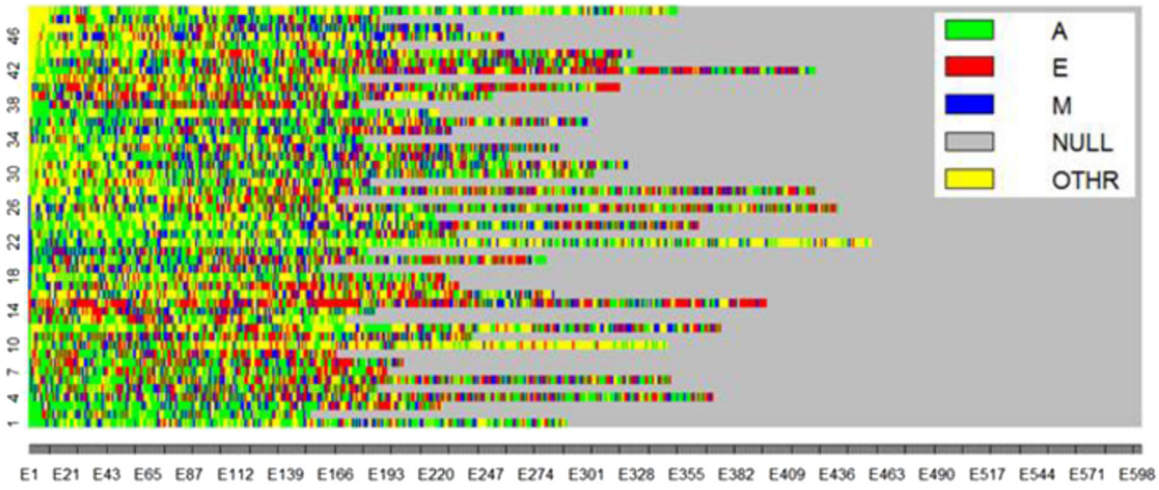

Fig. 10. Heatmap representing SHORT86 class executions.

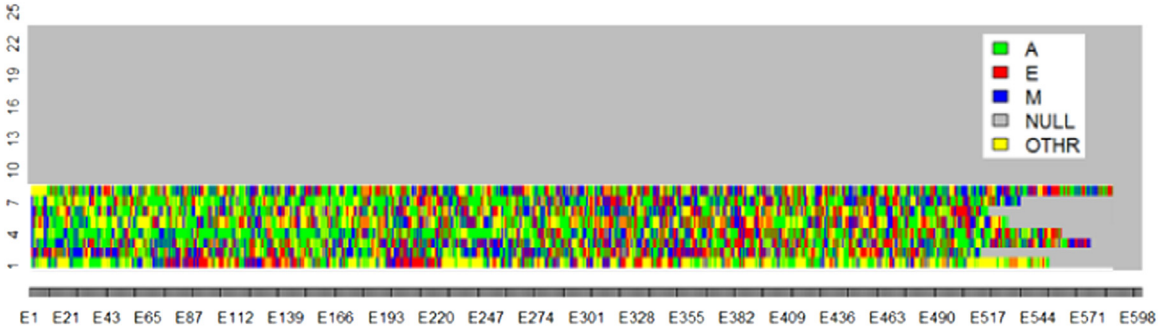

Fig. 11. Heatmap representing LONG6 class executions.

option is useful because we suspect that motifs repeat multiple times within a single sequence.

- *Motif width*: run with motif length parameter ranging from l= [6,20] (larger motifs are visually difficult to analyze and shorter than 6 were discarded by domain experts because a CR session rarely includes less than 6 task executions).
- *EM Algorithm*: Iterations of EM to run from any starting point (default= 50).
- *Performance measure:* MEME searches for the motif with the smallest E-value.

MEME is then run with the parameters specified above for each identified cluster sequence and Fig. 12 shows the obtained sequence of logos for $M=\{M_{C_1}\ldots M_{C_\xi}\}$

$\forall C \in P, M_C=\{m^6_{SHORT70}\ldots m^{20}_{SHORT70,} m^6_{SHORT86}\ldots m^{20}_{SHORT86,} m^6_{LONG6}\ldots m^{20}_{LONG6}\}$

With a total of 14 motifs for each of the 3 analyzed classes.

4.7.7.1. Determine a level of minimum quality for motifs. For convention $\alpha=0.05$ is taken

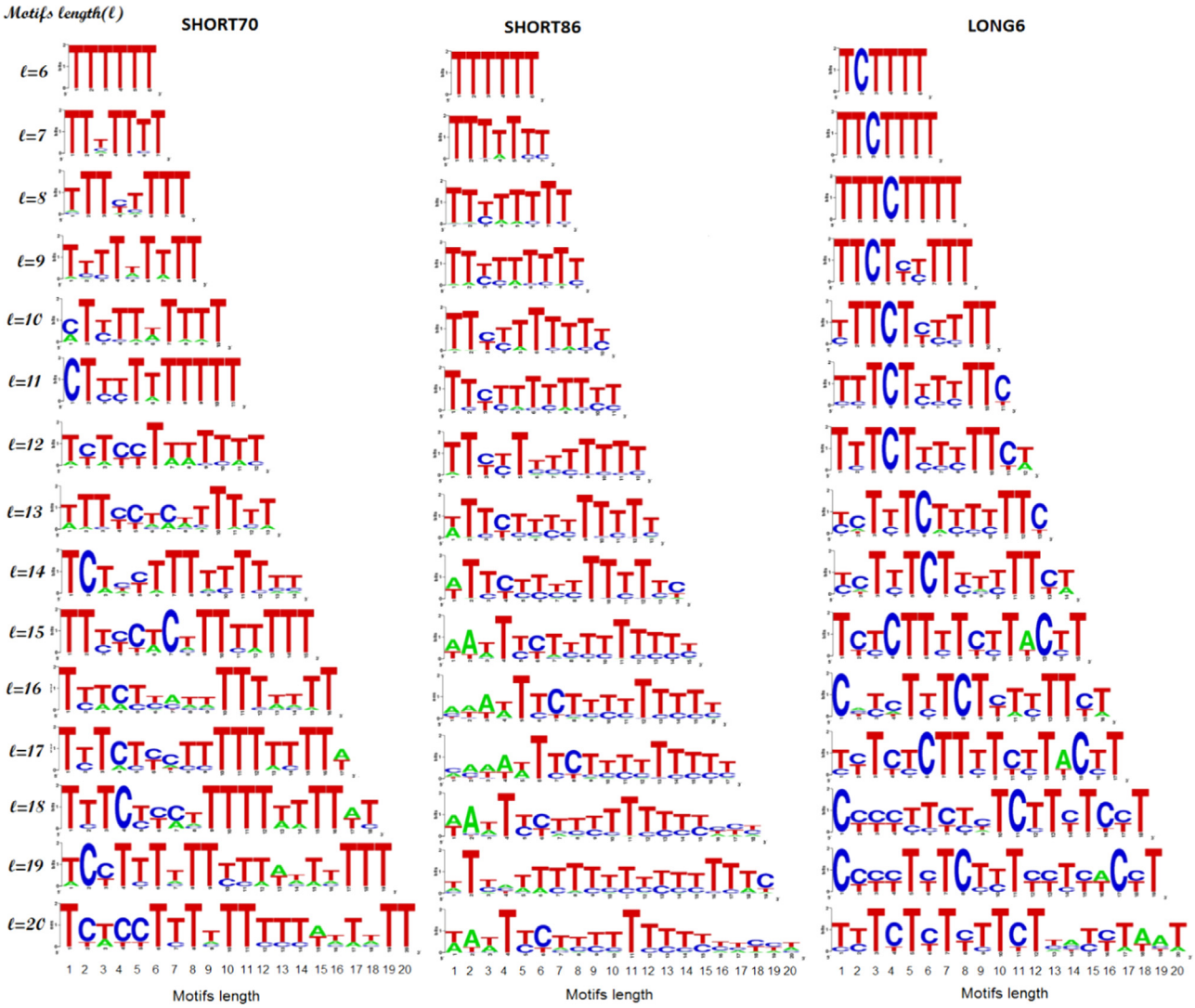

Fig. 12. Logos by motif lengths per class. Motif length ranges from 6 to 20 tasks.

4.7.7.2. Pruning motifs: retain more frequent motifs for interpretation. For each motif π_C^l and l length, a weighted median of the E-values of the three classes is calculated, being the weighting factor the number of patients n_c of each class as shown in Table 5. The matrix with the E-values is shown in Table 6.

For each motif a π_C^l matrix is given, which is input into the motif viewer. The obtained $\pi^{20}_{SHORT86}$ is shown in Table 7.

4.7.8. Visualize motifs per class

Motif analysis leads to the following descriptions:

- SHORT70 class shows mainly executions of tasks oriented to executive functions (shown as T) and some memory tasks (C), mainly in the first part of the sequences.
- SHORT86 class includes less executive functions and memory tasks than the other classes but shows a higher number of attention tasks (A), mainly at the beginning.
- In class LONG6 the number of memory tasks clearly increases and is often combined with executive function tasks. Eventually some attention tasks are performed at the end of the identified motifs.

4.7.9. Project illustrative variables over the clusters

There are no significant differences in the characteristics of the patients for the three identified classes (GCS, age, PTA, gender and educational level), see Tables 8 and 9 where p-values for numerical and categorical variables are shown. Possible differences in response to the treatments might therefore be attributable to the task patterns followed.

However, one can get clear criteria to decide whether to assign a long or short treatment to a patient by analysing behaviour of NAB items pre-treatment (Table 10). It is observed that patients with low RAV015R (highly impaired recognizing memory) require long treatments, whereas patients with high RAV015 (mild impairment in short term memory) can successfully follow short treatments (other NAB items are insignificant).

4.7.10. Analyze the effect of executing activities over the different areas of impact

According to related previous work (Hart et al., 2005) a global index for each cognitive function is created as the average score for all items referring to that cognitive function. The effect of the treatment on a certain cognitive function is measured as the post-pre value observed in the corresponding index. As already stated, lower values in differences indicate higher deficit reduction or, in other words, a positive response to the CR treatment.

Fig. 13 shows the multiple boxplots with the conditional distributions of effect indexes versus the classes. Each graph represents the different effects of treatment on a certain cognitive

Table 6
E-values ranking for different lenghts.

e^{l}_{C}	Length/Class	SHORT86
e^{14}_{C}	14	2.8e-055
e^{15}_{C}	15	5.6e-051
e^{16}_{C}	16	2.6e-049
e^{12}_{C}	12	4.3e-049
e^{13}_{C}	13	2.4e-048
e^{11}_{C}	11	3.2e-046
e^{18}_{C}	18	3.0e-045
e^{17}_{C}	17	2.5e-045
e^{10}_{C}	10	7.7e-039
e^{20}_{C}	20	1.9e-039
e^{19}_{C}	19	3.1e-034
e^{9}_{C}	9	2.3e-032
e^{8}_{C}	8	1.8e-028
e^{7}_{C}	7	2.7e-026
e^{6}_{C}	6	2.5e-018

Table 7
Tabular representation of $\pi^{20}_{SHORT86}$ matrix.

A	C	G	T
0.435897	0.000000	0.000000	0.564103
0.769231	0.025641	0.000000	0.205128
0.384615	0.051282	0.000000	0.564103
0.000000	0.000000	0.000000	1.000000
0.000000	0.410256	0.000000	0.589744
0.000000	0.794872	0.000000	0.205128
0.102564	0.128205	0.000000	0.769231
0.102564	0.230769	0.000000	0.666667
0.025641	0.230769	0.000000	0.743590
0.025641	0.179487	0.000000	0.794872
0.000000	0.000000	0.000000	1.000000
0.000000	0.153846	0.000000	0.846154
0.000000	0.256410	0.000000	0.743590
0.025641	0.179487	0.000000	0.794872
0.000000	0.384615	0.000000	0.615385
0.153846	0.358974	0.000000	0.487179
0.256410	0.282051	0.000000	0.461538
0.102564	0.512821	0.000000	0.384615
0.230769	0.461538	0.000000	0.307692
0.307692	0.205128	0.000000	0.487179

function in each class. The first interesting observation is that all groups improve (deficit decreases) after treatment and the effects are all below 0 on average. The dimension tending to more negative values is attention, while memory seems to be the one with less improvement for all groups. In contrast, it can be seen that SHORT86 class is the one with better treatment results regarding attention, while it behaves very similarly to class SHORT70 in terms of memory and executive functions. It also appears that class LONG6 is more resistant to treatment than others, especially regarding memory.

4.7.11. Build final interpretation

Crossing the obtained profiles with the motifs and the effects of therapy it appears that:

SHORT70 represents short term treatments, no more than 150 task executions mainly oriented to executive functions, preceded in some cases by memory tasks, mainly in the initial part of the sequences. These persons show better response to treatment mainly in attention and executive functions than in memory, having an intermediate level of attention improvement compared with other classes.

SHORT86 represents intermediate duration treatments, with no more than 460 task executions including a higher number of attention tasks executed mainly at the beginning of the sequences. Persons in this class show a higher recovery in attention than in other functions, being the group with better results for treatment regarding attention.

LONG6 represents long term programs including more than 460 task executions with a higher proportion of memory tasks, often combined with executive functions tasks and possibly some attention tasks at the end of the sequences. However the persons in this class are more resistant to treatment than other classes in memory and attention.

5. Comparison with traditional approaches

Under a traditional approach, one would be tempted to reduce our problem to building a predictive model for the improvement of the patient and to solve it by using some machine learning classifier.

Preliminary analysis and problem representation provided appropriate data structures, data transformations, and domain knowledge for pattern discovery. Traditional classification techniques are proposed to study response to CR treatment.

Matrix χ is used for the classifier with a response variable Z (see Section 2):

$$Z=\begin{cases} YES\ ,\ patient\ improved\ after\ treatment \\ NO,\ patient\ didn't\ improve\ after\ treatment \end{cases}$$

Table 9
Categorical variables number of occurrences and p-values (χ^2 test) per class.

	GENDER		**EDU LEVEL**			
	Female	Male	Elemen	Interm.	High	Total
SHORT70	13	27	19	14	7	40
SHORT86	12	37	27	14	8	49
LONG6	2	6	4	3	1	8
χ^2 p-value	0.691		0.949			

Table 8
Mean, standard deviation and p-values (Kruskal-Wallis) of numerical variables per class.

	GCS			**AGE**			**PTA**		
	Mean	**StD**	**Media**	**Mean**	**StD**	**Median**	**Mean**	**StD**	**Median**
SHORT70	6.27	2.91	6	32.80	8.20	32.8	84.3	36.9	84.3
SHORT86	6.04	2.63	6	31.65	7.99	31.65	156.7	209.7	156.7
LONG6	6.88	3.09	7	35.13	9.57	35.13	117.67	13.65	117.67
KW p-value	0.667			0.433			0.176		

Table 10
NAB selected items vs classes.

	RAV075			RAV015			RAV015R		
	Mean	**StD**	**Media**	**Mean**	**StD**	**Median**	**Mean**	**StD**	**Median**
SHORT70	2.75	1.37	3.00	2.72	1.56	4.00	2.15	1.77	2.00
SHORT86	3.20	1.06	4.00	3.38	1.09	4.00	2.91	1.45	4.00
LONG6	2.37	1.50	3.00	2.25	1.90	3.00	1.87	1.80	1.00
KW p-value	0.136			0.042			0.056		

In this work traditional classification algorithms and some sequential pattern mining algorithms have been used.

5.1. Pattern discovery with classifiers

Algorithms that exploit four different machine learning principles have been used on our real application and compared with the proposed approach: decision tree learning (j48), instance-based learning (IBk), probabilistic learning (Naive Bayes), and RBF neural networks.

Waikato Environment for Knowledge Analysis (WEKA) (Hall et al. 2009), v 3.6.5 was the data mining platform for running classifiers. All of them were run with default parameters on a 3.4 GHz Pentium IV PC with 2 GB of RAM. The classifiers run in this application were:

- J48 is the WEKA implementation of the C4.5 decision tree (Quinlan, 1993).
- Naive Bayes implements the probabilistic Naive Bayes classifier (John and Langley, 1995).
- IBk is the implementation of KNN (Aha and Kibler, 1991) the k-nearest-neighbor classifier; parameter (k set in our tests to 1,2,3, and 5) setting the neighborhood size.
- RBFNetworks implements a popular type of feed-forward network, radial basis function (RBF) network (Witten, 2011).

The prediction performance of the models was measured by ten-fold cross validation and several parameter configurations were tested. In this study the data set was split into 9 subsets with 12 records and 1 subset with 15. Each classifier is trained 10 times, each time using a version of the data in which one of the subsets is omitted (testing data). Each trained classifier is then tested on the data from the subset, which was not used during training. The results are averaged to obtain an overall accuracy (Table 11).

Our solution proposes a set of motifs to be followed. The proportion of patients following the proposed motifs who improve after treatment is 81.33%, which can be used as an equivalent to accuracy and is noticeably higher than the predictive models obtained by all assessed machine learning methods.

5.2. Sequential pattern analysis

As presented in Section 1.1.2. sequential pattern mining (SPM) techniques are also suitable to find patterns of executions of CR tasks targeting cognitive functions, identified patterns might help to understand responses to treatment. The input is matrix χ and SPM algorithms were tested: CM-SPAM and CM-PREFIXSPAM as well as CM-SPADE.

Sequential Pattern Mining Framework (SPMF) version v0.96q was the data mining platform for the SPM algorithm executions. (Fournier-Viger et al., 2014). All of them were run with default parameters on a 3.4 GHz Pentium IV computer with 2 GB of RAM.

SPADE and SPAM are very efficient for datasets having dense or long sequences and have excellent overall performance, since performing joint operations to calculate the support of candidates does not require scanning the original database unlike algorithms using the horizontal format. For example, the well-known Prefix-Span algorithm, which uses the horizontal format, performs a database projection for each item of each frequent sequential pattern, in the worst case, which is extremely costly.

CM-SPADE is the SPMF implementation of SPADE algorithm (Fournier-Viger et al., 2014). The support of a sequential pattern is

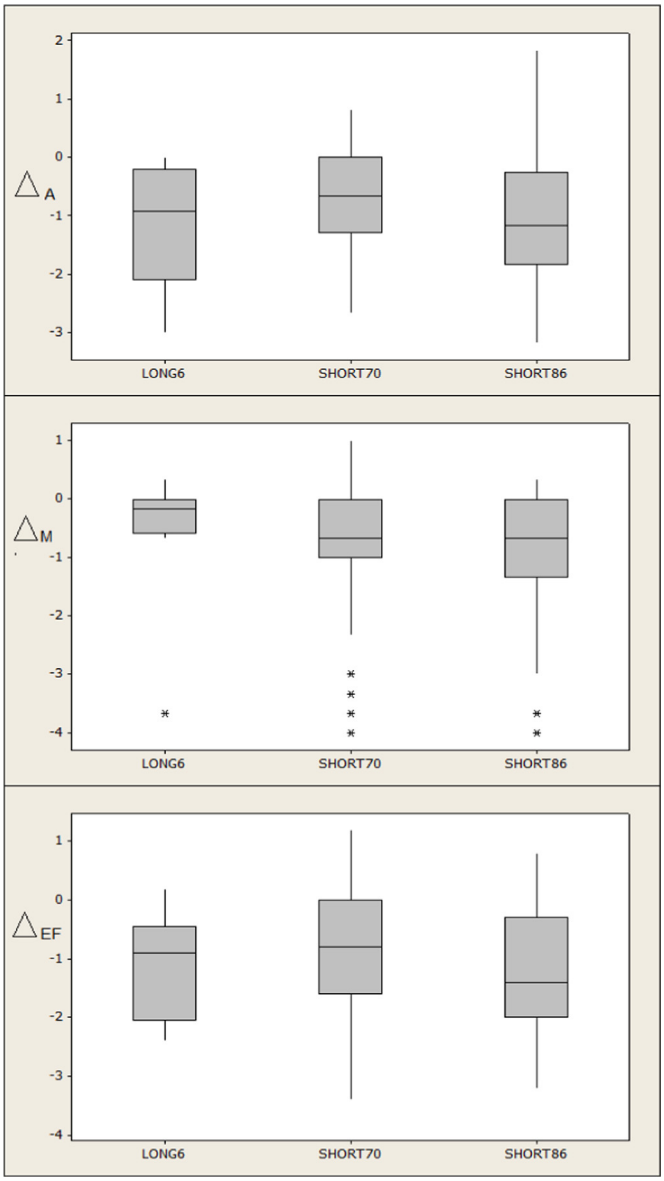

Fig. 13. Multiple boxplots of improvement versus class and cognitive function. For each cognitive function, a multiple boxplot of the corresponding improvement index Δ versus classes is visualized. Every boxplot displays the range between the minimum and maximum value of each Δ, the box indicates the interval between first and third quartile, horizontal mark in box indicates the median.

Table 11
Accuracy for each classifier after 10-fold cross validation, first column shows the number of CR task executions considered.

Attributes	C4.5 (J48)	Naive bayes	KNN (IBk)				RBFnetworks
			IB1	*IB2*	*IB3*	*IB5*	
10	57.72	54.47	52.84	50.40	53.65	57.62	56.91
20	56.09	52.84	56.09	54.47	58.53	56.91	47.15
30	57.72	58.53	56.91	58.53	64.22	58.53	56.09
40	57.72	56.91	53.65	51.21	56.91	61.78	59.34
50	53.65	58.53	57.72	57.72	62.60	58.53	59.34
60	51.21	57.72	57.72	56.91	57.72	56.09	58.53
70	60.97	57.72	57.72	56.91	60.16	59.34	52.84
80	59.34	59.34	56.09	54.47	62.60	63.41	54.47
100	63.41	55.28	56.09	52.03	60.97	61.78	49.59
600	64.41	61.78	59.34	55.28	60.16	60.16	46.34
1391	60.16	58.53	60.16	56.09	60.16	62.60	46.22

the number of sequences where the pattern occurs divided by the total number of sequences in the database (see Section 2).

Table 12 shows pattern found with support $>=0.88$. A total of 31501 patterns of length 15 are found (almost the size of the original dataset).

5.3. Sequential pattern mining on each class

An analysis local to each class is also performed to see if local analysis provides a more constrained set of solutions. SM-SPADE is applied on each of the identified classes, but as shown in Table 13 the number (N) of identified patterns in each class does not decrease.

5.4. Comparison

Table 11 shows results obtained with by-default parameters and other configurations, like j48 being tested with three different confidence factors (0.25, 0.30, 0.40) decreasing post-pruning, and varying the minimum number of objects per leaf. For Ibk, Euclidean distance (with and without weighting) was used and different window sizes were tested, also varying the number of neighbours (k parameter). For about 80% of the tests the obtained performance is below 60% and none of them reached 65% of accuracy after 10-fold cross validation. These results persist irrespective of the number of features (CR task executions) introduced into the different models. Table 11 shows results for models including only initial CR sessions (10 or 20 first tasks of the treatment) up to 600 or 1300 tasks. Intermediate values (e.g. 700, 800, 900 CR task sequences) were also tested with similar results in performance, which are not reliable enough to be used in real clinical practice. This contrasts with the 81.33% accuracy obtained under the proposed approach.

Regarding SPM algorithms, they show acceptable performance regarding support (e.g. 0.8 or 0.9), even better than the one obtained under our proposal in some cases. But as detailed in Table 13, the number of frequent sequences discovered is greater than the original dataset (i.e. with support $>=$ 0.8 CM-SPADE identifies 44690 frequent sequences of length 9; 16853 sequences of length 10 and 2415 of length 11), This increases problem complexity instead of decreasing it, since we originally had about 39000 task executions. SPM algorithms were also tested locally to classes after performing a ClBR clustering phase, but the results obtained were similar, i.e. shorter sequence clusters did not decrease the number of identified frequent sequential patterns, therefore did not lead to an easier process to understand how to build new CR plans.

6. Conclusions and future work

In this work a first application of motif discovery is integrated in the generic SAIMAP method used to find promising treatment patterns in cognitive rehabilitation. This provides further knowledge to that obtained in previous analysis where isolated tasks were analyzed.

The use of motifs is relevant because the cumulative effect of CR task execution is robust to the time period intervals occurring

Table 12
Sequential patterns identified by CM-SPADE for a minsupport=0.88. First column shows the length of the patterns and N column the number of identified sequences for each pattern length. Then mean and median support are shown together with other support statistics.

CM-SPADE

	LEN	N	Media	St Dev	Min	Max	Q1	Mediana	Q3
0.88	1	3	0.9675	0.0422	0.9187	0.9919	0.9187	0.9919	0.9919
	2	9	0.9431	0.0407	0.9024	0.9919	0.9106	0.9106	0.9837
	3	27	0.92442	0.03785	0.88618	0.99187	0.89431	0.90244	0.97561
	4	64	0.91527	0.03536	0.88618	0.99187	0.89431	0.90244	0.95325
	5	118	0.91264	0.03440	0.88618	0.99187	0.88618	0.89431	0.95325
	6	172	0.91591	0.03373	0.88618	0.98374	0.88618	0.89431	0.95122
	7	238	0.92150	0.03073	0.88618	0.96748	0.88618	0.93496	0.95122
	8	354	0.92609	0.02451	0.88618	0.96748	0.89431	0.93496	0.94309
	9	589	0.92715	0.01716	0.88618	0.95935	0.92683	0.93496	0.93496
	10	1064	0.92408	0.01164	0.88618	0.95122	0.91870	0.92683	0.93496
	11	2060	0.91756	0.00976	0.88618	0.94309	0.91057	0.91870	0.92683
	12	4097	0.91035	0.00907	0.88618	0.93496	0.90244	0.91057	0.91870
	13	8192	0.90385	0.00834	0.88618	0.93496	0.89431	0.90244	0.91057
	14	16339	0.89834	0.00760	0.88618	0.92683	0.89431	0.89431	0.90244
	15	31501	0.89391	0.00665	0.88618	0.91870	0.88618	0.89431	0.89431
	16	53247	0.89084	0.00549	0.88618	0.91870	0.88618	0.88618	0.89431
	17	69573	0.88902	0.00438	0.88618	0.91057	0.88618	0.88618	0.89431
	18	64130	0.88794	0.00348	0.88618	0.91057	0.88618	0.88618	0.88618
	19	38554	0.88730	0.00281	0.88618	0.90244	0.88618	0.88618	0.88618
	20	14341	0.88689	0.00230	0.88618	0.89431	0.88618	0.88618	0.88618
	21	3159	0.88651	0.00161	0.88618	0.89431	0.88618	0.88618	0.88618
	22	401	0.88618	0.000000	0.88618	0.88618	0.88618	0.88618	0.88618
	23	32	0.88618	0.000000	0.88618	0.88618	0.88618	0.88618	0.88618
	24	1	0.88618	*	0.88618	0.88618	*	0.88618	*

Table 13
Identified sequential patterns on each class.

CLASS SHORT70

	LEN	N	Media	St Dev	Min	Max	Q1	Mediana	Q3
0.5	1	8	0.7562	0.1223	0.5500	0.8750	0.6312	0.8000	0.8500
	2	52	0.6418	0.0977	0.5000	0.8250	0.5500	0.6500	0.7250
	3	220	0.58136	0.06786	0.50000	0.77500	0.52500	0.57500	0.62500
	4	540	0.54819	0.04859	0.50000	0.72500	0.50000	0.52500	0.57500
	5	658	0.53533	0.03937	0.50000	0.67500	0.50000	0.52500	0.55000
	6	481	0.52651	0.03073	0.50000	0.62500	0.50000	0.52500	0.55000
	7	214	0.51636	0.02314	0.50000	0.60000	0.50000	0.50000	0.52500
	8	42	0.51250	0.02084	0.50000	0.57500	0.50000	0.50000	0.52500
	9	2	0.50000	0.000000	0.50000	0.50000	*	0.50000	*
0.7	1	6	0.8167	0.0563	0.7250	0.8750	0.7625	0.8375	0.8562
	2	19	0.75000	0.04330	0.70000	0.82500	0.70000	0.75000	0.77500
	3	17	0.72794	0.02319	0.70000	0.77500	0.70000	0.72500	0.75000
	4	6	0.70833	0.01291	0.70000	0.72500	0.70000	0.70000	0.72500
0.8	1	4	0.8500	0.0204	0.8250	0.8750	0.8312	0.8500	0.8688
	2	4	0.81250	0.01443	0.80000	0.82500	0.80000	0.81250	0.82500

CLASS SHORT86

	LEN	N	Media	St Dev	Min	Max	Q1	Mediana	Q3
0.8	1	16	0.8200	0.1455	0.5800	0.9800	0.6800	0.8400	0.9750
	2	87	0.8480	0.1120	0.5600	0.9800	0.8200	0.8400	0.9600
	3	444	0.86032	0.06557	0.56000	0.9800	0.80000	0.86000	0.92000
	4	1827	0.85606	0.05152	0.56000	0.98000	0.82000	0.84000	0.90000
	5	6694	0.84476	0.04158	0.80000	0.98000	0.80000	0.84000	0.88000
	6	19163	0.83284	0.03304	0.80000	0.96000	0.80000	0.82000	0.86000
	7	38639	0.82293	0.02527	0.80000	0.94000	0.80000	0.82000	0.84000
	8	53869	0.81440	0.01874	0.80000	0.92000	0.80000	0.80000	0.82000
	9	44690	0.80805	0.01362	0.80000	0.90000	0.80000	0.80000	0.82000
	10	16853	0.80442	0.00991	0.80000	0.88000	0.80000	0.80000	0.80000
	11	2415	0.80206	0.00678	0.80000	0.86000	0.80000	0.80000	0.80000
	12	83	0.80289	0.00834	0.80000	0.84000	0.80000	0.80000	0.80000
	13	5	0.80000	0.00000	0.80000	0.80000	0.80000	0.80000	0.80000

CLASS LONG6

	LEN	N	Media	St Dev	Min	Max	Q1	Mediana	Q3
0.8	1	9	0.9583	0.0625	0.8750	1.0000	0.8750	1.0000	1.0000
	2	60	0.94375	0.06271	0.87500	1.00000	0.87500	1.00000	1.00000
	3	320	0.92852	0.06195	0.87500	1.00000	0.87500	0.87500	1.00000
	4	1355	0.91504	0.05835	0.87500	1.00000	0.87500	0.87500	1.00000
	5	4489	0.90541	0.05364	0.87500	1.00000	0.87500	0.87500	0.87500
	6	11659	0.89830	0.04868	0.87500	1.00000	0.87500	0.87500	0.87500
	7	23216	0.89364	0.04453	0.87500	1.00000	0.87500	0.87500	0.87500
	8	35347	0.88998	0.04059	0.87500	1.00000	0.87500	0.87500	0.87500
	9	39390	0.88649	0.03611	0.87500	1.00000	0.87500	0.87500	0.87500
	10	29588	0.88307	0.03072	0.87500	1.00000	0.87500	0.87500	0.87500
	11	13003	0.88003	0.02456	0.87500	1.00000	0.87500	0.87500	0.87500
	12	2860	0.87732	0.01686	0.87500	1.00000	0.87500	0.87500	0.87500
	13	250	0.87600	0.01116	0.87500	1.00000	0.87500	0.87500	0.87500
	14	7	0.87500	0.000000	0.87500	0.87500	0.87500	0.87500	0.87500

between task execution and small interferences in a certain sequence do not decrease their rehabilitative effect.

In the proposed methodology, a previous clustering process is performed in such a way that three CR program profiles are identified. Later, motif discovery local to each profile is performed to understand the structure of the task sequences associated with the classes and it has been seen that length of treatment seems to be a main class characteristic. Associated with length, specific sequence patterns appear and motifs for each class have distinctive characteristics, which provides the therapists a first conceptual framework to compose CR programs under long, short or intermediate lengths.

Statistical tests seem to indicate that basic demographic and clinical characteristics of the patients (GCS, PTA, gender, educational level, age) do not show significant differences vs the classes, thus indicating that differences among groups are due to the structure of the treatment itself. However, it has been seen that short treatments are associated with patients with mild impairment in short term memory (RAV015 NAB item), while long ones are associated with patients with high impairment on recognizing memory, this providing clear clinical guidelines to the therapist. It is also interesting to note that patients in class SHORT70 follow treatments shorter than 150 tasks, which, in fact, is much less than the current prescriptions (this providing also relevant information for future CR personalized treatment design). Indeed, currently, the hospital is prescribing a treatment of 3 months to all patients and intermediate evaluations are used to decide advanced end of treatment, or subsequent prolongation for

a second period of three months. Till now, this has been observed in real time during the treatments. With the proposed methodology, one can get clear criteria to recommend short or long treatment from the beginning, before starting it.

Afterwards, improvements of the patients for the different classes were studied by means of conditional distributions of improvement indicators (effect indexes) versus the classes. This seems to confirm that all groups improve in all cognitive functions, but different response patterns are associated with the classes, thus providing a better understanding of the CR effects to the therapists. Patients following intermediate length treatments improve their attention functions more than other groups; those following short treatments perform more executive functions and some memory tasks preceding them, show smaller improvement; those for long treatments show higher resistance to improve.

Thus, the proposed methodology provides useful tools to help therapists to both better understand effects of CR treatments on patients and to better design personalized CR treatment plans. These answers could not be provided using a traditional machine learning approach, as shown in Section 5, where the proposed method was compared with both traditional machine learning classifiers and sequential pattern mining methods. The former provided noticeably worse accuracies, whereas the latter improved it in regards to our results, but the results provided by the methods, far from helping experts, increased the complexity of the information to be analyzed and were proven to be unuseful for our purposes.

This is one of the first studies providing guidelines on the performance of the CR programs. The results presented here are eliciting some clinical hypothesis, which are currently being tested on a larger sample of patients. Research is also in progress to provide more detailed information regarding task executions (results, level of difficulty) and to identify specific tasks associated with higher improvements within profiles. Finally, the findings provided by SAIMAP are currently being related with the neurorehabilitation range of the tasks introduced in previous work (Garcia-Rudolph and Gibert et al., 2008) to enrich the current model with the number of repetitions required for each recommended task to maximize the expected improvement of the patient.

Conflict of interests

PREVIRNEC© is a registered trademark of Institut Guttmann-Hospital de Neurorehabilitació. Alejandro García Rudolph is currently working at Institut Guttmann-Hospital de Neurorehabilitació.

Acknowledgements

This research was supported by: Ministry of Industry, Tourism and Trade (Spain) AVANZA PLAN-Digital Citizen Subprogram (PT: NEUROLEARNING Grant no: TSI-020501-2008-0154); Institute of Health Carlos III (Spain) Strategic Action Health's Call (PT: Clinical implantation of PREVIRNEC platform in TBI and stroke patients / Grant no: PI08/900525); Spanish Ministry of Economy and Finance (PT COGNITIO – Grant Nr TIN2012 38450) and EU-FP7-ICT (PT PERSSILAA Grant Nr 610359). Special thanks to Alberto García Molina and José María Tormos from Institut Guttmann Neurorehabilitation Hospital for their support in NAB selection, KB rules definition and results interpretation.

References

Aha, D., Kibler, D., 1991. Instance-based learning algorithms. Mach. Learn. 6, 37–66.

Agresti, A., Franklin, C., 2012. Statistics: The art and Science of learning from data, Third Ed. Pearson.

Andrews, P.J.D., 2002. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: a comparison between decision tree analysis and logistic regression. J. Neurosurg. 97, 326–336.

Artiola i Fortuny, L., Hermosillo Romo, D., Heaton, R.K., y Pardee III, R.E., 1999. Manual de normas y procedimientos para la batería neuropsicológica en español. m Press, Tucson, AZ.

Ayres, J., Flannick, J., Gehrke, J., Yiu, T.: Sequential pattern mining using a bitmap representation. In: Proc. 8th ACM SIGKDD Intern. Conf. Knowledge Discovery and Data Mining, pp. 429–435. ACM (2002).

Bailey T.L. and. Elkan C.P. The value of prior knowledge in discovering motifs with MEME. In Procs of the 3rd Int'l Conference on Intelligent Systems for Molecular Biology, pages 21–29. AAAI Press, 1995.

Brown, A.W., Malec, J.F., McClelland, R.L., Diehl, N.N., Englander, J., Cifu, D.X., 2005. Clinical elements that predict outcome after traumatic brain injury: a prospective multicenter recursive partitioning (decision-tree) analysis. J. Neurotrauma 22 (10), 1040–1051.

Burred J.J. Genetic motif discovery applied to audio analysis. International Conference on Acoustics, Speech and Signal Processing (ICASSP), 2012 pp 361-364 IEEE.

Calinski, T., Harabasz, J., 1974. A dendrite method for cluster analysis. Commun. Stat.-Theory Methods 3, 1–27.

Cicerone, K.D., Langenbahn, D.M., Braden, C., Malec, J.F., Kalmar, K., 2011. Evidence-based cognitive rehabilitat-ion: updated review of the literature from 2003 through 2008 5. Arch. Phys. Med Rehabil. 92, 19–30.

D'Haeseleer, P., 2006. How does DNA sequence motif discovery work? Nat. Biotechnol. 24 (8), 959–961.

Das, M.K., Dai, H.K., 2007. A survey of DNA motif finding algorithms. BMC Bioinforma. 8 (Suppl), 7.

Fournier-Viger, P., Gomariz, A., Campos, M., Thomas, R. (2014). Fast Vertical Sequential Pattern Mining Using Co-occurrence Information. Proc. 18th Pacific-Asia Conf on KDDM (PAKDD 2014).

García-Rudolph, A., Gibert, K., 2014. A data mining approach to identify cognitive NeuroRehabilitation Range in Traumatic Brain Injury patients 09/. Expert Syst. Appl. 41-11, 5238–5251.

Garcia, M.C.M. Martins, E.T. ; Azevedo, F.M. Decision tree induction to prediction of prognosis in severe traumatic brain injury of Brazilian patients from Florianopolis city. Bioinformatics and Bioengineering (BIBE), 2013 IEEE 13th International Conference.

Gianutsos, R., 1980. What is cognitive rehabilitation? J. Rehabil., 36–40.

Gibert, K., Aluja, T., Cortés, U., 1998. Knowledge Discovery with Clustering Based on Rules. Interpreting Results, Procs of Principals of Data Mining and Knowledge Discovery. SPRINGER-VERLAG, pp. 83–92.

Gibert, K., García-Rudolph, A., García-Molina, A., Roig-Rovira, T., Bernabeu, M., Tormos, J.M., 2008. Knowledge discovery on the response to neurorehabilitation treatment of patients with traumatic brain injury through an AI&Stats and graphical hybrid methodology. FAIA 184. Ios Press, Netherlands, pp. 170–177.

Gibert, K., Izquierdo, J., Holmes, G., Athanasiadis, I., Comas, J., Sanchez-Marre, 2008. On the role of pre and post-processing in environmental data mining. Procs iEMSs 3, 1937–1958.

Gibert K. Zonicki Z. Classification based on rules and thyroids dysfunctions. Applied Stochastic Models in Business and Industry Special Issue: International Symposium on Applied Stochastic Models and Data Analysis VIII Volume 15, Issue 4, pages 319–324, October/December 1999.

Golden, C.J., 1994. Stroop, Test de colores y palabras. EdicionesTEA, Madrid.

Gomariz, A., Campos, M., Marin, R., Goethals, B., 2013. ClaSP: An Efficient Algorithm for Mining Frequent Closed Sequences. LNCS vol. 7818. Springer, Heidelberg, pp. 50–61.

Green, C., Bavelier, D., 2005. Digital Media:Transformations in Human Communication. Messaris Humphreys, Eds.

Güler, I., Gökçil, Z., Gülbandilar, E., 2009. Evaluating of traumatic brain injuries using artificial neural networks. Expert Syst. Appl. 36 (7), 10424–10427.

Gupta, A., Taly, A.B., 2012. Functional outcom following rehabilitation in chronic severe traumatic brain injury patients: A prospective study. Ann. Indian Acad. Neurol. 15 (2), 120.

Hanchang, S., Yuan, Y., Yibo, Wu, Hui, Liu, Jun S, Liu, Hongwei, Xie, 2010. Tmod: Toolbox of Motif Discovery. Bioinformatics 26 (3), 405–407.

Hart, T., Whyte, J., Kim, J., Vaccaro, M., 2005. Executive function and self-awareness of "real-world" behavior and attention deficits following traumatic brain injury. J Head Trauma Rehabil. 20 (4), 333–347.

Hall, M., Frank, E., Holmes, G., Bernhard, Pfahringer, Peter, Reutemann, Witten, Ian H., 2009. WEKA Data Min. Softw.: Update; SIGKDD Explor. 11 (1).

Heaton, R.K., Chelune, G.J., Talley, J.L., Kay, G.G., y Curtiss, G., 1997. WCST: Test de clasificación de tarjetas Wisconsin. Ediciones TEA, Madrid.

Hu, F., 2002. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr. Opin. Lipidol. 13 (1), 3–9.

IOM's New Report on Brain Injury Treatments Draws Conclusions Similar to ECRI Institute's Earlier Findings Cognitive Rehabilitation Therapy for Traumatic Brain Injury: What We Know and Don't Know about Its Efficacy. EDITORIAL NOTE 10/11/11.

Jagaroo, V., 2009. August 21. Neuroinformatics for Neuropsychologists, 1 edition. Springer.

Jawad A., Kersting K., Andrienko N. Where traffic meets DNA: mobility mining using biological sequence analysis revisited. In 19th ACM SIGSPATIAL ACM-GIS 2011, November 1-4, 2011, pp. 357-360.

John G.H., Langley P.: Estimating Continuous Distributions in Bayesian Classifiers.

In: Eleventh Conference on Uncertainty in Artificial Intelligence, San Mateo, 338-345, 1995.
Korn, L.J., Queen, C.L., Wegman, M.N., 1977. Computer analysis of nucleic acid regulatory sequences. Proc. Natl. Acad. Sci. U S A 74 (10), 4401–4405.
Klema, J., Novakova, L., Karel, F., Stepankova, O., Zelezny, F., 2008. Sequential data mining: A comparative case study in development of atherosclerosis risk factors. IEEE Trans. SMC: Part C 38 (1), 3–15.
Klepper, K., Drabløs, F., 2010. Priors Editor: a tool for the creation and use of positional priors in motif discovery. Bioinformatics 26 (17), 2195–2197.
Luria, A., 1978. Neuropsychology. Great Soviet Encyclopedia: A translation of the, third editionVol. 17. . Collier Macmillan, London, pp. 514–515.
Maas, A.I., Stocchetti, N., Bullock, R., 2009. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 7 (8), 728–741. http://dx.doi.org/10.1016/S1474-4422(08)70164-9, PMID 18635021.
Mabroukeh, N.R., Ezeife, C.I., 2010. A taxonomy of sequential pattern mining algorithms. ACM Comput. Surv. 43 (1), 1–41.
Millen, B.E., Quatromoni, P.A., Gagnon, D.R., et al., 1996. Dietary patterns of men and women suggest targets for health promotion: the Framingham Nutrition Studies. Am. J Health Prom. 11, 42–53.
Pang, B.C., Kuralmani, V., Joshi, R., Hongli, Y., Lee, K.K., Ang, B.T., Li, J., Leong, T.Y., Ng, I., 2007. Hybrid outcome prediction model for severe traumatic brain injury. J. Neurotrauma 24 (1), 136–146.
Pei, J., Han, J., Mortazavi-Asl, B., Wang, J., Pinto, H., Chen, Q., Dayal, U., Hsu, M., 2004. Mining sequential patterns by pattern-growth: the PrefixSpan approach. IEEE Trans. KDE 16 (11), 1424–1440.
Pignolo Pignolo, L., Lagani, V., 2011. Prediction of outcome in the vegetative state by machine learning algorithms: a model for clinicians? J. Softw. Eng. Appl. 4, 388–390.
Pradhan, G.N., Prabhakaran, B., 2009. Association rule mining in multiple, multidimensional time series medical data. IEEE Int. Conf. Multimed. Expo., 1716–1719.
Quinlan, R., 1993. C4.5: Programs for Machine Learning. Morgan Kaufmann Publishers, San Mateo, CA.
Reitan, R.M., Wolfson, D., 1993. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press, Tuscon, AZ.
Rey, A., 1964. L'examen clinique en psychologie. Presses Universitaires de France, Paris.
Rovlias, A., Kotsou, S., 2004. Classification and regression tree for prediction of outcome after severe head injury using simple clinical and laboratory variables. J. Neurotrauma 21 (7), 886–893.
Rohling, M.L., Faust, M.E., et al., 2009. Effectiveness of Cognitive Rehabilitation Following Acquired Brain Injury: A Meta-Analytic Re-Examination of Cicerone et al.'s (2000, 2005) Systematic Reviews. Neuropsychology 23 (1), 20–39.
Rughani, A.I., Dumont, T.M., Lu, Z., Bongard, J., Horgan, M.A., Penar, P.L., Tranmer, B. I., 2010. Use of an artificial neural network to predict head injury outcome. J Neurosurg. 113 (3), 585–590.
Sabb, F.W., Burggren, A.C., Higier, R.G., 2009. Challenges in phenotype definition in the whole- genome era: Multivariate models of memory and intelligence. Neuroscience 164 (1), 88–107.
Schneider, T.D., Stephens, R.M., 1990. Sequence Logos: A New Way to Display Consensus Sequences. Nucleic Acids Res. 18, 6097–6100.
Schroeter, M., Ettrich, B., Menz, M., Zysset, S., 2011. Max- Traumatic brain injury affects the frontomedian cortex–an event-related fMRI study on evaluative judgments. Neuropsychologia. 48 (1), 185–193.
Segal, M.E., et al., 2006. The accuracy of artificial neural networks in predicting long-term outcome after traumatic brain injury. J. Head. Trauma Rehabil. 21 (4), 298–314.
Sohlberg, M.K., Mateer, C.A., 2001. Cognitive Rehabilitation: An Integrative Neuropsychological Approach. Taylor and Francis Books Ltd, Andover.
Sohlberg, M.M., 2001. Cognitive Rehabilitation. In: Mateer, Catherine A. (Ed.), An interactive Neuropsychological Approach, ISBN: 9781572306134.
Sohlberg, M.M., 2005. Can disabilities resulting from attentional impairments be treated effectively?. In: Halligan, P.W., Wade, D.T. (Eds.), The Effectiveness of Rehabilitation for Cognitive DeficitsNew YorkOxford University Press, pp. 91–102.
Srikant, R., Agrawal, R., 1996. Mining Sequential Patterns: Generalizations and Performance Improvements. LNCS vol. 1057. Springer, pp. 3–17.
Syed, Z., Stultz, C., Guttag, J., 2010. Motif discovery in physiological datasets: A methodology for inferring predictive elements Article 2 (January. ACM Trans. Knowl. Discov. Data 4, 1.
Taly, A., Sivaraman, K., Muraly, T., 1998. Neurorehabilitation Principles and Practice. National Institute of Mental Health and Neurosciences, Bangalore. India.
Tan, P., Steinbach, M., Kumar, V., 2006. Introduction to Data Mining. Pearson Addison Wesley, Boston.
Tukey, J.W., 1977. Exploratory Data Analysis. Addison-Wesley.
Tormos, J.M., Garcia-Molina, A., Garcia Rudolph, A., Roig, T., 2009. 22 June. Inf. Commun. Technol. Learn. Dev. Rehabil. Int. J. Integr. Care – 9.
Wechsler, D., 1999. WAIS-III. Escala de inteligencia de Wechsler para adultos-III. Madrid. TEA.
Whyte, J., Hart, T., 2003. It's more than a black box; it's a Russian doll: defining rehabilitation treatments. Am. J Phys. Med Rehabil. 82, 639–652.
Witten I.H., Eibe F.,. Hall M.A. Data mining : practical machine learning tools and techniques.—3rd ed. / The Morgan Kaufmann series in data management systems - ISBN 978-0-12-374856-0.
Yan, X., Han, J., Afshar, R.: CloSpan: Mining closed sequential patterns in large datasets. In: Proc. 3rd SIAM Intern. Conf. on Data Mining, pp. 166–177 (2003).
Yuliana O.Y., Rostianingsih S. and Budhi G.S., Discovering sequential disease patterns in medical databases using FreeSpan mining approach, ICACSIS'09, U. Indonesia, Jakarta, Indonesia, 2009.
Zaki, M.J., 2001. SPADE: An efficient algorithm for mining frequent seq. Mach. Learn. 42 (1), 31–60.
Zambelli, F., Pesole, G., Pavesi, G., 2012. Motif discovery and transcription factor binding sites before and after the next-generation sequencing era. Brief. Bioinform.