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Evaluation of two treatment outcome prediction models for restoration of visual fields in patients with postchiasmatic visual pathway lesions

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ABSTRACT

Visual functions of patients with visual field defects after acquired brain injury affecting the primary visual pathway can be improved by means of vision restoration training. Since the extent of the restored visual field varies between patients, the prediction of treatment outcome and its visualization may help patients to decide for or against participating in therapies aimed at vision restoration. For this purpose, two treatment outcome prediction models were established based on either self-organizing maps (SOMs) or categorical regression (CR) to predict visual field change after intervention by several features that were hypothesized to be associated with vision restoration. Prediction was calculated for visual field changes recorded with High Resolution Perimetry (HRP). Both models revealed a similar predictive quality with the CR model being slightly more beneficial. Predictive quality of the SOM model improved when using only a small number of features that exhibited a higher association with treatment outcome than the remaining features, i.e. neighborhood activity and homogeneity within the surrounding 5° visual field of a given position, together with its residual function and distance to the scotoma border. Although both models serve their purpose, these were not able to outperform a primitive prediction rule that attests the importance of areas of residual vision, i.e. regions with partial visual field function, for vision restoration.

1. Introduction

When studying the efficacy of vision restoration training (VRT) or repetitive alternating current stimulation (rtACS) in patients with visual field loss after brain damage, the treatment outcome, i.e. the size of the restored visual field varies considerably between patients (VRT: Kasten, Wüst, Behrens-Baumann, & Sabel, 1998a; Mueller, Mast, & Sabel, 2007; Mueller, Gall, Kasten, & Sabel, 2008; Romano, Schulz, Kenkel, & Todd, 2008; Gall et al., 2008; Raemaekers, Bergsma, van Wezel, van der Wildt, & van den Berg, 2011; Schinzel et al., 2012; Gall & Sabel, 2012; rtACS: Gall et al., 2011; Fedorov et al., 2011; Gall, Antal & Sabel, 2013; Sabel et al., 2011a). Most recently, VRT and non-invasive electrical stimulation were combined to improve visual functions in patients with hemianopia (Halko et al., 2011; Plow, Obretenova, Jackson, & Merabet, 2012a; Plow, Obretenova, Fregni, Pascual-Leone, & Merabet, 2012b).

After VRT visual field enlargements were observed in 30–70% of all patients (Kasten et al., 1998a, 1999; Kasten, Poggel, & Sabel, 2000; Sabel & Kasten, 2000; Mueller, Poggel, Kenkel, Kasten, & Sabel, 2003; Sabel, Kenkel, & Kasten, 2004) and such vision improvements were predominantly seen in areas of the visual field that revealed residual vision at baseline before starting VRT (Sabel, Henrich-Noack, Fedorov, & Gall, 2011b). Visual field restoration was repeatedly documented using methods such as threshold perimetry and superthreshold, high-resolution perimetry (HRP) (e.g. Zihl & von Cramon, 1985; Kasten et al., 1998a; Mueller et al., 2007). HRP is a computer-based method that allows to test the central visual field with a higher resolution than standard automated perimetry. Since stimuli in HRP are presented above threshold, different visual field states (i.e. full function, partial function and absolute vision loss) are determined by superimposing test results of repeated HRP tests (Kasten, Strasburger, & Sabel, 1997; Kasten, Wüst, & Sabel, 1998b).

Guenther, Mueller, Preuss, Kruse, and Sabel (2009) developed a treatment outcome prediction model (TOPM) using HRP baseline features that were included in the TOPM either by empirical association with treatment outcome or by identifying relevant features from the literature. Guenther et al. (2009) chose the Self-Organizing-Map (SOM) as a classifier because it also allows data visualization and, furthermore, it is considered to be a

Abbreviations: (VRT), Vision restoration training; (TOPM), Treatment outcome prediction model; (HRP), High-resolution perimetry; (SOM), Self-organizing map; (CR), Categorical regression; (ARV), Areas of residual vision; (*k*-NN), *k*-nearest neighbor; (rtACS), Repetitive alternating current stimulation.

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suitable tool for medical applications (Wyatt & Altman, 1995). SOMs are also efficient in dealing with huge datasets and robust even when applied on noisy data (Xiao, Dow, Eberhart, Miled, & Oppelt, 2003). Moreover, the algorithm performs mapping and learning while preserving the topology of the data distribution (Tasdemir & Merényi, 2009). Hence, SOM was selected to construct a TOPM based on data obtained from 52 patients affected by visual field defects to predict post-therapy change of certain areas of the visual field at baseline (Guenther et al., 2009). A further analysis of individual features was most recently published (Sabel, Wolf, & Guenther, in press).

Several global and local features were identified to be associated with treatment outcome as assessed by prior studies and as described in the literature of VRT (Guenther et al., 2009). Global features refer to the patients' HRP visual field charts as a whole, thus describing a patient's visual field and the extent of defects. The following paragraph gives an overview of global features that were identified as being relevant for treatment outcome prediction.

(1) The *size of the area of residual vision (ARV)*, i.e. the proportion of the visual field where inconsistent stimulus detection occurs when stimuli are presented above threshold in HRP. Residual vision is typically located at the border region between intact and blind visual field (transition zone). In case of a more gradual transition the subjective impression within this ARV corresponds to "uncertain vision", or "shadowy vision". In standard-automated threshold perimetry residual vision is reflected by relative defects, i.e. positions were light stimuli are perceived at increased luminance levels above the age-appropriate physiological value. Residual vision is considered to be of therapeutic value for achieving visual field improvements by means of training. (2) The *size of defect area* which is in contrast to the ARV more compact and contiguous and may comprise a large portion of the visual field such as in hemianopia or quadrantanopia when approximately up to half or, respectively, a quarter of the visual field is affected by the blindness. Some vision restoration may be observed in these areas of absolute blindness but they are typically less likely to improve than ARV. (3) The *mean reaction time within the intact visual field* is treated as a global feature since reaction time is a measure of general temporal processing. Although, in standard-automated static perimetry and HRP, reaction times do not affect the detection result, unless the subjects' answers fall outside of a specified time window, temporal processing deficits in the intact visual field demonstrate that visual system lesions have more widespread consequences on perception (Bola, Gall, & Sabel, 2013). (4) *Conformity to hemianopia or* (5) *to quadrantanopia*, i.e. the degree of similarity of the visual field of a given patient with a complete hemi- or quarter field loss while the remainder half field respectively the remainder three quadrants were intact. A high conformity to hemianopia or quadrantanopia implies a very sharp visual field border that is unlikely to improve. The degree of conformity is smaller in case of incomplete hemianopia or quadrantanopia which implies a larger ARV. (6) *Border diffuseness*, i.e. the ratio of partially damaged spots amongst all spots located at the visual field border. With this parameter the border can be described as "sharp", when there are only few partially damaged (gray) positions, i.e. the ARV is only small and unlikely to improve, or as "diffuse" (with many gray positions) in the contrary case. The importance of this parameter was often reported to determine visual field improvements after VRT (Sabel & Kasten, 2000; Kasten et al., 1999; Sabel et al., 2011b).

In contrast, local features address the attributes of each tested position during HRP (hereafter termed "spots"), therefore characterizing the functional state of perception at each test position and its immediate surroundings in the visual field. *Local features* contributing to the TOPM were the following. (1) The *residual function* of a spot is equal to the detection rate at a given visual field position. Residual function is observable in all spots with at least inconsistent stimulus detection though it is hypothesized that spots with higher residual function are more likely to improve. Since visual field border shifts occur more frequently in peripheral visual field defects (Poggel, Mueller, Kasten, & Sabel, 2008) (2) the *horizontal* and (3) *vertical coordinate* in degrees of visual angle were considered relevant to be included in the TOPM. (4) *Neighborhood activity,* i.e. the mean of detection rates of all spots within a 5° radius of a given visual field position is considered a relevant local feature for prediction because visual information is integrated over a certain distance in visual cortex (Stettler, Das, Bennett, & Gilbert, 2002). It is hypothesized that improvement of residual vision is more likely if residual function of adjacent spots is better. Within the same context two further variables were included in the TOPM: (5) *neighborhood homogeneity*, i.e. the standard deviation of detection rates of all spots within a 5° radius, and (6) the *distance to the scotoma*, i.e. the Euclidean distance from a spot to the scotoma border measured in cortical coordinates considering the cortical magnification factor (Guenther et al., 2009).

The previous TOPM by Guenther et al. was designed to predict only the outcome of severely or absolutely damaged test positions (spots). However, by doing so an important area of the visual field with great potential for improvement was neglected, the mild (relative) defects. Moreover, this model was constructed in a way that predicted treatment outcome was either improvement or no improvement of a given spot. Hence, this TOPM allowed predicting treatment outcome only quite vaguely (Guenther et al., 2009).

The main purpose of the present study was to evaluate the value of the previously developed TOPM with a new clinical sample now including also those visual field regions with mild relative defects and, in addition, using a more precise treatment outcome definition. Further, it was investigated whether the rather numerous prediction variables of the TOPM can be reduced, thus simplifying the procedure, and whether an alternative approach, categorical regression (CR), may serve the same purpose. TOPM and CR were finally compared to a rather primitive prediction rule. The .632+ estimator, a method based on bootstrapping developed by Efron and Tibshirani (1997), was applied to evaluate the predictive validity of the TOPM and CR. Since prediction models were also intended to enable clinicians to visualize the topography of visual field changes after VRT, as well as to convey a picture to the patient of what kind of treatment effects could be expected, exact treatment outcome predictions were derived from the results of the models and then visualized with "predicted visual field charts".

Finally, it was investigated whether both prediction models are also useful to predict the outcome of another treatment approach: non-invasive rtACS was reported to improve visual fields in patients with optic nerve damage (Gall et al., 2011; Fedorov et al., 2011; Gall et al., 2013; Sabel et al., 2011a). Recently, a clinical trial with postchiasmatic lesioned patients was initialized and preliminary results were available to evaluate the power of both prediction models for this new treatment method as well.

2. Methods

2.1. Sample description and database

2.1.1. Training sample (VRT)

Diagnostic data were selected from a large pool of 377 patients receiving clinical treatment with VRT at NovaVision (Magdeburg, Germany) between January 2001 and March 2010. A total of 149 patients with postchiasmatic lesions (predominantly homonymous scotomata) were included into the present study. The sample comprises 140 binocular and 17 monocular measurements. Supplementary Fig. 1 gives an overview of reasons for exclusion of patients from further