FUNCTIONAL STATUS AND THE EYE-TRACKING RESPONSE

A Data Mining Classification Study in the Vegetative and Minimaly Conscious States

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Abstract: Eye-tracking is defined as the "*pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli"*; it is a key descriptor of the evolution from the vegetative (VS) to the minimally conscious (MCS) state and predicts better outcome. In this study, several physiological parameters (such as heart beat, Galvanic Skin Response [GSR], Blood Volume Pulse [BVP], respiratory rate and amplitude) were recorded while a medical examiner searched for eye-tracking by slowly moving a visual stimulus horizontally and vertically in front of the subject. Seven patients in VS and 8 in MCS were studied. The Heart Rate Variability (HRV) was analyzed to obtain time and frequency descriptors. Different classification methods were adopted to search for a plausible relationship between the subject psycho-physiological state and observable eye-tracking to stimuli. The performance of different classifiers was computed as Balanced Classification Accuracy (BCA) and evaluated through suitable validation technique. A Support Vector Machine (SVM) classifier provided the most reliable relationship: BCA mean was about 84% on fold cross validation and about 75% on an independent test set of 6 patients (3 VS and 3 MCS).

1 BACKGROUND & RATIONALE

Eye-tracking, the pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli (Vanhaudenhuyse, Schnakers, Brédart and Laureys, 2008), it is usually observed in 20% and 82% of subjects in the vegetative (VS) and minimal conscious (MCS) states, respectively (Giacino, Zasler, Katz, Kelly, Rosenberg, and Filley, 1997; Royal College of Physicians, 1996; Schnakers, Vanhaudenhuyse, Giacino, Boly, Majerus, Moonen and Laureys, 2009).). It is a key descriptor of the evolution from VS to MCS.

We retrospectively observed eye-tracking in 73% of 395 patients in a vegetative state, referred to the S. Anna - RAN Institute from intensive care, neurological or neurosurgery units in the years 1998-2008. These 395 patients could be clustered by etiology of brain damage in 3 different groups: posttraumatic (n=248), vascular (n=119) or anoxic-hypoxic (n=28). Eye-tracking was already observed within 50 days from brain injury in about 50% of posttraumatic and vascular subjects and in 20% of anoxic-hypozxic patients. After 230 days, eye-tracking had re-appeared in about 90% of posttraumatic and vascular subjects and in 67% of anoxic patients. Subjects with early recovered eye-tracking had a better outcome at discharge or at the

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end of follow-up (Spearman nonlinear correlation coefficient=-0.365, p-value<0.001). In this respect, eye-tracking proved an efficient predictor of outcome also in a study assessing at regular time intervals the presence/absence of 21 neurological signs. A data mining decision tree model identified eye-tracking as the best predictor of favorable outcome in the vegetative state (Dolce, Quintieri, Serra, Lagani and Pignolo, 2008; Pignolo, Riganello, Candelieri and Lagani, 2009).

We also searched for eye-tracking at different times over the day (3 observations in the morning and 3 in the afternoon) in subjects in VS (n=9) or MCS (n=13). Eye-tracking was observed at any time during the day in 62% of MCS subjects, and never in 67% of VS patients. About 33% of subjects in VS presented eye-tracking at least once in the day, while 38% of subjects in MCS never showed it. These percentages are consistent with the reported rate of misdiagnosis between VS and MCS and suggest that eye-tracking may depend on the subject's psycho-physiological condition to occur (submitted).

We decided to test the relationship between eye-tracking and the physiological condition as characterized by Heart Rate Variability (HRV) analyses. HRV is an emerging objective measure of the continuous interplay between sympathetic and parasympathetic subsystems (Task Force of European Society of Cardiology and North American Society of Pacing and Electrophysiology of Circulation, 1996) and provides information on complex brain activation as well (Dolce, Riganello, Quintieri, Candelieri and Conforti, 2008; Riganello, Quintieri, Candelieri, Conforti and Dolce, 2008; Appealhans and Luecken, 2006, Friedman, (2007) Kreibig, 2010). In previous studies on controls, brain injured conscious patients and subjects in a vegetative state we obtained evidence f a correlation between the response to external stimuli and HRV (mainly expressed by the normalized low-frequency [0.04-0.15 Hz] band power descriptor *nuLF*) (Riganello, Pignolo, Lagani and Candelieri, 2009; Riganello and Candelieri, 2010; Riganello, Candelieri, Quintieri, Conforti and Dolce, 2010).

In this respect, our working hypothesis is that a subject's physiological status can be (partially) described by the HRV parameters and that a consistent response, in our case an eye-tracking, may depend on its variations.

2 MATERIALS & METHODS

Eye-tracking was searched for in 9 and 13 patients in VS and MCS, respectively. Three different visual stimuli, namely a mirror, a green light and a bright red ball were used. The test was repeated several times for each subject in the absence of indications of sleepiness, stress, pain or discomfort. During this procedures, several physiological parameters were recorded (Nexus-10 device, Mind Media BW, Roermond-Herten, NL): Galvanic Skin Response (GSR), respiratory rate and amplitude, heart rate, coherence between the heart and respiratory rates, blood volume pulse (BVP), and the heart rate variability normalized band power and peak frequency in the low frequency interval (*nuLF* and *peakLF*). A dataset including 220 test conditions (also including the stimulus used to elicit an eye-tracking response and clinical condition [VS or MCS]) was built for the data mining classification task.

Data Mining classification approaches were to identify the fuctional condition that best correlated with the observation of eye-tracking. The established updated data mining techniques provided by WEKA (Waikato Environment for Knowledge Analysis) open-source software were used in the classification task (Witten and Eibe, 2005). Decision Trees, Rule-based Learning algorithm (OneR, Ridor and JRip) and Support Vector Machines (SVM) were used.

A Chi-Squared Feature Selection method was used to rank the study variables based on their correlation with the class value (presence and absence of eye-tracking). Such an approach usually improves the classifiers performance and should provide medical experts with information on the physiological parameters facilitating eye-tracking.

The classifiers' reliability was evaluated by the Balanced Classification Accuracy (BCA) computed as the mean of correct classifications among classes. In addition, all instances related to a single patient were entered into a separate fold; the training was performed on all remaining folds and the extracted model was tested on the fold left apart. Such a cross validation procedure (repeated for each patient and comparable to the leave-one-out validation) avoids over-fitting, dependency by the patient related information, circularity in the analysis (double dipping) (Kriegeskorte, Simmons, Bellgowan and Baker, 2009), and estimates the reliability of the extracted criteria.

3 RESULTS

The Chi-Squared feature selection separately performed on each fold and the anaysis of the resulting ranked list selected three parameters best correlating with eye tracking: nuLF, peakLF and clinical condition (Table 1).

Table 1: First, second and third ranked features on 15 folds (each fold consists in several observations of a single patient).

	Chi-Squared-based Features Ranking		
	First	Second	Third
Fold 1	nuLF	peakLF	condition
Fold 2	condition	nuLF	peakLF
Fold 3	nuLF	peakLF	condition
Fold 4	nuLF	peakLF	condition
Fold 5	stimulus	condition	Resp.Rate
Fold 6	nuLF	peakLF	condition
Fold 7	nuLF	peakLF	condition
Fold 8	nuLF	peakLF	condition
Fold 9	nuLF	peakLF	condition
Fold 10	stimulus	condition	Resp.Rate
Fold 11	nuLF	peakLF	condition
Fold 12	nuLF	peakLF	BVP
Fold 13	condition	nuLF	peakLF
Fold 14	nuLF	peakLF	condition
Fold 15	nuLF	peakLF	condition

nuLF ranked as the best correlating parameter, peakLF ranked second and clinical condition third. No consistent trend of correlation was observed for other parameters.

In a first classification task, J48, Ridor, JRip, OneR and SVM were used to define a reliable classification model explaining the relationship between the three variables and eye-tracking. The best model was provided by OneR algorithm (with bucket size=3) which only used nuLF value to predict eye-tracking. This decision model provided BCA=81.80% averaged on the 15 folds (standard deviation=14.92%) and BCA=82.66% on overall validation phase.

All the other classification algorithms presented averaged BCA lower than 80%.

Consistent with the study purpose, etiology was excluded and analysis focused on nuLF and peakLF. The operation did not change the OneR's performance, but increased BCA for most of the other approaches (between 0.02% and 1.34% for J48, JRip and Ridor), in particular for SVM (with radial basis function kernel and gamma=25) which resulted the most reliable model of the entire analysis, with overall BCA=85% and BCA=84.10% averaged on folds (standard deviation=16.56%).

When only 2 parameters (nuLF and peakLF) were used, the non-linear relationship learned through SVM (figure 1) proved able to convey new information of possible medical use.

The actual reliability of the learned criterion was estimated by applying without any retraining the SVM model to a dataset from 6 patients (3 in VS

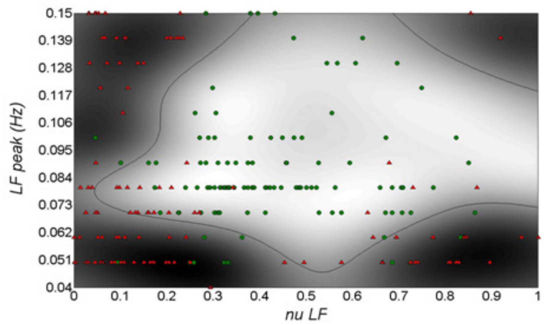

Figure 1: Presence (green) or absence (red) of eye tracking (green for present and red for absent) against decision function predictions (white regions as high probability for eye tracking, black regions as high probability for no eye tracking).

and 3 in MCS, 167 and 216 eye-tracking observations respectively). The assessment performed by the model based on the physiological parameters value was compared to that by a medical examiner with no information on the subject's physiological parameters. The model proved reliable, with an overall BCA of 74.92%, (84.54% and 73.45% for VS and MCS, respectively). The worse performance on MCS subjects depends on a lower sensitivity, due to eye-tracking detected by the medical examiner when the decision model indicated a non-optimal status. This kind of error suggests that patients in MCS may be able to provide eye-tracking even if their physiological condition is evaluated as border-line by the SVM-based criterion. A plausible reason may concern a recovery of more complex consciousness patters requiring less strong constraints on physiological condition, respect to VS (Bosco, Lancioni, Olivetti Belardinelli, Singh, O'Reilly and Sigafoos, 2010; Andrews, Murphy, Munday and Littlewood, 1996).

4 CONCLUSIONS

A relationship between the physiological status of subjects in the VS or MCS and their eye-tracking response to a visual stimulus would be crucial to a better understanding of the evolution from the former to the latter clinical condition. The relationship among a number of physiological parameters and eye-tracking presence/absence (as assessed by a medical examiner) was studied by several data mining classification approaches provided by the WEKA open-source tool. Two parameters obtained by HRV Analysis (nuLF and peakLF) proved highly correlated to eye-tracking. A SVM classifier provided a reliable criterion to predict eye-tracking simply by evaluating these two HRV spectral parameters. Reliability, computed as Balanced Classification Accuracy (BCA), proved remakably high for this SVM model.

The training set size (220 instances) warrants caution and additional research on large datasets is advisable. Although preliminary, our results are quite interesting and encouraging because the reliability obtained on an independent data set (383 instances).

The correlation between the physiological status (as indicated by the HRV descriptors) and eye-tracking nevertheless appears applicable to mark with better precision the evolution from the vegetative to the miniman conscious state and reduce misdiagnosis.

Further research is planned to assess the criterion diagnostic reliability and the suitability of extended application to calibrate type and timing of (visual) stimulation paradigms potentially supporting recovery of consciousness in VS and MCS patients.

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