Altered Low Frequency Oscillations of Cortical Vessels in Patients with Cerebrovascular Occlusive Disease – A NIRS Study

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Phillip, Dorte, Helle K. Iversen, Henrik W. Schytz, Juliette Selb, David A. Boas, and Messoud Ashina. 2013. “Altered Low Frequency Oscillations of Cortical Vessels in Patients with Cerebrovascular Occlusive Disease – A NIRS Study.” Frontiers in Neurology 4 (1): 204. doi:10.3389/fneur.2013.00204. http://dx.doi.org/10.3389/fneur.2013.00204.

Published Version
doi:10.3389/fneur.2013.00204

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879369

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Altered low frequency oscillations of cortical vessels in patients with cerebrovascular occlusive disease – a NIRS study

Dorte Phillip1, Helle K. Iversen2, Henrik W. Schytz1, Juliette Selb3, David A. Boas3 and Messoud Ashina1 *

1 Danish Headache Center, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark
2 Stroke Unit, Department of Neurology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark
3 Photon Migration Imaging Laboratory, Athinoula A. Martinos Center for Biomedical Imaging, Harvard Medical School, Boston, MA, USA

INTRODUCTION

Cerebral autoregulation is an intrinsic protective mechanism of the cerebral vessels to insure hemodynamic stability despite changes in the systemic blood pressure (1). A response of the middle cerebral artery velocity (Vmca) as assessed by transcranial Doppler (TCD) after spontaneous changes in arterial blood pressure (ABP) in the low frequency range is described as spontaneous cerebral autoregulation (2) and has become an established method of assessing cerebral autoregulation in cerebrovascular diseases (3, 4). While there is no gold standard for assessing spontaneous cerebral autoregulation it has been commonly examined by analysis of phase shift and gain (amplitude ratio) between ABP measured by the finger cuff method and 0.1 Hz low frequency oscillations (LFOs) of Vmca, measured by TCD (2). Examination with TCD by the finger cuff method and 0.1 Hz low frequency oscillations of phase shift and gain (amplitude ratio) between ABP measured (1). A response of the middle cerebral artery velocity (Vmca) as assessed by transcranial Doppler (TCD) after spontaneous changes in arterial blood pressure (ABP) in the low frequency range is described as spontaneous cerebral autoregulation (2) and has become an established method of assessing cerebral autoregulation in cerebrovascular diseases (3, 4). While there is no gold standard for assessing spontaneous cerebral autoregulation it has been commonly examined by analysis of phase shift and gain (amplitude ratio) between ABP measured by the finger cuff method and 0.1 Hz low frequency oscillations (LFOs) of Vmca, measured by TCD (2). Examination with TCD allow for the major arteries to be investigated, but does not directly assess smaller vessels.

Instead near infrared spectroscopy (NIRS) may be used as a non-invasive optical method to investigate regional changes in oxygenated (oxyHb) and deoxygenated hemoglobin (deoxyHb) in the outermost layers of the cerebral cortex. Beyond its widespread use for task-related functional imaging, it is also emerging as a novel modality to measure spontaneous cerebral oscillations and derive information about dynamic cerebral autoregulation (2, 5–7). We have previously shown, that LFOs phase shift between ABP and NIRS-derived oxyHb showed little inter-hemispheric variability in healthy subjects (8). Thus, NIRS may be an ideal tool to measure subtle inter-hemispheric differences in spontaneous LFOs of oxyHb in cortical vessels in patients with hemodynamic impairment.

In the present study we examined cortical cerebral autoregulation by measuring oxyHb LFOs in patients with both symptomatic carotid occlusive disease and cerebral hypoperfusion. We compared hypoperfusion side versus the contralateral side and one side in healthy controls for phase shift and gain parameters. Furthermore, we compared hypoperfusion patients versus healthy controls for phase shift and gain parameters. These preliminary results suggest an impairment of autoregulation in hypoperfusion patients at the cortical level detected by NIRS.

Analysis of cerebral autoregulation by measuring spontaneous oscillations in the low frequency spectrum of cerebral cortical vessels might be a useful tool for assessing risk and investigating different treatment strategies in carotid artery disease and stroke. Near infrared spectroscopy (NIRS) is a non-invasive optical method to investigate regional changes in oxygenated (oxyHb) and deoxygenated hemoglobin (deoxyHb) in the outermost layers of the cerebral cortex. In the present study we examined oxyHb low frequency oscillations, believed to reflect cortical cerebral autoregulation, in 16 patients with both symptomatic carotid occlusive disease and cerebral hypoperfusion in comparison to healthy controls. Each hemisphere was examined with two NIRS channels using a 3 cm source detector distance. Arterial blood pressure (ABP) was measured via a finger plethysmograph. Using transfer function analysis ABP-oxyHb phase shift and gain as well as inter-hemispheric phase shift and amplitude ratio were assessed. We found that inter-hemispheric amplitude ratio was significantly altered in hypoperfusion patients compared to healthy controls (P = 0.010), because of relatively lower amplitude on the hypoperfusion side. The inter-hemispheric phase shift showed a trend (P = 0.061) toward increased phase shift in hypoperfusion patients compared to controls. We found no statistical difference between hemispheres in hypoperfusion patients for phase shift or gain values. There were no differences between the hypoperfusion side and controls for phase shift or gain values. These preliminary results suggest an impairment of autoregulation in hypoperfusion patients at the cortical level detected by NIRS.

**Keywords:** cerebral autoregulation, low frequency oscillations, hypoperfusion, stroke, carotid artery disease, Doppler, near infrared spectroscopy

**SUBJECTS**

We recruited 16 patients (14 male and 2 female, mean age 65, range 54–78) diagnosed with symptomatic carotid occlusion and hypoperfusion (Table 1). All patients were diagnosed with...
Table 1 | Patient detail

| Sub | Neurological examination | CT/MRI | Diagnosis | SPECT | Stenosis hypoperfusion side (%) | Stenosis contralateral side (%) |
|-----|--------------------------|--------|-----------|--------|---------------------------------|---------------------------------|
| 1   | Normal                   | Normal | TIA       | Unilat | 80–99                           | 60–79                           |
| 2   | Normal                   | Basal ganglia | TIA       | Unilat | 80–99                           | 0                              |
| 3   | Normal                   | Normal | TIA       | Unilat | 100                             | 0                              |
| 4   | Hemiparesis              | Frontal/occipital | Infarct   | Unilat | 100                             | 0                              |
| 5   | Normal                   | Subcortical | Infarct   | Unilat | 100                             | 0                              |
| 6   | Normal                   | Normal | TIA       | Unilat | 100                             | 0                              |
| 7   | Normal                   | Parietal/temporal | Infarct   | Unilat | 100                             | 60–79                          |
| 8   | Normal                   | Parietal | Infarct   | Unilat | 100                             | 0                              |
| 9   | Normal                   | Normal | TIA       | Unilat | 100                             | 0                              |
| 10  | Hemiparesis              | Frontal | Infarct   | Global | 0                               | 0                              |
| 11  | Normal                   | Normal | TIA       | Global | 100                             | 0                              |
| 12  | Normal                   | Normal | TIA       | Unilat | 0                               | 0                              |
| 13  | Normal                   | Parietal/occipital | Infarct   | Unilat | 0                               | 0                              |
| 14  | Normal                   | Parietal | Infarct   | Unilat | 0                               | 0                              |
| 15  | Hemiparesis              | Frontal | Infarct   | Unilat | 100                             | 0                              |
| 16  | Normal                   | Normal | TIA       | Unilat | 100                             | 0                              |

Unless otherwise stated, neurological deficits and imaging findings are on the hypoperfusion side. Diagnosis is based on clinical examination and imaging. CT/MRI, place of lesion; CT, computer tomography; MRI, magnetic resonance imaging; TIA, transitory ischemic attack on the hypoperfusion side; Infarct, infarct on the hypoperfusion side; SPECT, single photon emission computer tomography. 

CT/MRI with signs of older infarction.

The median time from the first symptoms occurred to examination was 18 months (range 1–108). For comparison, we used data from a group of 44 healthy controls (21 male, 23 female, mean age 47 years, range 28–69 years), which have previously been published (8).

The Biomedical Research Ethics committee in the Capital Region of Denmark approved the study (H-B-2008-088). All subjects gave informed consent to participate in the study, which was undertaken in accordance with the Helsinki Declaration of 1964, as revised in Edinburgh in 2000.

NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy measurements were performed using continuous wave NIRS (NIRS2; TechEn Inc., Milford, MA, USA). The NIRS optodes were placed with two sources and four detectors on each side of the head with a distance of 3 cm between source and detector, each light source emitting two different wavelengths (690 and 830 nm). On each hemisphere, one source was placed on the forehead with one detector placed laterally, avoiding the midline sinus. The other source was placed on C3/C4 according to the International 10–20 system of EEG with the three detectors in front, above, and behind the source. Thus, the detectors measured the cerebral cortex in the territory supplied by the middle cerebral artery (MCA). NIRS recordings were acquired at a sampling rate of 200 Hz.

ARTERIAL BLOOD PRESSURE

Continuous non-invasive ABP recording was achieved via a finger plethysmograph (CNAP500) using the subjects left hand, positioned at heart level. Data from the finger plethysmograph was stored with the NIRS data for subsequent off-line analysis.

PROCEDURES

Before the experiments, each participant underwent a general physical and neurological examination. All experiments were performed with the patients placed in a supine position in a silent room with a constant temperature and the light dimmed. After 15 min of rest in the supine position, data acquisition was started with a 10 min trial of spontaneous breathing. This was followed by a 5 min trial with paced breathing at a rate of six respiration cycles per minute (0.1 Hz).

DATA ANALYSIS AND STATISTICS

Data are presented as mean ± SD. All signals were analyzed in successive 50% overlapping time segments of 100 s. The NIRS light intensity at 690 and 830 nm were first converted to time series of variations in oxyHb concentrations using the modified Beer–Lambert law. On each time segment, we then computed the power spectra of all signals (ABP, oxyHb), the coherence spectra for ABP-oxyHb and the complex transfer function for ABP-oxyHb (The Math Works, Inc., Natick, MA, USA) The phase shift and gain between ABP oscillations and oxyHb were obtained as the phase and absolute value of the complex transfer function respectively. The LFO frequency was selected as the frequency with maximal ABP oscillation power in the 0.09–0.11 Hz range. In this manner, for each run we obtained 5 (5 min run) or 11 (10 min run) overlapping segments each characterized by a coherence value, a phase shift, and a gain for ABP-oxyHb. As in our previous study we selected the segments for which the coherence was above an arbitrary threshold of 0.7 (8), and averaged the gain (linear average)
and the phase shift (circular average) over these selected segments. If the total number of segments with coherence above 0.7 was less than 3 for a specific run, we discarded that run.

In the healthy controls the inter-hemispheric phase shift (LFO time difference between hemispheres) and amplitude ratio (LFO amplitude ratio between hemispheres) were obtained. In patients with hypoperfusion the inter-hemispheric phase shift was defined as the phase shift between the hypoperfusion and contralateral sides. Thus, a positive phase shift implied that the hypoperfusion side was ahead in time compared to the contralateral side. The inter-hemispheric amplitude ratio was defined as the amplitude ratio of contralateral/hypoperfusion sides. Thus, an amplitude ratio above 1 implied that the amplitude was lower on the hypoperfusion side compared to the contralateral side.

We also analyzed the absolute values of inter-hemispheric phase shift and inter-hemispheric amplitude ratio percentage difference, to examine the inter-hemisphere synchronicity and amplitude differences. These analyses investigate whether the inter-hemispheric phase synchronicity and the inter-hemispheric amplitude differences are significantly different in the healthy group and the hypoperfusion group, independently of whether the hypoperfusion side is behind or ahead in time or whether it presents larger or smaller amplitude of oscillations in comparison to the contralateral side.

Given that the hypoperfusion patients were clinically heterogeneous, we divided them into two groups: (1) Patients with unilateral hypoperfusion and ipsilateral occlusion or stenosis of internal carotid artery (n = 9) and (2) Patients with global hypoperfusion (n = 2) unilateral hypoperfusion without internal carotid artery occlusion (n = 3) or hypoperfusion treated with EC-IC bypass before the examination (n = 2).

The primary end-points were to compare for phase shift and gain for:

(A) Hypoperfusion side versus contralateral side in group 1 patients.
(B) Hypoperfusion side in group 1 patients versus healthy controls.
(C) Direct inter-hemispheric phase shift and amplitude ratio in group 1 patients versus healthy controls.

Near infrared spectroscopy values between hemispheres were compared for hypoperfusion patients using the non-parametric Wilcoxon signed-rank test. NIRS values between patients and healthy controls were compared using multiple regression analysis with age, gender, and hypoperfusion patient/healthy control status as independent parameters.

All analyses were performed with SPSS (18.0). We made no adjustment for multiple analyses. Thus, the level of significance at 0.05 was accepted for each comparison.

RESULTS
All patients completed the study, but one subject in group 1 was only examined with forehead recordings due to technical limitations.

In group 1 the percentage of recordings excluded because of low coherence (less than three windows) from the forehead were 22% on the hypoperfusion side (seven subjects remaining for analysis), and 44% (five subjects remaining for analysis) on the contralateral side which was not statistically different from healthy controls (24% excluded), P = 0.711. The percentage excluded from the parietal recordings was 63% on the hypoperfusion side and 29% on the contralateral side, which was not statistically different (P = 0.804). Because of the low number of patients and the low coherence in the parietal recordings, analysis was based on the results from the forehead. For the inter-hemispheric relation between hemispheres, 22% of the forehead recordings had low coherence in hypoperfusion patients (seven subjects remaining for analysis), and 7% in healthy controls, P = 0.200. With paced breathing at 0.1 Hz we attempted to modulate the LFOs, but it showed very low coherence in general, and was therefore not analyzed further.

HYPOPERFUSION VERSUS CONTRALATERAL SIDE
The LFO ABP-oxyHb phase shift on the hypoperfusion side (31 ± 30°), tended to be higher than on the contralateral side (70 ± 50°), P = 0.080, Figure 1A. There was no significant difference in ABP-oxyHb gain between the hypoperfusion side (0.7 ± 75%), and the contralateral side (1.2 ± 133%), P = 0.225, Figure 1B.

HYPOPERFUSION PATIENTS VERSUS HEALTHY CONTROLS
Forehead measurements from the hypoperfusion side were compared to the left side of healthy controls. We found no difference in phase shift between patients (31 ± 30°) and healthy controls (13 ± 25°), P = 0.186, Figure 1A. There was also no difference in gain between patients (0.7 ± 75%) and healthy controls (0.3 ± 190%), P = 0.389, Figure 1B.

INTER-HEMISPHERIC RELATION IN PATIENTS VERSUS HEALTHY CONTROLS
Mean phase shift from the hypoperfusion side to the contralateral side (14 ± 34°) was not different compared to left to right phase shift in healthy controls (4 ± 13°), P = 0.463, Figure 1C. There was a trend toward higher inter-hemispheric absolute phase shift in hypoperfusion patients (23 ± 27°) compared to healthy controls (9 ± 10°), P = 0.061.

There was a significantly higher mean amplitude ratio for contralateral/hypoperfusion side in patients (1.3 ± 0.5) compared to healthy controls (0.9 ± 0.2), P = 0.010, Figure 1D. The mean percentage amplitude difference in hypoperfusion patients (44 ± 32%) was also higher compared to healthy controls (16 ± 14%), P = 0.003. Phase shift and gain values for group two patients are presented in Table 2.

DISCUSSION
We found that inter-hemispheric amplitude ratio was significantly altered in hypoperfusion patients compared to healthy controls, due to relatively lower amplitude on the hypoperfusion side. There was a trend toward increased phase shift in inter-hemispheric phase shift in patients. We found no statistical difference between hemispheres for hypoperfusion patients for phase shift or gain, and no difference for hypoperfusion side compared to healthy controls for phase shift or gain values.
Assessing cerebral autoregulation through examination of spontaneous LFO with NIRS or TCD has the advantage of being without discomfort during recording, which ensure high compliance from the patients. Furthermore, NIRS directly investigates local changes in the cortical vessels, opposed to measurements of changes in Vmca via TCD.

Previous studies of LFOs in carotid artery stenosis and occlusion has primarily investigated phase shift and gain between Vmca and ABP during spontaneous (3, 9) or paced breathing (10–12). These studies have showed a significantly lower phase shift for both spontaneous (9, 13) and paced breathing (12) on the affected side. Interestingly, LFOs gain between MAP and Vmca has also
been shown to decrease with increasing levels of stenosis (13). Phase shift was examined in combination with CO\textsubscript{2} reactivity by Reinhard et al. and both were found to be reduced on the affected side, but no correlation was found between the two measurements (10). LFOs phase shift has also shown equally good sensitivity and specificity for detecting high-grade carotid stenosis and occlusion as conventional tests such as CO\textsubscript{2} vasoreactivity (13) and tilt test (3), making it a promising tool for CA assessment. Cortical vessels appear to be affected by large artery stenosis. Thus, Ziyeh et al. demonstrated decreased blood oxygen level dependent (BOLD) effect within the internal carotid artery territory in patients with high-grade carotid stenosis and occlusion, which also had impaired CO\textsubscript{2} reactivity measured with TCD (14).

Only one study has examined changes in LFO phase shift with NIRS and TCD simultaneously in asymptomatic patients paced breathing (6). The study showed that both ABP-oxyHb and ABP-TCD phase shift was right-shifted in comparison to the contralateral side. Thus, the study suggests that oxyHb measurements may detect similar changes suggestive of cerebral autoregulation impairment asVmca measurements (6).

In the healthy brain, the inter-hemispheric phase shift is expected to be close to 0° and the inter-hemispheric amplitude ratio close to 1 (8), as a sign of the two hemispheres being synchronous and at the same level of cerebral autoregulation. In the present study, the direct inter-hemispheric relation showed a higher amplitude ratio and percentage amplitude difference in patients with hypoperfusion and ipsilateral carotid artery stenosis or occlusion compared to healthy controls. This novel finding is likely due to arterioles being compensatively dilated in the hypoperfusion hemisphere by the demand of adequate perfusion and oxygen delivery distal to the stenosis. This could affect the capacity for LFO and thereby decrease the amplitude on the ipsilateral hemisphere distal to the stenosis. This mechanism is supported by previously mentioned studies showing reduced CO\textsubscript{2} vasoreactivity on the side of carotid stenosis or occlusion (9, 10). Furthermore, a previous NIRS study (15) reported that frontal OxyHb LFOs were reduced in patients with previous ischemic infarction compared to healthy controls. This suggests that cerebrovascular disease may result in decreased vasodilatory capability or increased vascular stiffness.

The absolute inter-hemispheric phase shift showed a trend toward less synchronicity between hemispheres in hypoperfusion patients compared to healthy controls. However, there was no significant difference when analyzing the inter-hemispheric phase shift from hypoperfusion to contralateral side. Thus, there was no indication of oscillations on the hypoperfusion side being systematically ahead or behind in time to oscillations on the healthy side. However, these results need to be interpreted with care due to the low number of subjects, which could lead to type 2 errors.

The strength of analyzing inter-hemispheric differences is that each subject serves as its own reference. ABP-oxyHb values will be more sensitive to errors due to the actual geometry of each head. Thus, by measuring inter-hemispheric differences, we are less sensitive to variability between subjects and thereby minimize model errors.

Group 2 was a very heterogenous group and statistic comparison within the group was not possible. When looking at the
REFERENCES

1. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev (1959) 39:183–238.
2. Diehl RR, Linden D, Lucke D, Berlit P. Spontaneous blood pressure oscillations and cerebral autoregulation. Clin Auton Res (1998) 8:7–12. doi:10.1007/BF02267598
3. Haubrich C, Klemm A, Diehl RR, Moller-Hartmann W, Klotzsch C. M-wave analysis and passive tilt in patients with different degrees of carotid artery disease. Acta Neurol Scand (2004) 109:210–6. doi:10.1034/j.1600-0404.2003.00210.x
4. Vernieri F, Tubazzi F, Pasqualetti P, Rosati N, Passarelli F, Rossini PM, et al. Transcranial Doppler and near-infrared spectroscopy can evaluate the hemodynamic effect of carotid artery occlusion. Stroke (2004) 35:64–70. doi:10.1161/01.STR.0000106486.26626.E2
5. Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhäupl K, et al. Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. Neuroimage (2000) 12:623–39. doi:10.1006/nimg.2000.0657
6. Reinhard M, Wehrle-Wieland E, Grabak D, Roth M, Guschlbauer B, Timmer J, et al. Oscillatory cerebral hemodynamics – the macro- vs. microvascular level. J Neurol Sci (2006) 250:103–9. doi:10.1016/j.jns.2006.07.011
7. Cheng B, Shang Y, Hayes D Jr, Saha SP, Yu G. Noninvasive optical evaluation of spontaneous low frequency oscillations in cerebral hemodynamics. Neuroimage (2012) 62:1445–54. doi:10.1016/j.neuroimage.2012.05.069
8. Phillip D, Schytz HW, Selb J, Payne S, Iversen HK, Skovgaard LT, et al. Low frequency oscillations in cephalic vessels assessed by near infrared spectroscopy. Eur J Clin Invest (2012) 42:1180–8. doi:10.1111/j.1365-2362.2012.02704.x
9. Reinhard M, Roth M, Muller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. Stroke (2003) 34:2138–44. doi:10.1161/01.STR.0000087788.65566.AC
10. Reinhard M, Hetzel A, Lauk M, Lucking CH. Dynamic cerebral autoregulation testing as a diagnostic tool in patients with carotid artery stenosis. Neurol Res (2001) 23:55–63. doi:10.1179/016164101011918299
11. Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Transfer function analysis for clinical evaluation of dynamic cerebral autoregulation – a comparison between spontaneous and respiratory-induced oscillations. Physiol Meas (2003) 24:27–43. doi:10.1088/0967-3334/24/1/303
12. Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Dynamic cerebral autoregulation and collateral flow patterns in patients with severe carotid stenosis or occlusion. Ultrasound Med Biol (2003) 29:1105–13. doi:10.1016/S0301-5629(03)00954-2
13. Hu HH, Kuo TB, Wong WJ, Lu YO, Chern CM, Hsu LC, et al. Transfer function analysis of cerebral hemodynamics in patients with carotid stenosis. J Cereb Blood Flow Metab (1999) 19:460–5. doi:10.1097/00004467-199904000-00012
14. Ziyeh S, Rick J, Reinhard M, Hetzel A, Mader I, Speck O. Blood oxygen level-dependent MRI of cerebral CO2 reactivity in severe carotid stenosis and occlusion. Stroke (2003) 36:751–6. doi:10.1161/01.STR.0000157593.03470.3d
15. Li Z, Wang Y, Li Y, Wang Y, Li J, Zhang L. Wavelet analysis of cerebral oxygenation signal measured by near infrared spectroscopy in subjects with cerebral infarction. Microvasc Res (2010) 80:142–7. doi:10.1016/j.mvr.2010.02.004
16. Reinhard M, Muller T, Roth M, Guschlbauer B, Timmer J, Hetzel A. Bilateral severe carotid artery stenosis or occlusion – cerebral autoregulation dynamics and collateral flow patterns. Acta Neurochir (Wien) (2003) 145:1053–9. doi:10.1007/s00701-003-0137-8

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 September 2013; accepted: 03 December 2013; published online: 16 December 2013.

Citation: Phillip D, Iversen HK, Schytz HW, Selb J, Boas DA and Ashina M (2013) Altered low frequency oscillations of cortical vessels in patients with cerebrovascular occlusive disease – a NIRS study. Front. Neurol. 4:204. doi: 10.3389/fneur.2013.00204

This article was submitted to Stroke, a section of the journal Frontiers in Neurology. Copyright © 2013 Phillip, Iversen, Schytz, Selb, Boas and Ashina. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.