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Functional transcranial Doppler: Selection of methods for statistical analysis and representation of changes in flow velocity

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Abstract

Introduction: Transcranial Doppler (TCD) is a method used to study cerebral hemo-dynamics. In the majority of TCD studies, regression analysis and analysis of variance are the most frequently applied statistical methods. However, due to the dynamic and interdependent nature of flow velocity, nonparametric tests may allow for better statistical analysis and representation of results.

Method: The sample comprised 30 healthy participants, aged 33.87 ± 7.48 years; with 33% (n = 10) females. During a visuo-motor task, the mean flow velocity (MFV) in the middle cerebral artery (MCA) was measured using TCD. The MFV was converted to values relative to the resting state. The results obtained were analyzed using the general linear model (GLM) and the general additional model (GAM). The fit indices of both analysis methods were compared with each other.

Results: Both MCAs showed a steady increase in MFV during the visuo-motor task, smoothly returning to resting state values. During the first 20 seconds of the visuo-motor task, the MFV increased by a factor of 1.06 ± 0.07 in the right-MCA and by a factor of 1.08 ± 0.07 in the left-MCA. GLM and GAM showed a statistically significant change in MFV (GLM:$F_{(2, 3598)} = 16.76$, $P < .001$; GAM:$F_{(2, 3598)} = 21.63$, $P < .001$); together with effects of hemispheric side and gender (GLM:$F_{(4, 3596)} = 7.83$, $P < .005$; GAM:$F_{(4, 3596)} = 2.13$, $P = .001$). Comparing the models using the χ^2 test for goodness of fit yields a significant difference $\chi^2 (9.9556) = 0.6836$, $P < .001$.

Conclusions: Both the GLM and GAM yielded valid statistical models of MFV in the MCA in healthy subjects. However, the model using the GAM resulted in improved fit indices. The GAM's advantage becomes even clearer when the MFV curves are visualized; yielding a more realistic approach to brain hemodynamics, thus allowing for an improvement in the interpretation of the mathematical and statistical results. Our results demonstrate the utility of the GAM for the analysis and representation of hemodynamic parameters.

1 | INTRODUCTION

Transcranial Doppler (TCD) is a non-invasive imaging method, with high temporal resolution. It is robust, less expensive, and easier to use than other neuroimaging techniques used to assess cerebral blood flow.[1,2] One drawback of TCD, however, is the lack of a direct neuroanatomical image.[1,2] Over the past few decades, TCD has been used to study cerebral hemodynamics in the main cerebral arteries[1,3] in a wide range of neurological and psychiatric conditions, thereby increasing our knowledge of the pathophysiological anomalies of such disorders.[1,4-7] Furthermore, it is also used to refine diagnostic and prognostic approaches in conditions such as stroke, vascular cognitive impairment, and vascular depression.[8-10]

The general linear model (GLM) can accommodate both quantitative and categorical variables in a mathematical model. The label "linear modelling" has traditionally been used to refer to regression analysis; however, technically ANOVAs are particular instances of the GLM.[11] The suitability of the GLM for many different types of study design accounts for its widespread use in a wide range of research areas, including psychology, medicine, and biology. The majority of studies of hemodynamics employing TCD use the GLM (as either regression modeling or analysis of variance) for statistical analysis; analysis is generally conducted at group level, pooling change in flow velocity over several subjects.[1,2,4,5] Due to the dynamic nature of flow velocity and its dependence on previously achieved velocity, the graphic representation of a linear model may be counter-intuitive. Nonparametric tests, including time-series analysis and the general additional model (GAM), allow for a better representation of dynamic and interdependent results; however, their mathematical and statistical analysis is more complex than for the GLM and therefore comparison is more demanding.[11,12]

The aim of this study is to improve the statistical analysis and representation of the hemodynamic parameters obtained using functional TCD. During a visuo-motor control task, the mean flow velocity (MFV) in the middle cerebral artery (MCA) in healthy subjects was measured using TCD. The results obtained were analyzed using the general linear regression and the general additional models. The results of both methods of analysis were compared with each other in terms of model fit and interpretability. Analyzing dynamic and interdependent variables such as flow velocity, we expect nonparametric statistical analysis such as the GAM to outperform parametric methods such as the GLM regarding statistical modeling and interpretability of the data.

2 | METHODS

2.1 | Sample population

Thirty healthy right-handed subjects with no medical, neurological, or psychiatric condition at the time of examination participated in this study. The participants had a mean age of 33.87 ± 7.48; 33% (n = 10) females. All participants were native German speakers, with a mean education of 19.17 ± 4.06 years and average intelligence of IQ 127.60 ± 8.13 as measured using the multiple-choice vocabulary intelligence test [German: Mehrfachwahl-Wortschatz-Intelligenztest: MWT-A].[13,14] The ethics committee of the Canton of Zurich-Switzerland approved the study (BASEC: 2019-00814), and all participants provided written informed consent.

### 2.2 | Equipment and cerebral flow measurements

Doppler measurements were performed using a Multi-Dop X instrument (DWL Elektronische Systeme GmbH, Sipplingen—Germany). Two dual 2 MHz transducers were used to insonate both MCAs at depths of 48-55 mm through the temporal bone window.[15] The transducers were fixed with a headband, so motions of the head did not alter the position of the transducers. As indicated by measurement artifact data, we screened for MFV values outside the 60% to 150% range of the mean MFV recording of a subject. This approach is supported by published evidence, demonstrating that functional TCD is robust to position and movement artifacts.[16,17]

2.3 | Visuo-motor task and cerebral hemodynamics

Caffeine and nicotine can influence brain hemodynamics; therefore, subjects were asked to abstain from the consumption of both 2 hours prior to examination.[18] Vital parameters, including respiratory frequency, heart rate, and blood pressure, were measured before placing and after removal of the transducers. All participants had normal vital parameters; no signs of anxiety or distress were observed.[19,20] MFV data were recorded continuously before, during, and after the visuo-motor task, integrating MFV data for each cardiac cycle. In a paper-pencil visuo-motor task, participants were asked to randomly connect circles (placed in a 10 by 10 cm square) with lines. Lines had to be drawn at a pace of 1.0 Hz. This task simulates the visual scanning and hand movements, which usually occur during a neuropsychological paper-pencil test, thus controlling for neurocognitive effort.[21-25]

2.4 | Statistical analysis

For the purposes of analysis, the MFV was converted to values relative to steady state, following procedures used in previous
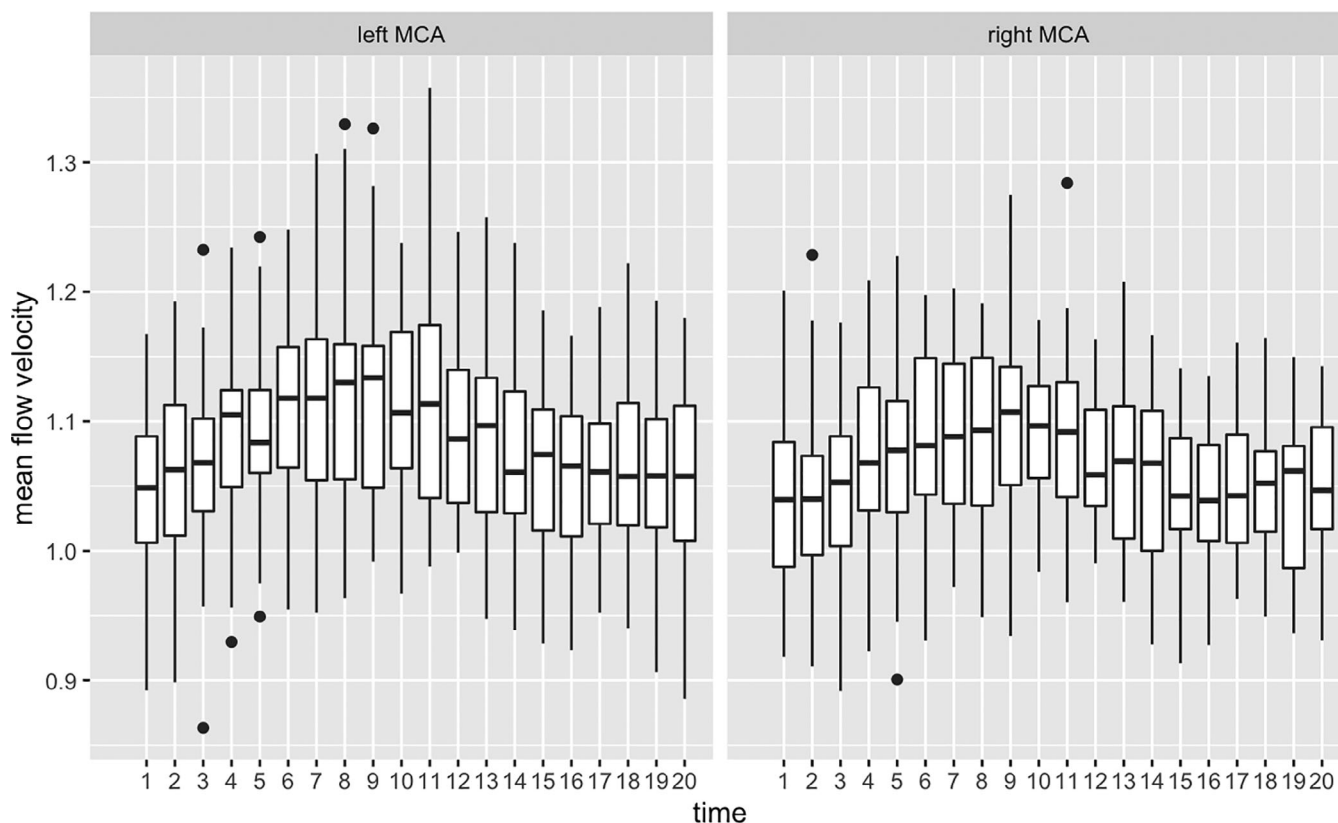
FIGURE 1 Distribution of measured mean flow velocity (MCA, middle cerebral artery)

studies[23,24,26]: (a) integration of MFV from 100 Hz sampling to 1 Hz; (b) normalization of digitized data with reference to pre-and post-task rest phases (60 seconds intervals of rest with 30 seconds between the first and last 15 seconds); and (c) relative MFV values (relative to the resting state) were averaged and converted to percentage values. All MFV values in this article are relative MFV, that is, the change in cerebral blood flow velocity compared with resting phase values.[16,24] The visuo-motor task comprised a time frame of at least 20 (range 20 to 22) seconds for all participants; thus, the first 20 seconds will be considered for analysis.

Data are presented in tables, using simple descriptive statistics (mean, SD, percentages). The data were fitted in a general linear model (GLM) and a general addition model (GAM), to model the change in MFV during the visuo-motor task (ie, time). The fit indices (Akaike information criterion—AIC; generalized cross-validation—GCV; and R^2) of the models were extracted for comparison, and an ANOVA was performed to assess the statistical differences between models. Finally, both models were presented visually.

3 | RESULTS

3.1 | Hemodynamics

The MFV for the first 20 seconds increased by a factor of 1.07 ± 0.07 in relation to the resting state; the MFV in the right MCA increased

by a factor of 1.06 ± 0.07; and the MFV in the left MCA increased by a factor of 1.08 ± 0.07. The distribution of the MFV raw values for each time unit (second) is represented in Figure 1. For both MCAs, there is a steady increase in flow velocity lasting approximately 8 seconds, returning to the resting state after approximately 15 seconds. The increase in flow velocity is slightly higher for the left MCA (see Figures 1 and 2).

3.2 | General linear model (GLM)

We calculated the GLM change for the MFV during the course of the measurement period ($F_{(2, 3598)} = 16.76$, $P < .001$). We found a significant hemispheric difference ($F_{(3, 3597)} = 4.534$, $P = .033$), together with differences attributable to hemispheric side and gender ($F_{(4, 3596)} = 7.828$, $P = .005$). The fit indices across the models remained stable. For further details, see Table 2.

3.3 | General additional model (GAM)

We calculated the GAM change for the MFV during the course of the measurement period ($F_{(2, 3598)} = 21.63$, $P < .001$). A hemispheric side difference was also demonstrated ($F_{(3, 3598)} = 4.687$, $P = .03$), together with differences attributable to hemispheric side and gender ($F_{(4, 3596)} = 2.129$, $P = .001$). The fit indices, particularly R^2, were
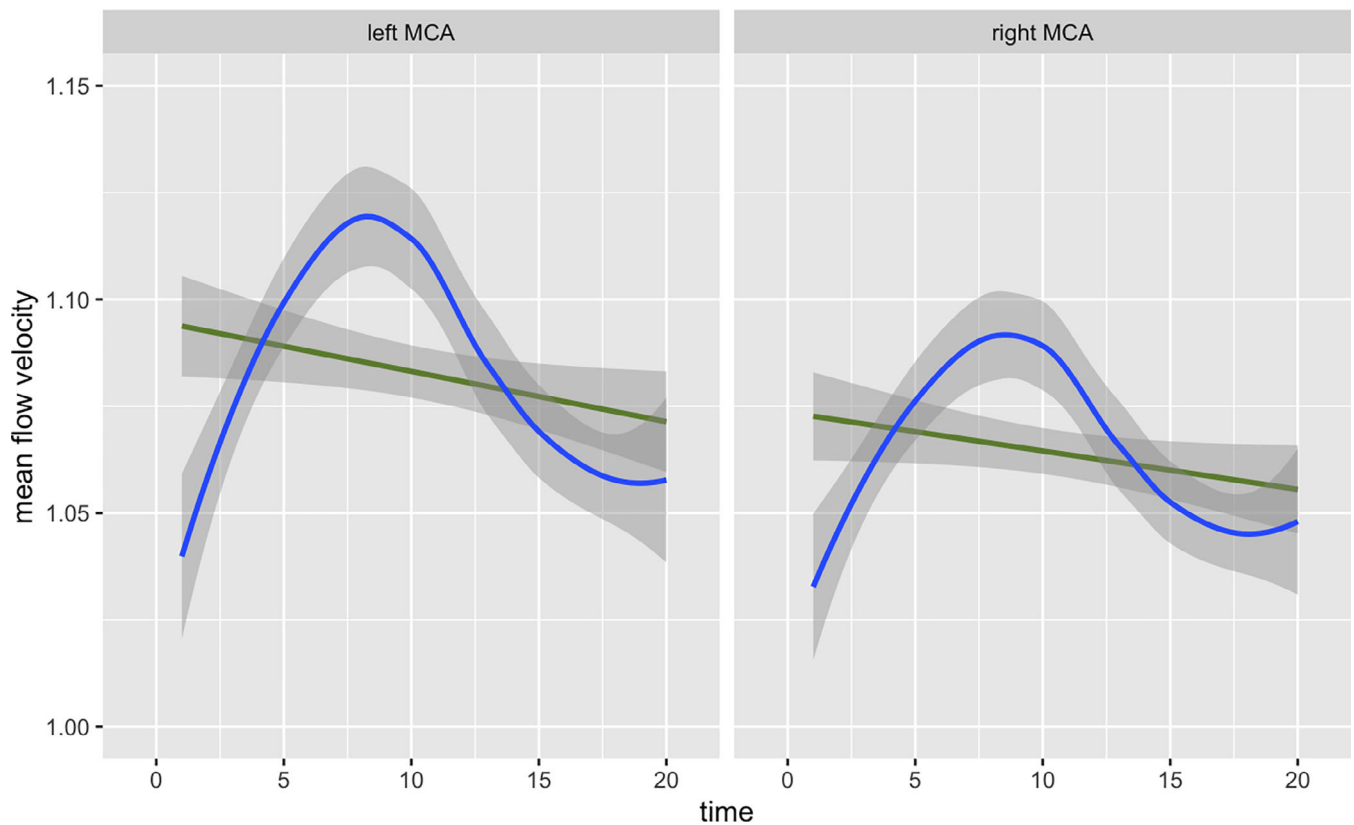
FIGURE 2 Mean flow velocity curves using the general linear model (GLM) (green) and the general additional model (GAM) (blue) models

Model	Variables	AIC	GVC	R^2	Statistic	P
GLM	Time	−7564.34	0.0072	0.004	$F_{(2, 3598)} = 16.76$	<.001
GLM	Time, side	−7566.87	0.0072	0.005	$F_{(3, 3597)} = 4.534$	=.033
GLM	Time, side, gender	−7578.45	0.0071	0.009	$F_{(4, 3596)} = 7.828$	=.005
GAM	Time	−7679.25	0.0069	0.036	$F_{(2, 3598)} = 21.63$	<.001
GAM	Time, side	−7681.94	0.0069	0.038	$F_{(3, 3597)} = 4.687$	=.03
GAM	Time, side, gender	−7762.64	0.0067	0.062	$F_{(4, 3596)} = 2.129$	=.001

TABLE 1 Fit indices and statistics for the general linear model (GLM) and the general additional model (GAM); the difference between the models is statistically significant: $\chi^2_{(9.9556)} = 0.6836$, $P < .001$; AIC, akaike information criterion; GCV, generalized cross-validation; and R^2

improved when additional variables were added to the model. For further details, see Table 1.

3.4 | Model comparison

Comparing the models using a chi-square test for goodness of fit yields a significant difference ($\chi^2_{(9.9556)} = 0.6836$, $P < .001$). For further details, see Table 1.

4 | DISCUSSION

In a sample of healthy participants, we measured the MFV in the MCA during a visuo-motor task without cognitive effort, using TCD. The resulting hemodynamic curve demonstrated a steady increase in

MFV, smoothly returning to resting state values. The obtained pattern resembles previous findings in healthy probands,[21,27-29] as well as those with a psychiatric or neurologic condition.[26,30,31] The resulting hemodynamic curve probably results from the activation of brain areas responsible for visuo-motor activity.[32,33] The left MCA showed a slightly greater increase in MFV; this finding is most likely attributable to the fact that our study sample was exclusively right-handed.[33,34]

Through the assessment of MFV, during a visuo-motor task in healthy probands, we avoid the effects of cognitive effort and pathophysiological anomalies of any given disorder.[22,27,31,35,36] This removes the requirement for clinical interpretation of our hemodynamic findings,[5,18,37,38] allowing the focus to remain on the statistical analysis and visual representation of MFV.

The change in MFV in the MCA during a visuo-motor task was analyzed using both the GLM and the GAM. Both approaches were

valid for analysis and yielded similar results. However, the model using the GAM resulted in better measurement of fit indices, with this difference between indices reaching statistical significance. This is particularly the case when gender is included as a variable in the statistical model, resulting in improved fit indices and allowing further differentiation of the hemodynamic curves between groups. Age is also a known factor influencing brain hemodynamics.[39] However, an interim analysis demonstrated no significant differences for the age groups represented in our sample, which we consider to be a reflection of the somewhat homogeneous age range of our sample.[40] The GAM's advantage becomes even clearer when the MFV curves are visualized, yielding a more realistic appreciation of brain hemodynamics. The curve obtained using the GAM demonstrates a remarkable similarity to the distribution of the raw MFV values. The modeling procedure, statistical analysis, and interpretation of hemodynamic parameters are a complex task.[11] The use of mathematical and statistical modeling identifies statistical differences between hemodynamic patterns; however, it is the visual inspection of such patterns, which facilitates the inference of clinical relevance..[2,7,11,18]

The advantage of nonparametric, in comparison with parametric or linear models, lies in their greater flexibility regarding assumptions about data, minimizing the impact of measurement outliers,[11,41,42] while remaining sensitive to small changes, which might occur in only a fraction of the observation period or in a limited time frame.[43,44] This certainly applies to brain blood flow velocity, where changes occur gradually over time. This results in minimal differences between near measurement neighbors (ie, in short time slots) but increasing differences with more distant (ie, in larger time slots) measurement points.[12,43,44]

Our study has some limitations, which must be taken into account when interpreting our results. We conducted our analysis exclusively with MFV measured using TCD in the MCA during a visuo-motor task.[3] While the MCA is undoubtedly the most important cerebral artery from a neuroanatomical perspective, the remaining cerebral arteries and the basilar artery also have waste irrigation territories, with their own clinical implications/relevance.[15,33,45,46] Although MFV is the most commonly analyzed TCD index, there are others that are considered important.[15] TCD parameters such as peak systolic velocity, end-diastolic velocity, pulsatility index, and resistivity index all provide insight into brain hemodynamics from a different physiological perspective.[47] Taking into account the underlying data structures of these indices, together with the robustness of nonparametric analysis, our opinion is that the use of the GAM would also lead to better statistical modeling and visualization for these indices.

Nonparametric tests, such as the general additional model, have several advantages over parametric tests. They have greater flexibility regarding assumptions about data.[11,41,42] Furthermore, they offer a better representation of dynamic and interdependent results, such as blood flow.[41] Using the GAM we were able to present a realistic visualization of cerebral flow velocity, thus facilitating the understanding of its clinical implications.[43,44] However, the mathematical and statistical analysis and, consequently, comparison of the GAMs outcomes is more demanding than for parametric methods. In our view, combining these with parametric tests may help to overcome these difficulties.[11,12,26] Our results demonstrate the additional utility of performing nonparametric tests for the analysis of dynamic and interdependent measurements (such as cerebral flow velocity), thus allowing for an improvement in visualization and interpretation of the mathematical and statistical results, leading to a more intuitive understanding of complex physiological processes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

TRANSPARENCY STATEMENT

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

AUTHORS' CONTRIBUTIONS

Conceptualization: Stephan T. Egger, Stefan Vetter, Daniel Schuepbach
Formal Analysis: Stephan T. Egger, Daniel Schuepbach
Investigation: Stephan T. Egger, Daniel Schuepbach
Methodology: Stephan T. Egger, Stefan Vetter, Daniel Schuepbach
Project Administration: Erich Seifritz, Stefan Vetter, Daniel Schuepbach
Resources: Erich Seifritz, Stefan Vetter, Daniel Schuepbach
Supervision: Julio Bobes, Erich Seifritz
Writing—Original Draft Preparation: Stephan Egger
Writing—Reviewing and Editing: all authors

These authors have contributed equally to this work: Stefan Vetter, Daniel Schuepbach.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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