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Diagnosing migraine using structural brain MRI data

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Aim
Migraine is diagnosed using operational criteria according to ICHD II/III-beta. Changes in brain structure or function, or other biomarkers are not currently considered in the diagnostic process. Using multicenter high-resolution structural MRI data, we tested the ability of a machine learning technique to distinguish migraineurs from healthy subjects on the basis of cortical thickness and subcortical morphology.

Methods
T1-weighted MPRAGE data of 131 migraineurs (40 with aura; 31±9yo; 109 women; monthly attack frequency: 3.2±2.5; disease duration: 14±8.4y) and 115 matched healthy subjects (29±7yo; 81 women) acquired at four different centers at 3 Tesla were pooled. Cortical thickness and subcortical morphology were assessed using FreeSurfer and MAGeT. A linear support vector machine (SVM) algorithm was used to determine the diagnostic accuracy in separating migraineurs from healthy subjects based on 90 unselected variables describing cortical thickness in distinct gyri and subcortical volumes. Another SVM was trained to distinguish migraineurs with versus without aura. In both SVMs, the training of the classifier was conducted on 70% of data, while their performance was evaluated on the remaining 30%. Age, gender and center were included in both analyses.

Results
The SVM classifier yielded an accuracy of 74.4% (sensitivity 71.4%, specificity 77.8%) for distinguishing migraineurs from controls. An accuracy of 85% (sensitivity 83.3%, specificity 85.7%) was reached when separating patients with from those without aura.

Conclusion
The data support the view that migraine is a brain disorder with distinctive cortical/ subcortical anatomical features. Although the diagnostic accuracy currently remains too low for clinical practice, it is a good starting point for a future supplementary diagnostic tool.
Pain modulation is affected differently in medication-overuse headache and chronic myofascial pain – A multimodal MRI study.

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Background
Neuroimaging studies revealed structural and functional changes in medication-overuse headache (MOH), but it remains unclear whether similar changes could be observed in other chronic pain disorders.

Methods
We investigated functional connectivity (FC) with resting state fMRI and white matter integrity using diffusion tensor imaging (DTI) to measure fractional anisotropy (FA) and mean diffusivity (MD) in patients with MOH (N=12) and in patients with chronic myofascial pain (N=11) compared to controls (CN; N=17).

Results
In a data driven approach we found hypoconnectivity in the fronto-parietal attention network in both pain groups. In contrast, hyperconnectivity in the saliency network (SN) was detected only in MOH, which correlated with FA in the right insula. In a seed-based analysis we investigated FC between the periaqueductal grey (PAG) and all other brain regions. In addition to overlapping changes seen in both patient groups, MOH had a distinct connectivity pattern with lower FC to pain modulatory as well as occipital regions and higher FC to orbitofrontal regions. FA changes were more widespread in MOH, involving bilateral insula and cingulate regions. FA in the right insula correlated with headache frequency.

Conclusions
Hyperconnectivity within the SN along with associated white matter changes therein suggest a particular role of this network in MOH. In addition, impaired connectivity between the PAG and other pain modulatory regions in MOH are consistent with dysfunctional central pain control.

Comments
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L Michels and F Christidi contributed equally.
Human gait and the nigro-striatal pathway

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Aims
Although gait disorders are common in patients with parkinsonian syndromes, the relationship between the nigro-striatal pathway and quantitative gait parameters is poorly understood. This cross-sectional study aims to determine the contribution of the nigro-striatal pathway to the quantitative gait parameters in patients with parkinsonian syndromes.

Methods
Twenty-four consecutive parkinsonian patients without Parkinson’s disease, who performed a DAT-Scan and a gait analysis, were included in this analysis. Gait analysis and DAT-Scan were performed within three months of each other. Gait parameters were obtained at self-selected speed on a 10 meter walking distance with a seven-camera opto-electronic system (VICON Mx3+, Vicon Motion Systems, Oxford, UK, sampling rate of 100 Hz). A volume of interest-based analysis of uptake ratios focused on the caudate and putamen relative to the occipital cortex and a voxelwise analysis were performed. At the time of the study, all patients were drug naive for neuroleptic and antiparkinsonian medication or other medications affecting the dopaminergic system.

Results
The twenty-four parkinsonian patients (mean age: 73.6 ± 8.2 years; 29% female) included in this study presented a mean disease duration of 22.3 ± 28.6 months. We reported an inverse correlation between age and DAT-Scan uptake. After correction for multiple comparisons, we did not observe any association between regional DAT-Scan uptake ratio and quantitative spatio-temporal gait parameters including walking speed, stride length, cadence, stride time, step width and step height.

Conclusions
Nigro-striatal denervation, as measured by DAT-Scan, is not related to alterations of spatio-temporal gait parameters in patients with parkinsonian syndromes. The clinical implication of the study findings supports a non-dopaminergic mechanism underlying gait disorders in patients with parkinsonian syndrome and the use of non-dopaminergic agents to improve gait disorders in parkinsonian patients without Parkinson’s disease.

Acknowledgments
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Abnormal self-relevant motor representation in Functional (psychogenic) Neurological Disorders.

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Aims
The ventromedial prefrontal cortex (vmPFC) has been linked to self-related information processing, such as judgment of our own personality traits, our own past and even our own goals, as well as affective and motivational processing[1]. Abnormal vmPFC activity has been repeatedly observed in Functional Neurological Disorders (FNDs), when attempting to move[2, 3], sense or see[4] through different imaging paradigms. This suggests abnormal representation of the "self" in FNDs, which may account for the neurological symptom. Our aim was to test in an fMRI paradigm differential activation patterns in the vmPFC in motor FNDs during stimuli (words) that call for motor or bodily representations.

Methods
12 patients suffering from motor FNDs were presented different word categories that include neurological symptoms relevant or not to the patient’s disorder (e.g. paralysis or tremor), respiratory symptoms (e.g. cough), motor bodily parts (e.g. leg), respiratory parts (e.g. lung), and a neutral word category (objects). Whole brain responses to each category were analysed using a second-level flexible factorial model with the following contrasts: motor bodily symptoms and/or motor bodily parts relative to the respiratory ones, as well as self-relevant versus non-relevant motor symptoms. In addition, an a priori region of interest analysis was performed for the vmPFC as determined by a separate localiser task delineating brain areas recruited during "self" processing. Peaks at p < 0.001 uncorrected with a number of voxels > 10 are reported.

Results
Among the 12 patients with motor FNDs, 8 had negative symptoms (paresis), 3 positive symptoms (tremor/dystonia) and 1 both. The rectal orbitofrontal gyrus [MNI: -9, 32, -20] and posterior vmPFC [MNI: 3, 14, -11] were selectively reduced in response to words related to the motor system (body part & symptom), as compared with words related to the respiratory system. These changes partly overlapped with a self-related region of interest in vmPFC identified in the localiser "self" processing task.

Conclusions
Our study showed a decrease in vmPFC activity during the evocation of motor symptoms and body parts in motor FNDs patients, which may reflect a reduction in self attribution processes operating on motor and body related signals; this affective disengagement may correspond to the clinical concept of "la belle indifférence" and play a role in the production of the functional motor symptoms.

References
**FM 05**

**Vascular risk factors but not transesophageal echocardiography (TEE) features are associated with stroke recurrence in patients with cryptogenic stroke (CS) and patent foramen ovale (PFO) – from the International PFO Consortium (NCT00859885)**

From September 2008 to March 2013, the International PFO Consortium enrolled 993 patients with ischemic stroke or transient ischemic attack (TIA) and newly diagnosed PFO. In this analysis of baseline data, we included 386 patients with first-ever CS and no radiological evidence of prior cerebral ischemia (first-ever CS group, mean age, 52y) as well as 71 patients with recurrent CS and multiple ischemic lesions on CT and/or MRI (multiple CS group, mean age, 59y). Patients with TIA as index event, those with first-ever CS but additional “silent” ischemic lesions on imaging as well as those with recurrent CS without radiological findings of prior cerebral ischemia were excluded. We used nonparametric tests for independent samples and the Bonferroni correction for multiple comparisons.

**Results**

Age > 55y (63% vs. 44%, P=0.001), hypertension (52% vs. 30%, P=0.001), hyperlipidemia (64% vs. 44%, P=0.003), and coronary artery disease (15% vs. 3%, P=0.001) were significantly more frequent in the multiple CS than in the first-ever CS group. The frequencies of male gender, current smoking, diabetes, migraine with or without aura, associated ASA, RLS size, and RLS at rest did not differ between groups. At baseline, patients with multiple CS were more likely to be on antplatelets (50% vs. 18%), antihypertensive (51% vs. 22%) or lipid lowering drugs (44% vs. 10%, P=0.001 for each comparison) than patients with first-ever CS. The frequency of anticoagulant treatment did not differ between groups.

**Conclusion**

In patients with CS, vRF but not specific PFO features were associated with prior cerebral ischemic events. The ongoing prospective part of the International PFO Consortium will hopefully shed light upon the role of vRF control for secondary stroke prevention in patients with PFO.

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Objective
To assess the relationship between seizure burden on continuous EEG (cEEG) and functional as well as cognitive outcome 3 months after SAH.

Methods
The study included all consecutive patients with a spontaneous SAH admitted to the Columbia University Medical Centre Neurological Intensive Care Unit in New York (USA) and monitored with cEEG between 1996 and 2013. Seizure burden was defined as the duration, in hours, of seizures on cEEG. Cognitive outcomes were measured with the Telephone Interview Cognitive Status (TICS, ranging from 0 to 51, indicating poor to good global mental status).

Results
Overall, 402 patients with SAH were included with a median age of 58 years (interquartile range [IQR]: 46-68 years). The median duration of cEEG monitoring was 96 h (IQR: 48-155 h). Seizures were recorded in 50 patients (12%), in whom the median seizure burden was 6 h (IQR: 1-13 h). At 3 months, in multivariate analysis, seizure burden was associated with both unfavorable functional and cognitive outcome. Every hour of seizure on cEEG was associated with an odds ratio 1.10 (95%-confidence interval [CI]: 1.01-1.21, P=0.04) to 3-month disability and mortality, and the TICS-score decreased, on average, by 0.16 points (adjusted coefficient -0.16, 95%-CI: -0.30 – [-0.03], P=0.02).

Conclusion
In this study, after adjusting for established predictors, seizure burden was associated with functional outcome and cognitive impairment 3 months after SAH.
Characterization of encephalitogenic CD8+ T cells in an animal model of multiple sclerosis

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Multiple sclerosis (MS) is the most common inflammatory demyelinating disorder of the central nervous system (CNS) causing disability in young adults. Histopathological studies suggested that CD8+ cytotoxic T lymphocytes (CTLs) may contribute to CNS tissue damage in MS. However, most MS animal models are mostly mediated by encephalitogenic CD4+ T helper cells. Recently a transgenic mouse model expressing ovalbumin (OVA) as a neo-“self” antigen in oligodendrocytes was described (ODC-OVA). We took advantage of this new animal model, to monitor the microbial capacity of two recombinant pathogens expressing OVA (Lm-OVA and LCMV-OVA) to elicit an encephalitogenic CTLs response. Adoptively transferred OVA-specific CTLs (OT-1) expanded to a similar extent showing clonal differentiation into effector CTLs in ODC-OVA mice upon peripheral infection with either Lm-OVA or LCMV-OVA. However, EAE disease was only observed upon LCMV-OVA infection. To identify a gene expression signature that may characterise encephalitogenic brain invading CTLs, we performed a transcriptome analysis on FACS-sorted brain infiltrating OT-1 cells after LCMV-OVA or Lm-OVA challenge. We found that the core transcriptional signature was similar in the two experimental groups, but some genes were differentially regulated in CTLs in diseased versus non-diseased animals. The implication of these differentially expressed genes was further investigated in functional readouts and correlated to the encephalitogenic property of CTLs. Thus, our study may provide new insights into the underlying mechanisms that govern functional and transcriptional regulation of an encephalitogenic CTLs.
**MS 02**

**Oxysterols and human memory T lymphocytes: an attractive story**

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**Aims**

Oxysterols, hydroxylated cholesterol metabolites, modulate the immune response and promote inflammation (1). We are interested in studying the role of the oxysterol 7α25-hydroxycholesterol (7α25-OHC), the strongest ligand of the Epstein-Barr virus-induced G-protein coupled receptor 2 (EBI2). Using the experimental autoimmune encephalomyelitis, an animal model for multiple sclerosis (MS), we previously showed that memory CD4+ T lymphocytes migrate specifically in response to 7α25-OHC via EBI2. Furthermore EBI2-deficient lymphocytes depict delayed migration to the central nervous system compared to their wild type counterparts (2). However, the expression and the role of EBI2 in human lymphocytes during Multiple Sclerosis (MS) have not been studied. We now propose to study EBI2 expression and function in human lymphocytes in healthy donors and MS patients.

**Methods**

EBI2 expression on human peripheral blood mononuclear cells was measured by flow cytometry using a specific anti-human EBI2 antibody. The function of EBI2 in cell migration was assessed using a transwell assay.

**Results**

We observed maximal EBI2 expression on memory CD4+ T cells; memory subsets of B and CD8+ T cells also depicted a modestly increased EBI2 expression compared to naive populations. Transwell migration assay experiments showed maximal migration of memory CD4+ T cells in response to 7α25-OHC. Even if globally less responsive to 7α25-OHC than the latter, memory subsets of B and CD8+ T cells were also found to migrate more strenuously than their naive counterparts. This chemotaxis was specific to EBI2 as selective EBI2 inhibition unequivocally abrogated migration. Finally, EBI2 expression and migration pattern are modified during MS compared to healthy donors.

**Conclusion**

These data suggest an important role for EBI2 in human T cell migration. Selective targeting of immune cell trafficking has become an important tool in the clinical setting to dampen autoimmunity, in particular during MS. Uncovering the role of EBI2 in T cell trafficking, in particular its ability to direct human CD4+ T cell chemotaxis, may open new avenues for understanding the pathogenesis of autoimmunity and may promote novel therapeutic approaches.

**Acknowledgments**

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**References**

Endothelial ALCAM (CD166) is not required for encephalitogenic T cell migration across the blood-brain barrier

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Aim of study
Extravasation of circulating CD4+ effector/memory T cells (TEM cells) across the blood-brain barrier (BBB) is a tightly regulated multi-step process. Each step of the extravasation cascade is mediated by different adhesion and signalling molecules expressed on the TEM cell and on the brain endothelial cell. Our previous work has shown essential but differential roles of vascular cell adhesion molecule (VCAM)-1, endothelial intercellular adhesion molecule (ICAM)-1 and ICAM-2 for the shear resistant arrest, crawling and diapedesis of TEM cells. Activated leukocyte cell adhesion molecule (ALCAM) is another endothelial cell adhesion molecule expressed on the human BBB. The observation that an anti-ALCAM antibody ameliorated experimental autoimmune encephalomyelitis (EAE) disease course in the mouse, supported a role of ALCAM in TEM cell trafficking to the CNS. This prompted us to investigate the role of endothelial ALCAM for the extravasation of CD4+ TEM cells across the mouse BBB.

Methods
Primary mouse brain microvascular endothelial cells (pMBMECs) from ALCAM-knockout (ko) or wild type (wt) C57BL/6J mice as in vitro BBB model. T cell diapedesis under static conditions. In vitro live cell imaging under physiological flow. Quantitative polymerase chain reaction and Western Blotting to assess ALCAM expression. Immunofluorescences of histological sections of the mouse or human brain or spinal cord. Experimental autoimmune encephalomyelitis (EAE).

Results
Diapedesis of TEM cells across unstimulated ALCAM-ko pMBMECs was reduced compared to wt pMBMECs. In contrast, under physiological flow conditions the dynamic interaction of CD4+ TEM cells with ALCAM-ko or wild type pMBMECs remained comparable. Detectable ALCAM mRNA levels in wild type pMBMECs did not translate into detectable ALCAM protein levels under unstimulated or cytokine stimulated conditions of the pMBMECs. However, ALCAM protein was readily detected in mouse brain and spinal cord lysates confirming presence of ALCAM in the CNS. Immunofluorescence staining of brain or spinal cord sections from wild type mice proved ALCAM protein below detection limit on parenchymal CNS vessels in the mouse. Finally, EAE in ALCAM-ko mice was rather aggravated when compared to wild-type littermates.

Conclusion
Our data point to a role of ALCAM in autoimmune CNS inflammation of the mouse that is different from mediating the migration of encephalitogenic CD4+ TEM cells across the BBB.
Spinal cord gray matter atrophy in early multiple sclerosis

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Aims
Spinal cord gray matter (GM) atrophy has been recently described in vivo in patients with long-standing Multiple Sclerosis (MS) and has been shown to correlate with disability and disease type. The goal of this study was to assess whether spinal cord GM atrophy starts early in the disease and whether it equally affects the cervical and thoracic cord.

Methods
40 patients at an early stage of MS (mean age 36.5 years, 29 women, mean disease duration from first symptom onset: 1.3 years (range 0-3.7 years)) and 20 age and sex matched healthy controls were scanned at 3T. Axial 2D-phase sensitive inversion recovery MR images were acquired at the intervertebral disc levels C2/C3 and T9/T10. Total cord areas (TCA) were segmented semi-automatically, spinal cord GM areas were segmented manually, and spinal cord white matter (WM) areas were calculated as their difference. Differences in areas between patients and controls were assessed with age and sex as covariates using multivariable regression analysis.

Results
In the cervical and thoracic spinal cord MS patients had significantly smaller spinal cord GM areas than age and sex matched controls (Coefficient of variation (COV) 7%, p<0.001 at C2/C3 and 7%, p=0.04 at T9/T10), but had no significant difference in either the spinal cord WM area or TCA.

Conclusions
These observations demonstrate that spinal cord GM atrophy can be detected already at an early stage of MS, in the absence of WM atrophy, and equally affects both the cervical and thoracic cord. Longitudinal, prospective studies are necessary to clarify the role of cord GM changes in monitoring and predicting MS disability and progression.

Disclosures
RS has received grants from the Swiss MS Society and the Gottfried and Julia Bangerter-Rhyner Foundation, Switzerland. Her institution (University Hospital Basel) has received advisory board fees from Biogen, which were exclusively used for research support.

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Aims
The two hallmarks of chronic Multiple Sclerosis (MS) lesions are (1) absence of significant spontaneous remyelination and (2) primary as well as secondary neurodegeneration due to chronic axonal demyelination and inflammation. Both of these pathogenic characteristics may be influenced by the presence of inhibitory factors preventing myelin and neuronal repair. A factor potentially involved is the myelin-associated protein Nogo-A which is known as an inhibitor of neurite outgrowth. Several lines of evidence support the involvement of Nogo-A in the pathogenesis of MS: First, Nogo-A-antibody treated mice with Experimental Autoimmune Encephalomyelitis (EAE) show improved functional outcome and neuronal survival (Karnezis et al., Nat. Neurosci., 2004). Second, Nogo-A deficient mice show enhanced myelinogenic potential and remyelination after lysolecithin-induced demyelination (Chong et al., PNAS, 2012). However, several questions remain to be answered: First, how do Nogo-A-antibodies mediate enhanced functional recovery and second, does pharmacological blockade of Nogo-A by function blocking antibodies against Nogo-A improve remyelination? Therefore, we aim at investigating in this study the potential of anti-Nogo-A immunotherapy to enhance neuronal regeneration and remyelination in two animal models for MS.

Methods and Results
After induction of a focal EAE lesion in the dorsal funiculus of the cervical spinal cord of rats, improved recovery of forelimb function was observed in the anti-Nogo-A treated group. By anterograde BDA tracing of the corticospinal tract in pilot experiments, the anti-Nogo-A group showed increased neuronal sprouting of the injured tract. Moreover, rats treated with anti-Nogo-A antibodies showed enhanced remyelination after lysolecithin-induced demyelination of the cervical spinal cord as demonstrated by an increased count of remyelinated axon within the lesion.

Conclusions
These preliminary findings hint towards Nogo-A-antibodies as a possible new treatment approach for MS. This may be particularly interesting for treating the chronic progressive phase of MS where the neurodegeneration and remyelination failure are hallmarks.

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Dendritic cells represent a heterogeneous pool of professional Antigen Presenting cells (APCs) playing a pivotal role in Immunity. Conventional dendritic cells (cDC) function as key APC during both priming and effector phases of EAE. To define the contribution of MHCII-mediated Ag presentation by plasmacytoid DC (pDC), we have studied the development of EAE in mice exhibiting a selective loss of MHCII expression by pDCs. We have previously shown that MHCII expression by pDCs results in encephalitogenic T cell priming inhibition and promotes the development of regulatory T cells (Treg) in secondary lymphoid tissues. The present work investigates the mechanisms underlying pDC-mediated Treg expansion and EAE protection. Using mice in which Treg can be selectively depleted, we show that EAE development is severely exacerbated in absence of Treg during the priming phase of the disease, to similar extent compared to mice lacking MHCII expression by pDCs. Aggravated EAE symptoms correlated with increased encephalitogenic T cell priming in draining lymph nodes (LN). We then addressed the possible mechanisms accounting for pDC-mediated Treg development. We observed that the expression of Indoleamine-2,3-dioxygenase (IDO), which has been shown to play a role in Treg generation and maintenance and to be link to pDC tolerogenesis, is preferentially expressed in pDCs compared to other cell types in LN. Importantly, we demonstrate that IDO expression by pDCs is mandatory to confer suppressive functions to Treg and, consequently, to dampen EAE severity.
Inhibition of T cell mediated neuroinflammation by Btn2a2, a novel immunomodulatory molecule co-regulated with MHC class II genes

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Aims
The aim of our project is to elucidate the role of Btn2a2, a distant relative of the B7 family of costimulatory molecules, in the modulation of T cell responses. This could potentially lead to new therapeutic applications for autoimmune conditions and inflammatory disorders such as multiple sclerosis (MS).

Methods
Approaches included gene-expression studies, generation Btn2a2/-/- mice, analysis of in vivo CD4+ T cell responses in Btn2a2/-/- mice, analysis of the susceptibility of Btn2a2/-/- mice to MOG-induced experimental autoimmune encephalomyelitis (EAE), an animal model for MS, and in vitro T cell activation studies performed in the presence of a Btn2a2-Ig fusion protein.

Results
Human BTN2A2 and mouse Btn2a2 genes were found to be co-regulated with MHC class II (MHCII) genes in antigen presenting cells (APCs) and IFN-α induced cells, suggesting a role in MHCII-mediated antigen presentation to CD4+ T cells. Generation and analysis of Btn2a2/-/- mice confirmed this. Immunization experiments demonstrated that CD4+ T helper (Th) cell responses were markedly enhanced in Btn2a2/-/- mice. Accordingly, EAE, a CD4+ Th-cell mediated autoimmune disease of the central nervous system, was strongly exacerbated in Btn2a2/-/- mice. Btn2a2/-/- mice exhibited accelerated disease onset, higher cumulative and maximum disease scores, and greater disease incidence. Exacerbated disease was associated with increased infiltration of the spinal cord by pathogenic IFN-γ and IL-17 producing Th cells. Conversely, frequencies of infiltrating CD4+Foxp3+ regulatory T cells (Treg) were reduced. EAE experiments performed with reciprocal bone marrow chimeras (Btn2a2/-/- into WT and WT into Btn2a2/-/-) demonstrated that disease exacerbation was due to loss of Btn2a2 expression by cells of hematopoietic origin. TCR-transgenic T cell transfer experiments indicated that Btn2a2 expression by APCs modulates CD4+ T cell responses in vivo, leading to dampened Th responses in favor of increased Treg expansion. Finally, in vitro T cell activation assays performed in the presence of a Btn2a2-Ig fusion protein confirmed that Btn2a2 inhibits CD4+ T cell activation and proliferation, impairs Th cell differentiation and enhances Treg development.

Conclusions
Our results demonstrate that Btn2a2 is a novel negative regulator of T cell responses, and that it protects against the development of T cell mediated neuroinflammation.

Acknowledgements
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The Neurotrophic Hepatocyte Growth Factor Negatively Regulates The Cytotoxic T-Lymphocyte Activity of Murine CD8+ T cells

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Aims
Controlling the mechanisms that govern the functions of encephalitogenic T cells is critical in the context of Multiple Sclerosis (MS) intervention. We recently showed that hepatocyte growth factor (HGF), a potent neuroprotective factor, restrains CD4+ T cell-mediated autoimmune neuroinflammation at least in part through the generation of tolerogenic dendritic cells (DCs) (1, 2). Due to the increasing appreciation in MS for the role of CD8+ T cells, also known as cytotoxic T lymphocytes (CTLs), we chose to further investigate whether cytolytic CTL responses can be modulated by HGF.

Methods
Effector CD8+ T cells from gp100-specific T cell receptor transgenic (Pmel-1) mice were generated in vitro. The phenotypic characteristics of CTLs were analyzed by flow cytometry. The cytolytic function of effector CD8+ T cells was examined using established models of CTL-mediated killing.

Results
We observed that HGF restrained the generation of effector cytotoxic CD8+ T cells from naïve splenocytes. Importantly, CTLs generated in the presence of HGF showed a lower level of cytolytic activity, as measured by specific in vitro and in vivo killing of antigen-pulsed target cells, including primary cortical cells. Mechanistically, HGF reduced the production of inflammatory cytokines and cytolytic enzymes by CTLs, including interferon-γ, tumor necrosis factor, perforin, and granzyme B. While HGF further lessened the expression of membrane-bound death receptor Fas ligand, a non-redundant lytic mechanism with cytolytic granule release in CTL-mediated killing. treatment of CD8+ T cells with concanamycin A, an inhibitor of the perforin-mediated cytotoxic pathway, abrogated CTL cytotoxicity indicating that blockade of the perforin-dependent killing is a major mechanism by which HGF diminished cytolysis of target cells. Of specific importance, similar results were obtained when HGF-treated DCs were cultured with naïve purified CD8+ T cells.

Conclusions
These results indicate that HGF limits the effector function of CTLs via DCs. Complementary to its impact on CD4+ T-cell CNS autoimmunity and myelin repair, our findings further suggest that HGF treatment could be exploited to control CD8+ T-cell-mediated, MHC I-restricted autoimmune dysfunctions such as MS.

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References
Extending the spectrum of anti-MOG antibody positive inflammatory CNS disease: Results from the Swiss Lupus Cohort Study

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Background
Myelin oligodendrocyte glycoprotein (MOG) has long been controversially discussed as potential autoantigen in multiple sclerosis (MS). Only recently, with the use of cell-based assays, we and others have shown that anti-MOG antibodies are indeed present in about 25% of children with MS and acute demyelinating encephalomyelitis (ADEM) and that antibody levels correlate with the disease course. More recently, we among others identified anti-MOG IgG (immunoglobulin G) in a subgroup of aquaporin-4 (AQP4)-seronegative patients with neuromyelitis optica spectrum disease (NMOSD) presenting with a distinct, more benign clinical phenotype as compared to AQP4-seropositive patients. The frequently observed coexistence of disease-specific anti-AQP4 IgG with other autoantibodies, including antinuclear antibody and antibodies to extractable nuclear antigens, in NMOSD patients raises the question of how the clinical syndrome of NMO correlates with a systemic rheumatologic disease in these patients. Previous studies investigating the relationship between NMOSD and systemic lupus erythematosus (SLE) have pointed towards an overlap syndrome between SLE and NMO in a subgroup of patients which is most likely caused by autoantibody-mediated demyelinating lesions rather than cerebral vasculitis. However, the target antigen(s) up to now remains elusive.

Methods
We analyzed the presence of anti-MOG IgG in a large, blinded, unbiased cohort of SLE patients from the Swiss Lupus Cohort (n=173) at baseline and follow-up. In addition, antibodies against AQP4, neurofascin and a variety of neuropil antibodies will be tested in all baseline samples.

Results
Of the 173 SLE patients included in the study, 15 patients (8.7%) were tested positive for anti-MOG IgG during the disease course with a female preponderance (12/15, 80%). Follow-up samples were available in 10 patients, of which 6 showed fluctuating antibody titers. 3 of the 15 patients developed antibodies during the disease course (after 3 and 5 years) and one patient lost the IgG at follow-up. The clinical and MRI data as well as the correlation to other autoantibodies tested will be presented at the meeting.

Conclusion
Anti-MOG IgG can be detected in a subgroup of SLE patients with and without apparent neurological deficits. Thus, anti-MOG IgG could serve as a potential biomarker to identify SLE patients with an overlapping demyelinating syndrome and possibly lead to a more targeted therapy (i.e. B cell depletion).
Comparison of subjective and objective adherence in patients with multiple sclerosis using RebiSmart™

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Aims
The RebiSmart autoinjector delivering subcutaneous (sc) interferon (IFN)-1a records objective adherence data and enables patients with multiple sclerosis (MS) to overcome factors leading to poor adherence. The aim of this study was to compare objectively recorded dosing history using RebiSmart with subjectively patient-reported adherence, and identify potential factors impacting therapy adherence in patients using RebiSmart.

Methods
A Swiss, multicenter, observational practice survey of MS patients treated with sc IFN-1a 44/22 μg using RebiSmart for 9 months. Primary endpoint was the difference between objective adherence measured using RebiSmart and subjective adherence captured by a patient questionnaire (one-way analysis of variance). Secondary endpoints: i) difference between objective adherence 9 months before baseline (retrospective) and 6 months after baseline (prospective, Wilcoxon matched pairs test); ii) questionnaire-based identification of potential dependent variables in patients with low (<90%), medium (90–99.99%), and high (>99.99%) objective adherence (ordinal regression). Self-reported adherence and non-adherence were defined as missing 0 and 1 injections, respectively, during 9 months preceding baseline. Data are mean±SD.

Results
53 of 56 patients (age 48.2±12.1 years; 22.6% male) completed the study. Objective adherence with RebiSmart in the self-reported compliant (n=33) and non-compliant groups (n=20) was 97.4±0.4% and 78.0±7.6%, respectively (p=0.001). Retrospective and prospective adherence measured with RebiSmart was 90.1±3.9% and 90.7±3.5%, respectively (p=0.75). Objective adherence was significantly associated with increasing age (low=42.3±12.0, medium=47.6±11.5, high=53.1±11.0; p=0.006) and Expanded Disability Status Scale (low=1.6±0.9, medium=2.2±1.4, high=2.7±1.2; p=0.006), neurologists’ estimations of adherence (low=8.5±2.3, medium=8.9±1.2, high=9.6±0.7; p=0.023), the importance of simplicity (low=8.3±1.5, medium=9.1±1.7, high=9.7±0.9; p=0.01), ease of storage (low=6.9±2.6, medium=7.3±2.8, high=8.7±1.7; p=0.032), and good information about RebiSmart features (low=9.5±0.7, medium=9.7±0.6, high=10±0.0; p=0.009).

Conclusions
MS patients in Switzerland using sc IFN-1a via RebiSmart had very high real-life treatment adherence. Objectively measured adherence was associated with both patient self-reported and neurologists’ estimated adherence. Older and more disabled patients tended to be more adherent to treatment.
Anti-Aβ passive immunization using encapsulated cell technology lowers brain amyloid burden and tau pathology: a novel delivery system applicable to disease prevention

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Aims
Passive immunization therapies with anti-Aβ monoclonal antibodies (mAbs) for Alzheimer’s disease (AD) have recently demonstrated evidences of clinical efficacy on biomarker and cognitive outcomes, when patients were treated in early AD. Data from different trials suggest that anti-Aβ therapy efficacy may be dose-dependent: low mAb regimens do not impact on AD biomarkers whereas higher dosage is associated with side effects such as vasogenic edema. Therefore, maintaining constant mAb levels in the therapeutic range and avoiding peak concentration due to iterative injections may optimize efficacy and tolerability. The implantation of engineered cells continuously secreting controlled levels of the mAb is an attractive approach, which could resolve practical drawbacks of passive immunization. However, it is critical to design systems to (i) achieve therapeutic mAb levels over the long term, (ii) facilitate the removal of grafted cells to interrupt the treatment if needed, (iii) transplant allogeneic cells to standardize the therapy for large cohorts of patients. Here, we address these questions using an ex vivo gene therapy strategy based on a novel encapsulated cell technology (ECT).

Methods
We engineered cell lines secreting high level of mAb-11, an anti-Aβ IgG2a or its f(ab)2 fragment. We designed a scalable ECT device dedicated to subcutaneous implantation that supports the long-term survival of grafted cells in allogeneic recipients. We implanted TauPS2APP AD mice for months with devices releasing therapeutic anti-Aβ mAbs. The Aβ and tau pathology was quantified at the end of experiments using immunohistochemistry, biochemical analysis and whole brain imaging.

Results
The implantation of mAb-11 secreting ECT devices allowed for the continuous delivery of anti-Aβ mAb over 10 months at 50 g/ml plasma levels. After ECT immunization the presence of mAb-11 or its fragment was detected on brain Aβ plaques. Moreover, mice treated with mAb-11 IgG2a had significantly less brain Aβ accumulation. Interestingly, we demonstrate that Aβ clearance was mediated through microglia activation. Additionally, those animals had also less hyperphosphorylated tau deposition.

Conclusions
We present a proof-of-concept study, based on the subcutaneous implantation of encapsulated anti-Aβ mAb-secreting cells. We propose encapsulated transplants of engineered cells as an alternative mode of antibody delivery applicable to the prevention of neurodegenerative disorders.
**GS 03**

**NeuroCAVE. Observational study on neurological complications of acute virus E infection.**

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**Background**

Hepatitis E (HEV) seroprevalence among blood donors in Switzerland is approximately 4-22%, being lower than in other European countries and especially in Southern France, where it can reach up to 40%. In most cases hepatitis E occurs subclinically. Since 2009 about 20 case reports on neurological complications such as neuralgic amyotrophy (NA) and/or Guillain-Barré syndrome (GBS) associated with acute HEV infection have been published. The clinical spectrum of NA is variable and although most NAs show monolateral involvement, bilateral brachial paresis can also occur. In the Netherlands two epidemiological studies have shown that 10% of NA patients and 5% of GBS patients had acute concomitant HEV infection. In the last 5 months in Ticino 15 cases of acute HEV infection have been diagnosed. In our neurological center we observed so far 4 cases of HEV-related NA.

**Aims**

The NeuroCAVE project aims at studying the prevalence of peripheral nervous system (PNS) damage in patients with laboratory proven acute HEV infection in Southern Switzerland. Clinical and electrodiagnostic features of HEV-associated NA during the 6-month follow-up period, the treatment response and possible risk factors associated with the host or the viral genotype will be analyzed. Methods. Patients with laboratory proven acute HEV infection (IgM+ or HEV RNA PCR+) diagnosed in Ticino in 2015 underwent detailed neurological examinations and electromyogram studies during the disease course.

**Results**

The NeuroCAVE study is still ongoing. Preliminary analysis indicates that all patients with HEV-associated NA were middle age males who ingested contaminated meat and were infected with HEV type 3, developing sudden neurological symptoms 4-6 weeks later. Amyotrophic bilateral asymmetric brachial paresis seems to be the most frequent neurological complication related to acute HEV infection.

**Conclusions**

Since his discovery in 1980s, hepatitis E was thought to be restricted to developing countries, but this notion has been recently challenged. Autochthonous infection of HEV 3 occurring in Europe and in Switzerland seems to be frequently associated with PNS damage.

**Acknowledgments**

Giorgio Merlani; Enos Bernasconi; Darius Moradpour; Rohland Sahli; Montserrat Fraga; Vincent Aubert; Roland Sahli.

**References**


GS 04
Ischemic preconditioning by recent TIAs and strokes in 2’730 consecutive stroke patients

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Background
Preconditioning improves acute ischemic stroke (AIS) outcome in animals, and possibly in humans. The influence on AIS of preceding ischemic events (PIE) such as TIAs and AIS occurring at different intervals, sites and for different durations can be studied in humans.

Methods
Using consecutive AIS from the ASTRAL registry we compared in univariate analysis the initial stroke severity (NIHSS) of patients who never had PIEs (controls) with those with with PIEs; in addition, associations of PIE on NIHSS at different time points before the index stroke, at various locations (PIE within or outside the territory of the subsequent AIS) and for different durations (PIE lasting <24h vs. >24h) were examined.

Results
In 2,730 consecutive AIS, there were 162 acute PIEs (of which 126 TIAs), 83 subacute PIEs (of which 57 TIAs) and 2’485 control patients. Admission NIHSS was significantly lower in the PIE group (median NIHSS = 7.44) compared to control patients (9.24) with a greater NIHSS reduction seen in patients with multiple PIEs (8.17) compared to a single PIE (8.45). Also within the PIE group, patients with TIA’s in the same territory (8.07) had a significantly lower NIHSS at admission than the control group; also, multiple TIA’s reduced the NIHSS (6.82) significantly. On interaction analysis, timing of PIE had little influence on its protective effect on admission NIHSS.

Conclusions
In patients with AIS, we found a beneficial effect of PIE occurring before a stroke, in particular if occurring in the same territory and if they were of short duration (TIAs). Also multiple PIEs display a beneficial dose effect, whereas the time of occurrence of a PIE does not seem to influence the resultant beneficial PIE effect. If these univariate are confirmed by multivariate analysis, these findings may be useful to plan further interventional trials on ischemic preconditioning in humans.
**Effects of Intervals and Sites of PIE on stroke severity**

- No PIE
- Acute PIE (<24 hours)
- Sub Acute PIE (day 2 to 7)

**Effect of duration of PIE on stroke severity**

- TIA only (n=125)
- TIA and Stroke (n=15)
- Stroke only (n=17)

Mean adm NIHSS
Recanalization therapies in acute stroke patients – impact of prior treatment with non-Vitamin K oral anticoagulants on bleeding complications and outcome

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Background
Atrial fibrillation is a major risk factor for ischemic stroke. Non-vitamin-K oral anticoagulants (NOAC) are at least as effective as Vitamin K-antagonists (VKA) in preventing ischemic stroke in patients with atrial fibrillation. It remains uncertain how patients with ischemic stroke while taking NOAC should be treated. We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in ischemic stroke patients on NOAC (last intake <48 hours) compared to patients (i) taking VKA or (ii) without prior anticoagulation (no-OAC).

Methods and Results
We designed a multicenter cohort pilot study of 25 international Stroke Centers. Primary outcome measures were (i) occurrence of ICH in three categories - any intracranial hemorrhage (ICHany), symptomatic ICH according to the criteria of the ECASS-II (sICH-CASS-II) and the NINDS thrombolysis trial (sICHNINDS); and (ii) death (at 3 months). Cohorts were compared by using propensity score matching. Our NOAC cohort comprised 78 patients treated with IVT/IAT and the comparison groups of 441 VKA-patients and 8938 no-OAC patients. The median time from last NOAC intake to IVT/IAT was 13 hours (interquartile range [IQR] 8–22h). In VKA-patients, median pre-IVT/IAT INR was 1.3 (IQR 1.1–1.6). ICHany was observed in 18.4% NOAC patients versus 26.8% in VKA patients and 17.4% in no-OAC patients. sICH-CASS-II and sICHNINDS occurred in 2.6%/3.9% NOAC patients, compared to 6.5%/9.3% of VKA patients and 5.0%/7.2% of no-OAC patients, respectively. At 3 months, 23.0% of NOAC patients compared to 26.9% of VKA patients and 13.9% of no-OAC patients had died. Propensity score matching revealed no statistical significant differences.
Conclusion
IVT/IAT in selected patients with ischemic stroke under NOAC treatment has a safety profile similar to both, IVT/IAT in patients on subtherapeutic VKA-treatment or in those without prior anticoagulation. However, further prospective studies are needed, including the impact of specific coagulation tests.
Anti-KIR4.1 reactivity in multiple sclerosis

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Background
Recently, antibodies against the inward rectifying potassium channel KIR4.1 have been described to be present in 47% of adult patients with MS and clinically isolated syndrome (CIS) and an even higher number of pediatric patients, but in none of the healthy controls, using an enzyme-linked immunosorbent assay (ELISA) with either full-length KIR4.1 protein or peptide (amino acids 83-120). Subsequent independent studies using peptide ELISAs or a cell-based approach have failed to replicate these findings. However, none of the studies used the methods as originally described.

Methods
We have carried out a large, blinded replication-study with 141 patients (multiple sclerosis, n=59, CIS n=82) and 131 controls (other (non-inflammatory) neurological diseases (OND) n=48, neurodegenerative diseases (ND) n=48, other inflammatory neurological diseases (OIND), n=35) using the same peptide and protein ELISA as originally described.

Results
Neither the KIR4.1 recombinant protein ELISA nor the peptide ELISA distinguished patients from controls. Moreover, there was no correlation between the reactivities in the two assays. Comparing reactivity against mock transfected and KIR4.1 transfected protein preparation in a subgroup of patients revealed that the reactivity was mainly directed against proteins that were co-purified with KIR4.1. This was corroborated by additional characterization with western blot and mass spectrometry.

Conclusion
In our study, using the exact same techniques as originally described, we could not detect differential antibody reactivity to KIR4.1 between patients and controls. This might either be due to the absence of KIR4.1 autoantibodies or to the non-specificity of the assay. Thus, at this point, we do not consider KIR4.1 to be a valuable biomarker for diagnosing MS.

References
Development of a CNS in vitro model based on induced pluripotent stem cells derived from blood of multiple sclerosis patients

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Aim
In multiple sclerosis (MS), the mechanisms involving the interactions between the immune system and the central nervous system (CNS) are still poorly understood. This situation is partly due to the limited access to MS patients CNS samples. To overcome this issue, we propose to build an in vitro model based on induced pluripotent stem cells (iPSC) derived from blood cells of MS patients. These iPSC will be differentiated into neurons, astrocytes and oligodendrocytes to study the effects of the immune system of MS patients on autologous CNS cells.

Methods
Peripheral blood mononuclear cells (PBMC) are nucleofected with episomes coding for transcription factors OCT3/4, SOX2, KLF4, c-Myc and LIN28 (Yamanaka cocktail) and cultured in conditions adapted to iPSC cell culture. Stable and characterized iPSC cultures that can be differentiated into neural stem cells (NSC) are obtained after 5-6 months. NSC are differentiated by culturing iPSC colonies in neural induction conditions and expanded by addition of basic fibroblast growth factor and epithelial growth factor. To generate neurons, NSC are cultured with brain-derived neurotrophic factor and terminally differentiated by removal of all growth factors. For differentiation in astrocytes, NSC are cultured with ciliary neurotrophic factor or bone morphogenic protein 4.

Results
Up to now, we have generated at least 5 iPSC clones from PBMC of each of the 6 subjects enrolled (5 MS patients and 1 healthy control). These iPSC formed typical homogenous round-shaped colonies composed of small round cells, expressed pluripotency markers and had the capacity to differentiate into the 3 embryonic germ layers. Neurons as identified by a typical neuronal morphology, an dendrite network, and a MAP2 staining were 90% pure. Astrocytes are recognized by their star-like morphology and positive GFAP staining. Up to now, the maximal degree of purity was 46%.

Conclusion
These preliminary data show that it is possible to derive CNS cells from the PBMC. We are currently working on improving the degree of purity of astrocytes cultures to reach >90% GFAP+ cells, as well as developing the technique to obtain oligodendrocytes. Once fully developed, this “brain in a dish” system will be of a high value to study the interactions between autoreactive immune T cells and autologous CNS cells. This model should also serve as a pre-clinical screening assay to evaluate the neuroregenerative potential of candidate compounds in humans.
Mechanisms distinct from those used by CD4+ TEM cells regulate CD8+ TEM cell migration across the blood-brain barrier under flow conditions in vitro

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T cell trafficking into the central nervous system (CNS) is a crucial step in the pathogenesis of multiple sclerosis (MS) and is controlled by the highly specialized endothelial cells forming the blood-brain barrier (BBB). The molecular mechanisms mediating the multi-step extravasation of CD4+ effector T cells across the BBB are well described. Although there is accumulating evidence for an involvement of CD8+ T cells in MS pathogenesis it remains to be shown if they use similar or different cues from CD4+ T cells for crossing the BBB. To do so, we used primary mouse brain microvascular endothelial cells (pMBMECs) as an in vitro model of the BBB. A homemade flow chamber combined with a high magnification live cell imaging allowed us to visualize the interaction of CD8+ TEM with the BBB. By side by side comparing the interaction of CD8+ TEM cells versus CD4+ TEM cells with the BBB under physiological flow in vitro, we could observe that CD8+ TEM cells arrested almost 3-fold better than CD4+ TEM cells on pMBMECs under non-inflammatory and inflammatory conditions. Assessment of the dynamic behavior of these arrested T cells revealed that while for CD4+ TEM cells diapedesis required prior crawling, the vast majority of CD8+ TEM cells remained stationary before crossing. Diapedesis of CD8+ TEM cells was 2-fold higher than that of CD4+ TEM cells. Interestingly, while CD8+ TEM cells preferentially crossed the endothelium via a transcellular pathway, CD4+ TEM cell diapedesis was mostly observed via the the paracellular pathway. On pMBMECs lacking ICAM-1 and ICAM-2 arrest of CD8+ TEM cells was almost abolished while the arrest of CD4+ TEM was not significantly affected. Lack of ICAM-1 and ICAM-2 also led to a defect in crawling of both cells. Nevertheless, CD8+ TEM cells were still able to cross the BBB better than CD4+ TEM cells. In contrast to CD4+ T cell migration, Ag cross-presentation by brain endothelium may influence the migration of CD8+ T cells. We then have started to study the role of Ag presentation by the endothelium in mediating CD8+ TEM cell diapedesis focusing on defining which step of the multi-step process might be affected. Our study highlights that cellular and molecular mechanisms mediating CD8+ TEM cell extravasation across the BBB are distinct from those regulating CD4+ TEM cells in vitro. This opens new possibilities for subset-specific therapeutic targeting of T cell migration across the BBB during neuroinflammation like MS.
Characterisation of cells present in cerebrospinal fluid of MS patients and controls using Time-of-Flight mass cytometry

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Background
A central feature of multiple sclerosis is the presence of immune cells in the brain, which are likely to be involved in the disease’s debilitating pathology. A better understanding of these cells therefore promises to be valuable in understanding the disease. Since cells in the brain parenchyma are generally inaccessible to examination, the most closely related population, i.e., those found in the cerebrospinal fluid (CSF), are important targets for investigation. This requires techniques to maximise the amount of information obtained from small numbers of cells, and one attractive candidate is the recently developed cytometry by time-of-flight (CyTOF), which simultaneously can measure more than thirty phenotypic properties on each cell.

Aim
The aim of the project was to develop a CyTOF protocol to measure the frequencies and phenotypes of T cells in CSF and in peripheral blood.

Methods
Peripheral blood and CSF were collected during routine diagnostic procedures from informed, consenting individuals. Mononuclear cells (PBMCs) were separated from blood by density gradient centrifugation, and CSF cells by centrifugation. PBMCs and CSF cells were separately prelabelled to enable separation of the two populations, then mixed, fixed, permeabilized and labeled with lanthanide isotope-conjugated antibodies against a panel of markers (including HLA-DR, CD3, CD4, CD8, CD11b, CD11c, CD14, CD16, CD20, CD27, CD45RO, CD56, CD138, IgM, BAFFR, MCAM, CCR5, FoxP3, Tbet, CD14, CD11b, CD16, BAFFR, CD11c, CD45RO, CD27, HELIOS, GM-CSF, IgM, IL-4, IL-17A, IFNγ, MCAM, TNFa, GM-CSF, CCR5, CD138, IL-17A, CD45). To examine cytokine production, cells were stimulated with phorbol ester and ionomycin for 3 h in the presence of protein transport inhibitors, then fixed and labeled. Lanthanide-labels were detected by CyTOF and data analysed using Cytobank software.

Results
3,000 to 20,000 CSF cells were obtained from each patient, and more than twenty constitutively expressed antigens could be reliably labelled and measured simultaneously on these cells. Using the SPADE algorithm from Cytobank, all relevant immune cell populations could be identified. Establishment of a protocol for cell activation and intracellular cytokine labeling of CSF cells is ongoing.

Conclusion
CyTOF offers a promising approach to detailed phenotyping of the small numbers of cells found in CSF; further work is needed to enable the characterisation of their cytokine profiles.
Increased ex-vivo antigen presentation profile of B cells in multiple sclerosis

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Aims
Multiple sclerosis (MS) is thought to be triggered by environmental agents such as Epstein-Barr virus (EBV) in genetically-susceptible persons, a combination which will lead to autoimmunity but the precise mechanism remains enigmatic. Few studies have examined whether the innate immune response is dysregulated in MS patients. Here, we proposed to examine what stands upstream from T cell activation studying in detail the phenotype and activation level of different antigen-presenting cells (B cells and monocytes).

Methods
We enrolled 98 study subjects including patients suffering from relapsing-remitting (RR), secondary-progressive (SP), primary-progressive (PP) MS, other inflammatory neurological diseases (OIND) and healthy controls (HC). On the day of blood draw, monocytes and B cells were isolated and their ex vivo profile of activation, as reflected by surface expression of CD40, CD80, CD83, CD86, and HLA-DR was assessed by flow cytometry. Cells were then stimulated overnight using either specific ligands of toll-like receptors (TLR) 1 to 9 or EBV particles. Cytokine and chemokine secretion profiles (GM-CSF, IFN-a, IL-1a, IL-1b, IL-6, IL-10, IL-23p19, TNF-a) were finally assessed by Luminex assay in recovered supernatants. Following log- or rank-transformation of the measured values, differences among groups and stimulations were assessed in a linear model framework, adjusting for age and gender.

Results
We demonstrate that MS patients exhibit a significant increased expression of HLA-DR and CD40 at the surface of monocytes, and mostly of B cells, especially during relapses. No such increase of HLA-DR or CD40 was seen in OIND patients. Interestingly, this phenotype is associated with a decreased basal secretion of IL-6 and TNF-a by B cells of RR-MS, and of IL-1b by monocytes of SP and PP-MS patients. Upon stimulation, there is a rescue of the level of these cytokines, which reach similar levels in all conditions tested.

Conclusions
These data clearly suggest that the antigen presentation function of B cells and to a lesser extent of monocytes as well as their cytokine content is dysregulated in MS, but with different profiles depending on the stage of the disease.

Acknowledgment
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Longitudinal analysis of topographic VEP in relapsing-remitting patients with multiple sclerosis

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Background
Visual evoked potentials (VEP) are used to evaluate therapies aiming at remyelination in multiple sclerosis (MS) (Cadavid et al. AAN 2015). Topographic VEP analysis is more sensitive than conventional VEP when the configuration is pathologically altered since the P100 component is determined automatically (Hardmeier et al. 2014).

Objective
To evaluate whether topographic VEP measures can detect subclinical change in MS eyes with and without previous optic neuritis (ON).

Methods
57 relapsing-remitting MS patients (median age: 39 years, median EDSS: 2.0, interquartile range: 1.5-3.0) and 32 healthy controls (HC) had VEP at years 0, 1 and 2 using an 204 electrode array during full-field checkerboard stimulation. The topography of the field distribution was used to determine the P100 component in relation to a reference topography yielding a latency (Lat), amplitude (Amp) and correlation (Fit) measure for left (L) and right (R) eyes.

Results
Cross-sectional comparisons between HC and MS eyes with previous ON (MS-ON; n=16 L, n=17 R) and without (MS-nON) showed similar results at all time points: Lat discriminated best between groups (median value over years 0-2 and both eyes, HC: 104ms, MS-nON: 112ms, MS-ON: 134 ms; p<0.0001 for all comparisons), Fit (HC: 0.96, MS-nON: 0.94, MS-ON: 0.87; p-value range: not significant to p<0.0001) and Amp (HC: 1.43, MS-nON: 1.17, MS-ON: 0.80; p<0.05 to p<0.01) to a lesser extent. Test-retest-reliability in HC was highest for Lat (intra-class-correlation coefficient [ICC]: 0.91 R, 0.95 L) and Amp (ICC : 0.80 R, 0.83 L) but poor for Fit (ICC : 0.56 R, 0.51 L). Repeated measures ANOVA showed change over time in MS-ON (Fit R, p<0.01); however, visual acuity, EDSS as well as VEP Lat and Amp remained stable.

Conclusion
Topographically determined P100 latency is reliable and valid but reveals no change over two years in this clinically stable cohort of MS patients. The change in the topographic correlation measure (Fit) in eyes with previous ON over time may relate to subclinical changes ; however, this has to be confirmed by longer follow-up. The main advantage of topographic analysis lies in an automated determination of the P100 component and may yield additional VEP descriptors.
P07
Intensity-dependent impacts of exercise on cognitive functions in multiple sclerosis – preliminary results of a randomized controlled trial

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Background
The influences of exercising on cytokine response, cardiorespiratory and cognitive functions are important aspects of rehabilitation in persons with multiple sclerosis (pwMS) but have not been systematically investigated. Recent data study show positive connections between elevated neurotrophin concentrations, induction of neuroplasticity, recovery of the motor and cognitive functions and the applied training intensities in pwMS.

Objective
This study determines the immune response of neurotrophic factor BDNF and cognitive functions to 3-weeks of endurance training conducted a cycle ergometer and progressive resistance training. The main objectives are to (a) investigate whether intensive exercise has similar effects on growth factor BDNF, cognitive functions and cardiorespiratory fitness than normal exercise and to (b) examine which modality is more effective at affecting immune and cognitive functions in pwMS.

Methods
A randomized controlled clinical trial is conducted in 80 MS patients (Expanded Disability Status Scale range 1.0–6.5) however here only results of 20 pwMS are presented. Resting serum levels of brain-derived neurotrophic factor (BDNF) and the concentrations in response to cardiopulmonary exercise test (CPET), fatigue and cardiorespiratory values were determined at entry and discharge. Cognitive functions are assessed with the German version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and additionally, the German version of the Trail-Making-Pencil-Test versions A/B (TMT-A/B) were used. Cognitive assessments were performed at baseline (t1) and repeated at t2. Participants were allocated into a group that performed intensive (IT) or normal training (NT). Groups differ by means of frequency and the intensity of the training session. IT has less sessions that are attuned (3 active versus 3 passive). Daily training session sum-up to six in the IT and eight in the NT. NT is the conventional training performed in the Valens clinic.

Results
BDNF show significant differences between groups over the training intervention. Within NT BDNF resting and post-CPET concentrations (p<0.05) show a significant increase after the training intervention. Short-term effects on BDNF (CEPT) tended to increase at the start and significantly thereafter (p<0.05). No changes occurred in the NT group. Cognitive functions show time effects on the BVMT-R of the BICAMS over the training intervention Cardiorespiratory fitness improved significantly over time within both groups.

Conclusion
This study indicates that intensive exercise activates BDNF regulation and can be an effective training modality in pwMS.
P08
Time to relapse and disability progression in a long-term cohort of people with clinically isolated syndrome and relapse-onset multiple sclerosis treated with disease-modifying drugs: a prospective nationwide survey in Switzerland

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Background
The efficacy of disease modifying drugs (DMDs) to prevent relapses in relapsing-remitting multiple sclerosis (RRMS) has been shown in numerous Phase-III trials. However, the long-term effect on disability progression is still a matter of debate.

Aim
To determine time to relapse and disability progression in a large long-term MS cohort treated with DMDs.

Methods
Analysis of data from the Swiss Federation for Common Tasks of Health Insurances (SVK) that includes standardised annual information on diagnosis, disease onset, relapses and neurological status assessed using the Expanded Disability Status Scale (EDSS) of about 80% of all MS patients treated with DMDs in Switzerland. The case record forms provided by the treating neurologists were reviewed for completeness and internal plausibility and queries about missing or inconsistent data were issued by the SVK under the supervision of an independent physician. EDSS progression was defined as 1 step if EDSS was 5.0 and 0.5 if EDSS was 5.5 confirmed at two consecutive annual evaluations. Patients who switched or discontinued treatment before confirmation of the EDSS change were censored. Hazard ratios were propensity-score adjusted for clinically relevant baseline characteristics including age, gender, disease duration, disease subtype, EDSS at treatment start and time of DMD introduction.

Results
From 1995 to 2010, 8044 patients were included in this study: 472 clinically isolated syndrome, 6832 RRMS, 740 secondary-progressive MS (SPMS); mean age 39.6±11.3, disease duration 7.15±8.01 years, annualised relapse rate 0.91±0.66 [based on the two antecedent years], median EDSS at treatment start 2.5 (range 0-8), mean time of follow-up 4.4±3.94 years. In the year prior to treatment start, 16.6% of the patients were relapse-free. This proportion increased after one year of treatment to 60.6% similar across the treatment groups. After 10 years on DMD treatment, 15.1% of the patients had still relapses. Median time to confirmed EDSS progression was 7.92 years (interquartile range [IQR] 7.68-8.74) in RRMS and 4.96 years (IQR 4.33-5.97) in SPMS calculated from treatment start. In a propensity-score adjusted analysis, both the median time to relapse and confirmed EDSS progression was similar across the treatment groups.

Conclusions
In this comprehensive and large long-term MS cohort, time to relapse and confirmed EDSS progression was similar across interferon-beta products and glatiramer acetate.
P09
Correlation of Nine Hole Peg Test and MS related corticospinal tract damage assessed by the triple stimulation technique

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Introduction
Demyelinating lesions in Multiple sclerosis (MS) can affect the corticospinal tract and lead to motor impairment of the upper extremity (UE). UE function is usually evaluated using clinical assessments such as the Nine Hole Peg Test (9HPT). Impairment of the corticospinal tract can be electrophysiologically assessed using the triple stimulation technique (TST).

Aim
We aimed to assess the relationship between performance on the 9HPT and corticospinal tract damage as assessed by TST.

Methods
We performed 9HPT and TST in patients with MS on both arms. Pearson correlation (r) was used to investigate the relationship between 9HPT and TST. Correlation was assessed for left and right arm separately.

Results
We examined 45 MS patients (29 RRMS, 14 SPMS, 2 PPMS, Median EDDS 3.5 (1.5 – 7.0), Mean age 49.0 years (23-72). Results of the 9HPT ranged from 15.5 sec – 107 sec (left arm) and from 14.55 sec - 55.7 sec (right arm). We found a correlation between 9HPT and central motor conduction time (CMCT) for both arms (Pearson correlation left: r=0.53, p<0.001; right: r=0.52, p<0.001). The proportion of activated motor units and performance in the 9HPT was negatively correlated: (Left: r=-0.38, p=0.008; Right: r=-0.52, p<0.001).

Conclusion
In MS patients performance on the 9HPT is related to corticospinal tract damage as reflected by prolonged CMCT and a reduced number of activated motoneurons. The lower correlation between performance in the 9HPT and proportion of activated motor units might be related to the patients handedness as 93% of the patients were right hander. Performance of the non-dominant hand in the 9HPT is worse in healthy people and may have lower susceptibility for loss of neurons of the corticospinal tract.
P10
Spinal cord gray matter atrophy – a biomarker for MS progression

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Aims
In Multiple Sclerosis (MS) cerebral gray matter (GM) atrophy correlates more strongly with disability than does white matter (WM) atrophy. Advances in phase sensitive inversion recovery (PSIR) imaging now enable specific assessments of the spinal cord (SC) GM and WM. The goal of this study was to assess GM and WM areas in the cervical and thoracic SC and their relationship with disability and disease type in MS.

Methods
142 MS patients (25–75 years, 86 women) and 20 controls were scanned at 3T. Axial 2D- PSIR images were acquired at the disc levels C2/3, C3/4, T8/9 and T9/10. Total cord areas (TCA) were segmented semi-automatically. SC GM areas were segmented manually. Differences in areas between groups were assessed with age and sex as covariates. The relative contribution of demographics, clinical characteristics, and PSIR-derived measures to Expanded Disability Status Scale (EDSS) variability were investigated using analyses of relative importance of regressors in a linear model. Receiver operating characteristic (ROC) curves were compiled to assess sensitivity and specificity for predicting a progressive disease course based on the variables with the highest contribution to EDSS.

Results
In the cervical and thoracic SC relapsing MS patients had significantly smaller GM areas than controls (p< 0.001 at C2/3; p=0.003 at T8/9; p=0.011 at T9/10), but had no significant difference in either the SC WM area or TCA. Progressive MS patients showed smaller GM areas (p< 0.001 at all levels) and TCAs (p< 0.001 at C2/3, C3/4, T8/9; p=0.004 at T9/10) compared to relapsing MS patients. In multivariable models (including SC WM areas and T2-lesion number, brain WM volumes, T1- and FLAIR-lesion loads, age, sex, disease duration) cervical SC GM area had the strongest correlation with EDSS followed next by thoracic SC GM area and brain GM volume. The areas under the ROC curve were 0.68, 0.84 and 0.87 for the prediction of a progressive course based on logistic models with 1) brain GM volume, 2) cervical GM area and 3) cervical, thoracic GM areas and brain GM volume as predictors, respectively.

Conclusions
This study provides evidence for the clinical impact of cord GM atrophy in MS, as measured in vivo by PSIR imaging. GM atrophy is detectable at multiple cord levels in the absence of WM atrophy in relapsing MS. It is more pronounced in progressive MS than relapsing MS and contributes more to patient disability than SC WM or brain GM atrophy.

Disclosures
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The Swiss Multiple Sclerosis Registry (SMSR): a citizen science platform for MS research

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Aims

Multiple Sclerosis (MS) disease management requires active involvement of persons with MS (PwMS), families, and caregivers. It also depends on a well-organized interplay of health care professionals. However, in Switzerland there is a widely recognized lack of information and high quality evidence on disease epidemiology, long-term efficacy and safety of disease-modifying drugs, access to and uptake of MS treatments and care, or needs and preferences of PwMS.

Methods

The Swiss Multiple Sclerosis Registry (SMSR) is based on an initiative of the Swiss MS Society. It is a patient-centered, nationwide, longitudinal study that will be open to all adult PwMS living in Switzerland. Enrollment will start in early 2016. The SMSR takes a citizen science approach: it attempts to involve PwMS not only as study subjects but also as MS experts, whose opinions and experiences are valued. Other notable features of the SMSR are the flexible study design that allows participation at different commitment levels (i.e. from one-time surveys to longitudinal data collections), the ownership of data by registry participants (who will have access to their own data), and the possibility to include participant-provided, unstructured information such as medical reports. Main scientific objectives of the registry entail:

1. to estimate the prevalence of MS in Switzerland and to monitor epidemiologic trends over time, 2. to estimate the burden of MS for PwMS and families or proxies, and 3. to establish a flexible infrastructure and a network that enables and facilitates interdisciplinary research with all interested partners. Participation will be possible by paper questionnaire or by data entry into a newly designed online platform. This platform will also offer MS disease management tools for PwMS and physicians (e.g. life charts). Surveys will cover a wide range of topics on disease history, circumstances of living, mental health, MS treatment (drug and non-drug), or coping with MS. In addition to patient-reported survey outcomes, the SMSR will further collect clinical data through medical record abstractation.

Conclusions

The SMSR will be a unique addition to the Swiss and the European MS research landscape for its innovative design and strong involvement of PwMS and their relatives in data collection and research agenda design. Thereby, it will complement other ongoing longitudinal Swiss research efforts, with which the SMSR will seek close collaborations and interaction.

Acknowledgement

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The French version of the Multiple Sclerosis Questionnaire for Physiotherapists: a reliable and valid method for the evaluation of the treatment of persons with MS

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Objectives
To improve the quality of physiotherapeutic intervention of persons with MS, the Specialized Group Physiotherapy in MS of Physioswiss has developed the Multiple Sclerosis Questionnaire for Physiotherapists (MSQPT), a disease-specific self-rating questionnaire. This study evaluates the psychometric properties of the French version of the MSQPT.

Method
The German MSQPT was translated using the same procedure as the transcultural adaptation of the SF-36 into different languages. The quality of the translation, the reliability and validity of the French version and the acceptance by physiotherapists were evaluated. The survey was conducted in the French speaking part of Switzerland. Patients (pretest n=5, validity testing n=31, test-retest reliability n=16) were recruited in private practices, hospitals and rehabilitation centers. The intervention used the MSQPT and the SF-36. Furthermore the self-administered EDSS score was determined. The treating physiotherapist filled out a questionnaire to estimate the acceptance of the MSQPT.

Results
The rating of clearness, everyday speech and conformity of concept of the translation was high for most items except for one. It was excluded from the French MSQPT. The final MSQPT did not show any other problem in the pretest and was used for the validation survey. The quality of the validation data was high. The survey denoted few missing data (MSQPT 0.64%, test-retest 0.09%, SF-36 0.77%). The survey is not representative for the Swiss MS population (48% woman). Validity: The criterion validity between the MSQPT and the SF-36 was high (activity r=0.85, participation associated factors versus social functions, vitality and well-being r=0.47-0.74, pain r=0.64). Reliability: The French MSQPT has an overall intern consistency of 0.84 (Cronbach ). The two main groups have a Cronbach of 0.82 and 0.87. Many items have a high test-retest reliability. The activity group and the total score have a very high reliability(r=0.93 resp. 0.95). The participation group has a low reliability score (r=0.66). The MSQPT has a very high acceptance and was rated as simple, comprehensible, efficient, not time-consuming and very useful.

Conclusion
The French MSQPT is a well translated questionnaire of high quality. Its psychometric properties are good and comparable to the original German version. The results suggest that the French MSQPT can be used in the evaluation of the physiotherapeutic treatment of MS patients.
Patient Reported Questionnaire in MS rehabilitation: Testing Responsiveness and Minimal Important Difference of the French Version of the Multiple Sclerosis Questionnaire for Physiotherapists

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Objectives
The Multiple Sclerosis Questionnaire for Physiotherapists (MSQPT) is a German PRO questionnaire for the evaluation of the rehabilitation of persons with MS. The focus of this study is the evaluation of the responsiveness and Minimal Important Difference of the French version of the MSQPT.

Method
We used a combined anchor and distribution based approach with multiple anchors and multiple transition questions. The intervention (n=31) included the French MSQPT, the French Version of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS), the self-administered EDSS, 6 Meter Timed Walking Test (6TWT), Berg Balance Scale (BBS) and the 6 Minute Walking Test (6MWT). Responsiveness was evaluated using ES, SRM and Modified SRM. The distribution based estimates 0.33, 0.5 SD, SEM, MDC90 and MDC95 were calculated to evaluate the MID that were established for the German MSQPT. The specificity of the MID and the correlation between the physical tests and the items and groups of the MSQPT were determined. The relative efficiency between the French MSQPT and HAQUAMS was estimated.

Results
The main ES for deterioration lay between 0.41 and 0.93 and for improvement between 0.42 and 1.23. The SRM are generally higher than the ES (deterioration 0.89 to 2.14, improvement 1.08 to 2.14). Main Modified SRM range 0.03 to 0.31 and are acceptable. The specificity of the MID range from 0.25 to 0.83. Comparing responsiveness of the German and the French MSQPT, the data is not unambiguous, but in general the differences between estimates are small. The correlations between BBS and 6 MWT and the items and groups of the MSQPT are reasonable to high (0.51 to 0.74). The French MSQPT seems to be more efficient than the French HAQUAMS in detecting improvement but less in finding deterioration.

Conclusion
Due to the small sample size (n=31) the significance of this survey is limited. The available evidence indicate that the French MSQPT is a responsive PRO questionnaire, with similar psychometric characteristics as the original German MSQPT. The French MSQPT has adequate MID that may be used as thresholds for change in the physiotherapeutic treatment of persons with MS.
Multiple sclerosis (MS) is a common autoimmune disease with an underlying T cell-based etiology. Particularly T helper (TH) cell differentiation and cytokine production are critical mechanisms in the pathogenesis of MS. After the initial discovery of distinct TH1 and TH2 cell subsets that produce interferon-γ and IL-4 respectively, numerous additional polarization patterns (TH9, TH17, TH22, TFH) have been proposed. The exact identity of the TH cell polarization pattern and the responsible cytokines underlying MS pathology have been the focus of intense research for several decades, however these questions still remain unresolved. The aim of this study is to reveal the breadth of cytokine production profiles, chemokine receptor and activation marker expression of the entire TH cell landscape in MS. More specifically, we employ the recently developed mass cytometry technology for which we developed a 42 parameter panel to determine the exact identity of the MS-associated TH cell polarization pattern. To analyse those high-dimensional cytokine expression patterns in an unbiased manner, we apply unsupervised dimensionality reduction algorithms (t-SNE) followed by automatic classification (ACCENSE). In a next step, we currently apply this approach to peripheral leukocytes from healthy individuals in order to obtain a composite picture of the degree of cytokine co-production by TH cells in an unprecedentedly high-dimensional space. Finally, we plan to compare those TH cell landscapes from control and MS patients in various stages of disease. Therefore, we will employ algorithms performing automated identification of stratifying cellular subpopulations (citrus). Together, this analysis could thus indicate the chemokine receptor and cytokine expression profile of the true pathogenic T cell thus resolve longstanding controversies about the relative importance of different cytokines in MS.
P15

Claudin 3-deficient C57BL/6 mice display intact brain barriers

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During neurological disorders such as multiple sclerosis (MS) or its animal correlate experimental autoimmune encephalomyelitis (EAE), focal loss of blood-brain barrier (BBB) integrity is observed and associated with the formation of inflammatory lesions as visualized by gadolinium-enhanced magnetic resonance imaging (MRI). Claudin-3 is localized to tight junctions (TJs) of the endothelial blood-brain barrier (BBB) and the epithelial blood-cerebrospinal fluid barrier (BCSFB). A specific contribution of claudin-3 in BBB integrity has been suggested by its selective loss in microvessels surrounded by inflammatory infiltrates in EAE. Additionally, claudin-3/-/- mice on a mixed genetic background have recently been shown to develop aggravated EAE due to increased leakiness of the BCSFB. This prompted us to study EAE in the homogenous genetic background of C57BL/6 mice. To this end we have generated claudin-3/-/- mice and after their backcrossing for 10 generations on the C57BL/6 background studied EAE pathogenesis. To our surprise we did not observe any significant difference in disease development in Claudin-3/-/- C57BL/6 mice when compared to their WT littermates. These studies were accompanied by investigations on the barrier properties of the BBB and the BCSFB. Measuring transelectrical resistance and permeability of small and large molecular tracers across the BBB and the BCSFB in vitro and in vivo revealed no difference in barrier properties of WT or claudin-3/-/- C57BL/6 mice. Taken together, our results demonstrate that absence of claudin-3 in C57BL/6 mice does not impair brain barrier properties during health and autoimmune neuroinflammation.
Reprogramming inflammatory monocytes by antibodies to colony-stimulating factor 1 receptor prevents sickness behavior in inflammatory diseases

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Sickness behavior syndrome (SBS) as characterized by fatigue and depression impairs quality of life in patients with autoimmune and infectious diseases. Inflammation in mice induced by agonistic CD40 antibodies leads to SBS, which at sites of inflammation is associated with influx of Ly6Chigh monocytes and loss of the F4/80high macrophages and Ly6Clow monocytes. The aim of the study presented here is to test whether neutralization of colony-stimulating factor 1 receptor (CSF1R) protects from CD40 mediated SBS.

Results
Antibodies to CSF1R depleted the subset of CD11b+Ly6CnegCD115+ macrophages and CD11b+Ly6C+F4/80high macrophages, but polarized CD11b+Ly6Chi inflammatory monocytes to a mixed phenotype with increased TNF and IL-10. This immune phenotype was associated with protection of mice from SBS. Discussion: The increased expression of IL-10 in CSF1R antibody treated mice overrides the negative effects of pro-inflammatory cytokines on behavior and body weight. These data provide a major conceptual advance in understanding the molecular and cellular events leading to SBS.
Sterile inflammation in MS: Induction of cytokine production in human monocytes by T cell surface bioactive lipids

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Aims
Imbalance in cytokine homeostasis plays an important part in the pathogenesis of MS. Stimulated T cells display pathological effects through direct cellular contact with monocytes/macrophages, inducing a massive up-regulation of interleukin-1 (IL-1) and tumor-necrosis factor (TNF) in the latter cells. This suggests the presence of activating factors at the surface of stimulated T cells. Our recent results demonstrated the lipidic nature of these factors. The aim of our work is to characterize T cell bioactive lipids referred to as SAFT (surface activating factors on stimulated T cells).

Methods
Total lipids extracted from membranes of stimulated and unstimulated HUT-78 cells were subjected to serial solid phase extraction on 3 different types of cartridge. Lipid fraction activity was assessed on isolated human monocytes by measuring induction of IL-1 and its inhibitor IL-1Ra. Fractions were analyzed by high resolution mass spectrometry (MassSpec) on QExactive™ Hybrid Quadrupole-Orbitrap Mass Spectrometer. Lipid composition of active fractions generated from membranes of stimulated HUT-78 cells was compared to that of fraction obtained from unstimulated HUT-78 cells.

Results
Preliminary results ruled out the participation of acyl sphingolipid species, sterols, sterol esters, ether lipids, and neutral fatty acids in SAFT activity. The primary MassSpec analysis showed that 1421 m/z were increased more than 2 times in stimulated as compared to unstimulated HUT-78 cells. The comparison of lipids enhanced in active fractions of stimulated HUT-78 cells and absent in inactive fractions as well as in fractions isolated from unstimulated HUT-78 cells resulted in 6 putative lipid m/z which might display SAFT activity. None of the latter corresponded to a lipid in the LIPIDMAPS data base, i.e. the largest available lipid data base (www.lipidmaps.org). However, lipid data bases are currently under construction and thus do not contain all possible natural lipids. To circumvent this hurdle, the 6 m/z identified are currently subjected to fragmentation to obtain better insights into their structure.

Conclusions
Our current results demonstrate that upon stimulation, surface lipids of stimulated T cells are modified and in turn display the ability to induce cytokine production in human monocytes. The identification of these lipids might open the way to new therapeutic approaches in MS.

Acknowledgments
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Comparison of subjective and objective adherence in patients with multiple sclerosis using RebiSmart™

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Aims
The RebiSmart autoinjector delivering subcutaneous (sc) interferon (IFN) -1a records objective adherence data and enables patients with multiple sclerosis (MS) to overcome factors leading to poor adherence. The aim of this study was to compare objectively recorded dosing history using RebiSmart with subjectively patient-reported adherence, and identify potential factors impacting therapy adherence in patients using RebiSmart.

Methods
A Swiss, multicenter, observational practice survey of MS patients treated with sc IFN -1a 44/22 g using RebiSmart for 9 months. Primary endpoint was the difference between objective adherence measured using RebiSmart and subjective adherence captured by a patient questionnaire (one-way analysis of variance). Secondary endpoints: i) difference between objective adherence 9 months before baseline (retrospective) and 6 months after baseline (prospective, Wilcoxon matched pairs test); ii) questionnaire-based identification of potential dependent variables in patients with low (<90%), medium (90–99.99%), and high (>99.99%) objective adherence (ordinal regression). Self-reported adherence and non-adherence were defined as missing 0 and 1 injections, respectively, during 9 months preceding baseline. Data are mean±SD.

Results
53 of 56 patients (age 48.2±12.1 years; 22.6% male) completed the study. Objective adherence with RebiSmart in the self-reported compliant (n=33) and non-compliant groups (n=20) was 97.4±0.4% and 78.0±7.6%, respectively (p<0.001). Retrospective and prospective adherence measured with RebiSmart was 90.1±3.9% and 90.7±3.5%, respectively (p=0.75). Objective adherence was significantly associated with increasing age (low=42.3±12.0, medium=47.6±11.5, high=53.1±11.0; p=0.006) and Expanded Disability Status Scale (low=1.6±0.9, medium=2.2±1.4, high=2.7±1.2; p=0.006), neurologists’ estimations of adherence (low=8.5±2.3, medium=8.9±1.2, high=9.6±0.7; p=0.023), the importance of simplicity (low=8.3±1.5, medium=9.1±1.7, high=9.7±0.9; p=0.01), ease of storage (low=6.9±2.6, medium=7.3±2.8, high=8.7±1.7; p=0.032), and good information about RebiSmart features (low=9.5±0.7, medium=9.7±0.6, high=10±0.0; p=0.009).

Conclusions
MS patients in Switzerland using sc IFN -1a via RebiSmart had very high real-life treatment adherence. Objectively measured adherence was associated with both patient self-reported and neurologists’ estimated adherence. Older and more disabled patients tended to be more adherent to treatment.
The Role of the Junctional Adhesion Molecule (JAM)-B in the Pathogenesis of Experimental Autoimmune Encephalomyelitis

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Under physiological conditions the endothelial blood-brain barrier (BBB) maintains homeostasis in the central nervous system (CNS) by restricting the uncontrolled diffusion of molecules or trafficking of immune cells into the CNS. Paracellular diffusion of molecules across the BBB is inhibited by complex and continuous tight junctions (TJ) between the endothelial cells. Besides the transmembrane proteins occludin, claudin-3 and -5, the junctional adhesion molecules (JAM-A, JAM-B and JAM-C) have been show to be localized to BBB TJs. During multiple sclerosis (MS) focal loss of BBB integrity is a hallmark of disease pathogenesis as visualized by gadolinium-enhanced magnetic resonance imaging. In the animal model of MS, experimental autoimmune encephalomyelitis (EAE) autoaggressive T cells breach the BBB and cause inflammation, edema and demyelination, which set the stage for the development of the clinical disease. Targeting T cell trafficking across the BBB by blocking VLA-4 with the humanized antibody natalizumab has proven beneficial for the treatment of MS, however, comes with the risk of progressive multifocal leukoencephalopathy (PML). It is thus mandatory to further investigate BBB proteins allowing to selectively block the CNS entry of autoreactive immune cells. Based on the genuine role of VLA-4 in T cell trafficking into the CNS during EAE and MS, the observation that endothelial JAM-B can bind VLA-4 on human T cells is intriguing. Using novel transgenic mouse models with a constitutive lack of JAM-B we investigated its function in maintaining TJ integrity and how it influences the migration of different immune cell subsets across the BBB during EAE. We found that absence of JAM-B does not impair BBB integrity or influence T cell migration across the BBB in vitro. Interestingly, JAM-B−/− C57BL/6 mice showed ameliorated active EAE, while JAM-B−/− SJL/J mice developed EAE with the same severity as their wild-type littermates. This might be due to the significant differences in the VLA-4 expression on encephalitogenic T cells observed by us between the two mouse strains. Histological analysis of brain and spinal cord sections of JAM-B−/− C57BL/6 mice afflicted with EAE showed reduced parenchymal infiltration of CD45+ inflammatory cells accompanied by their increased accumulation in leptomeningeal and perivascular spaces when compared to wild-type littermates. At this stage our data point to a role of JAM-B in EAE pathogenesis in the C57BL/6 mouse.
Assessing Short and Graphically the Mobility in MS and Other Neurological Disease with the new IPhone App Sagas 10

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Background
Sagas 10 is a new iPhone app developed as an alternative to the MS Functional Composite (MSFC) and as a complement to the EDSS for the moderately disabled MS patients between EDSS 5.0 and 7.0. Assuming that this tool could also be used for other neurological diseases where walking and hand function is impaired, we set out to examine the validity and the responsiveness of Sagas 10 in neurological patients attending a rehabilitation facility.

Methods
646 consecutive patients with different neurological diseases (MS 296, stroke 152, Parkinson 21, neuromuscular disorders 42, trauma 42, others 93) were assessed at the beginning and at the end of their rehabilitation stay using the FIM (Functional Independence Measure), the RMI (Rivermead Mobility Index), the 2-minute timed walking distance at maximum speed (2MWD) and the 3 measures composing Sagas 10 (the 25 feet timed walk at fast speed with a flying start (T25FW) and the nine-hole peg test (9HPT) for each hand separately). Construct validity was assessed with correlations between FIM, RMI and the Sagas 10, where correlations above 0.7 were hypothesized. Responsiveness was assessed by a receiver operating characteristic curves (ROCs) analyses comparing changes in Sagas with minimal clinically important changes in the RMI. An area under the curve value (AUC) of at least 0.7 was considered as appropriate.

Results
The correlation of the Sagas 10 with the Rivermead Mobility Index is above 0.7 in all of the neurological diagnostic groups; the highest correlation coefficient was found in patients with stroke: 0.75 (95% CI 0.63 to 0.83). The correlation of the Sagas 10 with the FIM was over 0.7 for stroke and MS. The responsiveness was acceptable with AUCs of 0.71 (95% CI 0.59 to 0.83) for stroke and values over 0.7 for all groups, with the exception of MS (AUC 0.61, 95% CI 0.46 to 0.76). The effect-sizes were moderate to high, especially for stroke with Cohen’s d values of 0.48 for the whole group and higher values for those walking slower (ES 0.61 for under 1.04 m/s and ES 0.72 for speed under 0.96 m/s).

Conclusions
These results indicate that Sagas 10 is valid and sensitive to changes over time and that it could be a useful measure not only for patients with MS, but also for patients with other neurological diseases such as after stroke.
Safety of intravenous immunoglobulin 10% (KIOVIG) therapy in patients with autoimmune and Alzheimer's disease

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Aims
A prospective, uncontrolled, open-label, non-interventional, post-authorization safety study (PASS) assessed the safety and efficacy of intravenous immunoglobulin 10% (IVIG 10%; KIOVIG) in patients with autoimmune disease (acute immune thrombocytopenic purpura [ITP], Guillain Barré syndrome [GBS] and Kawasaki disease [KD]) and primary immunodeficiencies. A phase 3, double-blind, randomized placebo-controlled trial (RCT) assessed the safety and efficacy of IGIV 10% (KIOVIG) in patients with mild-to-moderate Alzheimer’s disease. We report safety results from the open-label PASS and phase 3 RCT in patients with autoimmune or Alzheimer’s disease.

Methods
The open-label PASS included 49 patients with autoimmune diseases of any age; all patients received IGIV 10% up to a maximum of 6 mL/kg body weight/hour for approximately 6 weeks to 12 months (dose/regimen based on condition). The phase 3 RCT included 390 patients aged 50–89 years; patients were randomized 1:1:1 to receive biweekly infusions of 400 mg/kg IGIV 10%, 200 mg/kg IGIV 10%, or 0.25% human albumin over 18 months. Safety parameters were assessed throughout the studies.

Results
In the open-label PASS (N=49 [ITP=26, GBS=14, KD=9]), adverse drug reactions (ADRs) occurred in 30.6% of patients, none of which were considered severe; the most common were headache, vomiting, pyrexia and chills. No serious ADRs were reported. In the phase 3 RCT (N=390), the most common non-serious adverse events (AEs) in patients treated with IGIV 10% included headache, rash, infusion-site extravasation, and diarrhea. Of the 16 serious ADRs in 13 patients, a lower number occurred with high-dose (n=4) vs. low-dose (n=7) IGIV 10% vs. placebo (n=5). Thromboembolic events occurred in none of the patients in the open-label PASS and in 1.9% (IGIV 10%) and 5% (placebo) of patients in the phase 3 RCT (p=0.11). In the phase 3 RCT, the rate of new or worsening renal failure was similar in all patients and there were no cases of respiratory failure. There was a slight median decline in hemoglobin in all treatment groups with a slightly larger decline in hemoglobin in IGIV 10% compared with placebo. The rate of infections was lower in treated versus control patients (34.0% vs 47.9%; P=0.08).

Conclusions
IGIV 10% (KIOVIG) was well tolerated in pediatric and adult patients with autoimmune diseases (6–12-months of treatment) and in adult patients with mild-to-moderate Alzheimer’s disease (18 months of treatment).
Discreet In-Home Monitoring of Activities of Daily Living of Alzheimer Patients using an Embedded Sensor Network

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Background
The steady increase of the average life expectancy gives rise to an higher prevalence of age-associated disorders such as Alzheimer Disease (AD) and other forms of dementia. With the progression of AD, the need for institutional care intensifies, which contrasts with the desire of most patients to live independently. In that respect, the occurrence, performance and duration of different activities of daily living (ADL) are important indicators of functional ability. To provide good and effective care and to support independent aging, caregivers need to know how well patients cope with ADL, particularly when left without supervision.

Objective
In contrast to other commercial products available on the market, our aim was to develop a passive, unobtrusive, embedded sensor network to capture ambient environmental data from the participant’s home and to develop necessary algorithms to subsequently distinguish multiple ADL.

Methods
The components of the embedded system are a number of wireless sensors that were distributed in key locations throughout the participant’s home. The system was set up in the homes of healthy control subjects (N=10) and dementia patients (N=10) and environmental data were accumulated over a period of 20 days. The data were categorized using an in-house classification algorithm. Thereafter, ADL activity maps were calculated to compare the behavioral patterns of healthy controls and dementia patients.

Results
Ten healthy participants (6 women, 4 men; mean age = 76.7 years; SD = 8.2 years; age range 64-94 years) and ten dementia patients (6 women, 4 men; mean age = 73.9 years; SD = 6.7 years; age range 63-87 years) were included in the study. From the retrieved environmental data, specific behavioral patterns were determined and allotted to eight ADL. The behavioral patterns of the two groups exhibit significant differences, particularly in regularity of patterns and in overall daily structure.

Discussion
The wireless sensor system is able to identify data patterns and assign these to eight specific ADL. Owing to its discrete approach, the system maintains a high level of participant privacy while providing detailed information about the person's cognitive status and capability to cope with ADL. Current and future clinical trials of new drug interventions in dementia patients will need to prove their effects on ADL and we believe that our approach offers an excellent solution.
P24
Development and pilot testing of a novel electromechanical device to measure wrist muscle tone

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Background
Quantitative assessment of wrist muscle tone is important when studying patients with neurological impairments. For the assessment of therapeutic progress, quantitative and sensitive outcome measures are needed. This article presents a novel electromechanical device, the Wrist Resistance Robot, used to quantify normal and pathological muscle tone such as in resistance of the wrist joint.

Methods
The Wrist Resistance Robot is equipped with an electrical motor to move the wrist joint over its full range of motion with different velocity profiles. The feasibility of the measurement procedure was tested in 12 healthy volunteers and in four participants with Parkinson’s disease. Each participant completed the procedure using three velocity profiles, tested in a randomized order, of 10°/s, 50°/s, and 100°/s.

Results
The outcome of the quantitative resistance of the wrist joint evaluation was performed using unpaired Welch-Satterthwaite t-tests and was consistent across groups. The comparison of the mean values between the groups (CI = 95%) showed a significant total difference for the right hand extension (p = 0.045) and flexion respectively (p = 0.005). More specifically, the 10°/s velocity showed good significant difference between the groups for both extension (p = 0.007) and flexion (p = 0.020), while the 50°/s and 100°/s velocity profiles showed the greatest significant difference for both extension (50°/s: p = 0.0004, 100°/s: p = 0.0003) and flexion (50°/s: p = 0.005, 100°/s: p = 0.002) respectively.

Discussion
The Wrist Resistance Robot is able to provide useful information on wrist joint movement due to the fact that it differentiates quantitative resistance of the right hand extension from flexion. However, a prospective cross-sectional observational study is needed to determine the inter-rater and intra-rater reliability as well as the validity of this electromechanical device compared to standard scales to assess muscular resistance.
Combining cognitive performance and daily living activities in a new Serious Game based assessment tool for Alzheimer’s patients: preliminary results

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Aims
Alzheimer’s disease (AD) is the most common form of dementia and requires early diagnosis in order to ensure better therapy outcomes. Laboratory tests are common methods in order to evaluate the cognitive abilities. However these tests do not indicate the functioning in daily living. To investigate the performance in instrumental activities of daily living (IADL), questionnaires are used. These questionnaires have the disadvantage of being subjective and being under the influence of patient’s anosognosia. Thus, Serious Games offer the possibility to recreate a virtual environment with daily living activities and cognitive evaluation. The idea of the present study is to develop and evaluate a new Serious Game based Assessment tool for patients with Alzheimer’s disease.

Method
5 patients (1 Male, Age M = 73; MoCA M = 21.2) and 13 healthy controls (8 Males, Age M = 76.5; MoCA M = 29.4) were recruited to participate in this study. A virtual scenario consisting of 4 daily living tasks was created: a navigation task, a shopping task, a cooking task and a table preparation task. The goal of the game was to accomplish these 4 daily living activities following a story line. If they didn’t remember what they had to do during the game, they had the possibility to press the button "Instructions” which was always available on the screen. Following measures were recorded during the game: task duration and inactivity time during the task, number of times they pressed the instructions button, correctness of ingredients to buy, correctness of way to go back home, actions precisions, actions order and actions repetitions.

Results
Preliminary results indicate a significant difference for the task duration (Ws = 78, z = -3.16, p = .002) and inactivity time (Ws = 78, z = -3.16, p = .002) in shopping, going back home (Ws = 89, z = -2.03, p = .045; Ws = 84, z = -2.53, p = .011) and for inactivity time in cooking (Ws = 87, z = -2.21, p = .027). Furthermore, only patients pressed instructions button, forgot ingredients during the shopping task and needed more actions to achieve tasks.

Conclusion
The new Serious Game based Assessment tool is an ecological way to evaluate cognitive abilities and it allows to distinguish Alzheimer’s patients performance from healthy controls.
P26
Study Design of a Phase III Efficacy, Safety, and Tolerability Study of Recombinant Human Hyaluronidase (rHuPH20)-Facilitated Subcutaneous Immunoglobulin (IGHy) in Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

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Aims
CIDP is an acquired, immune-mediated, progressive or relapsing peripheral neuropathological condition with significant disease burden. Corticosteroids, plasma exchange, and intravenously-administered immunoglobulin (IGIV) are current treatment options with limitations (eg, adverse events; time commitment). IGHy (HYQVIA) is a subcutaneously-administered immunoglobulin that may be self-administered at rates, volumes, and frequencies similar to IGIV but with better systemic tolerability. The design of a Phase III, prospective, multicenter study for the evaluation of the efficacy, safety, and tolerability of IGHy as maintenance therapy to prevent relapse of neuromuscular disability and impairment in patients with CIDP is presented.

Methods
Adults (N=174) with typical or atypical CIDP receiving stable IGIV for 3 months prior to screening will be randomized 1:1 to IGHy or placebo with rHuPH20 for 6 months. Treatment will be administered subcutaneously every 2, 3, and 4 weeks at the same monthly immunoglobulin dose (IGHy) (or matching infusion volume for placebo group) as the subject’s pre-enrollment IGIV treatment. Subjects who relapse during SC treatment will be provided IGIV to restore functional ability. The primary efficacy outcome measure is worsening of functional disability at study completion or last study visit, relative to pre-treatment baseline. Secondary/exploratory outcome measures include time to relapse, activities of daily living, hand grip strength, muscle strength, quality of life, health resource utilization, and treatment satisfaction.

Conclusions
IGHy may provide an alternative maintenance treatment option enabling self-administration of a full therapeutic dose every 2–4 weeks in patients with CIDP. Enrollment of patients into this Phase III study is planned for Q4 2015.
An anatomical and psychophysical comparison of subjective verticals in patients with right brain damage

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Introduction
Brain hemisphere lesions often cause a contralesional tilt of the subjective vertical (SV) a phenomenon related to spatial neglect and postural disorders. Depending on the method employed, different perceptual systems come into play when this gravitational vertical is assessed. Here, we compared the anatomical and psychophysical characteristics of modality-dependent SV biases in patients with right hemisphere stroke.

Methods
The SV was measured with visual, haptic and visual-haptic modalities (SV, SVV, SVHV) in 46 patients with a relatively recent stroke. Voxel-based lesion-symptom mapping (performed with NPM®) was used to highlight brain areas in which lesions best explained the severity of task biases (p < .05).

Results
Lesions explaining the SVV tilt (TSVV) were centered on the posterior part of the middle temporal gyrus, those explaining the TSHV were more limited and anterior, without convergence with the former. Lesions explaining the TSVHV were centered on the superior temporal gyrus and more anterior those explaining the TSVV, with convergence with lesions explaining both the TSVV and the TSHV. Patients showed counterclockwise deviations in the SVs. Constant and variable errors were greater for the SHV than for the SVV and for the SVHV. The TSVV and TVHV were closely related to the presence of left spatial neglect and hemianopia.

Conclusions
Errors in the SVV and (at a lesser degree) SVHV were preferentially related to lesions in visual associative cortex. The SVV and especially the SVHV provide valuable estimates of patient difficulties, in view of the lower associated variable errors (i.e., greater precision) and closer relationships with clinical disorders.
Retrospective evaluation of an inpatient rehabilitation program for medication overuse headache

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Background
Medication overuse headache (MOH) can be diagnosed if patients have headaches on more than half of the time, while taking acute pain medication at least 10 to 15 days per month. Most patients may benefit from a withdrawal of pain medication, while in some patients an inpatient withdrawal is indicated.

Methods
In this cross-sectional study, patients' health-related quality-of-life and headache-related disability was measured by the Short Form 36 (SF-36) and Migraine Disability Score (MIDAS). SF-36 data (100=best) were compared to German population norms, stratified by age, sex and co-morbidities.

Results
Fifty-one patients (72.5% female, mean age 47.3 years, SD=11.8) were included with an average headache duration of 25.3 years (SD=14.4). Time since the headache program varied between 6 and 30 months. A total of 68.6% of the patients changed to episodic headaches (<15 days per month) after participation in the program. Average headache severity was 6.51 on the MIDAS VAS (0-10, SD=2.04). Average SF-36 bodily pain was 40.3 (SD=20.3, norm=59.0, p<0.001), and SF-36 physical functioning was 78.4 (SD=21.4, norm= 83.3, p=0.497). All other SF-36 scales were significantly lower than expected from the norm (all p<0.001), with maximal difference on SF-36 social functioning (mean 56.8, SD=28.1, norm 82.5).

Conclusions
More than 2/3 MOH patients changed to episodic headaches, with a sustained effect up to 2.5 years after the program. As expected, pain and psycho-social impairment levels were higher than in the normal population. Functional impairment was high on the headache-specific scales but not on the generic SF-36.
Brain AVM and headaches: differential effect of closure of dural versus parenchymal arterial supply on persistence of headaches

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Background
Brain arterio-venous malformations (BAVM) with pure dural or mixed parenchymal and dural arterial supply present frequently with headaches. The mechanisms that lead to these headaches are still poorly understood but contribution of dural supply in the genesis of headaches is suspected. Headaches seem to disappear after complete or partial obliteration of dural (extracranial) arterial supply only.

Aim
To systematically analyze the effect of endovascular obliteration of the dural arterial supply on headaches in a consecutive series of BAVMs with both, parenchymal and dural arterial supply presenting with headaches. To discuss pathophysiological mechanisms of pain development and relief of headaches by selective occlusion of the dural supply. The understanding of these aspects of pathophysiology may also help in planning endovascular obliteration.

Patients and methods
In a consecutive series of 5 patients with BAVM presenting with headaches and parenchymal and dural arterial supply headaches were analyzed before and after endovascular treatment of the dural component.

Results
Headaches diminished or disappeared in all 5 patients after endovascular treatment of dural supply alone.

Conclusion
Dural arterial supply of brain AVM seems to partially or fully explain origin of headaches in these cases and serve as a pathophysiological model of headaches. The expected relieve of headaches after endovascular treatment of dural supply of BAVM may be considered in planning future treatments. These retrospective data need to be confirmed in a prospective data collection.
P30
Mechanical thrombectomy using the new ERIC-retriever is safe and reveals high rates of successful vessel recanalization in acute ischemic stroke

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Aim
Mechanical thrombectomy (MT) with new generation devices such as stent-retrievers are highly effective in acute ischemic stroke with large vessel occlusion (LVO). The aim of this pilot study was to determine the safety and feasibility of MT using the new ERIC-retrieval-device consisting of several interlinked cages.

Methods
Twenty-one consecutive patients suffering from acute ischemic stroke with LVO who have been treated with the new ERIC-retriever were included into this observational study. Onset to intravenous thrombolysis time 4.5h or wake-up-stroke with relevant CT-perfusion mismatch and NIHSS 4 represented the main inclusion criteria. We assessed baseline/stroke characteristics, treatment related parameters and outcome.

Results
Mean age was 69±12 years, 62% women. Median NIHSS on admission was 16 [IQR11-20] and onset to MT time was 7h59m [IQR6h50m-11h07m]. Eight patients received intravenous thrombolysis, 2 intraarterial urokinase. The new ERIC device was used as the sole retriever in 14 patients (67%) and as a rescue device in 7, with 3 of them supported by thrombus aspiration. Successful recanalization was achieved in 17 patients (81%) with TICI3 in 10/21 and 2b in 7/21, respectively. The median procedural time was 106min [IQR72-166]. No intraprocedural complications occurred. At 3months, fair outcome (mRS 3) was achieved in 62%, with 54% of them being independent (mRS 2). Symptomatic intracerebral hemorrhage unrelated to the device developed in 2 patients (mRS at 3mo: 3+6) and mortality at 3months was 29%.

Conclusion
The new ERIC-retrieval-device is technically safe and effective in removing thrombi in patients with acute ischemic stroke due to large vessel occlusion.
Utility of in patient video EEG monitoring in a cohort of persons with epilepsy difficult to treat.

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Methods
A retrospective study was performed in a tertiary epilepsy center collecting all the patients hospitalized during 2 years. Utility and delay in in-patient video monitoring resolving the clinical question on admission was determined. Classification of epilepsy or paroxysmal events not related to a seizure disorder were defined with demographic data and comorbidities were detailed.

Results
The cohort consisted of 57 patients with either epilepsy not responding to treatment or paroxysmal behavior of unknown cause where ambulatory care was regarded as insufficient. In 54/57 patients the clinical question was answered in a satisfaction during the hospitalisation. The mean duration for the hospitalisation was 24 days (SD 13]). After 14,4 days (SD 13,3) it was possible to resolve the initial question on admission. The demographic data as comorbidities (psychiatric, learning disability or altered cognition) will be presented in detail.

Conclusions
In a group of patients with epilepsy difficult to treat or presentation of atypical paroxysmal events, the ambulatory care is not always conclusive. In a small group of patients a hospitalisation with long term video EEG monitoring is indicated, to define either the type of epilepsy or seizures or exclude psychogenic or other non epileptic events. In our cohort a hospitalisation with an average of 14,4 days, the clinical problem could be resolved in 54/57 patients (95%). Psychogenic non epileptic seizures (PNES) showed up as a predictive factor and it was more frequent in patients with intellectual disability in this cohort. 26/57 patients had a significant score of anxiety. Surprisingly, the patients with PNES had a normal score.

Acknowledgments
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Aim
We investigated the difference between the upper and lower visual field (VH) with a novel visual test battery, involving comparisons of images in the two VHs. The tested hypothesis was: the performance of healthy is better in the lower VH.

Methods
Ten healthy volunteers performed the visual test battery. The tests consisted of two subtasks, in the first one two patterns of random dots moving with different speed, were presented in the upper and lower VH, in randomized order. In the second task, two ellipses with different shapes were presented. With an input device, the test persons changed the speed of one of the patterns until it moved with the same perceived speed as the other one. In the second task, the test persons changed the shape of one ellipse until it was perceived as identical to the other one. The tests were conducted under fixation control, and performed on a hemispherical screen (cupola).

Results and Discussion
The results of the pilot study confirmed the hypothesis because the performance on the visual test battery was better in the lower VH. Previc proposed that upper and lower VH differences are related to viewing distance (Previc, 1990). Stimuli located in the lower VH are in near space and more likely be encountered, thus processed with higher accuracy than stimuli in the upper VH. In our setup the eye-screen distance was fixed to 30 cm, and this distance is considered within the edge of the peripersonal space (Rizzolatti, 1997). Vertical asymmetries in favor of the lower VH may be also driven by an attentional bias (Rezec, 2004; Carrasco, 2001). However, in some studies, a "scanning bias" (serial scan of the display) could not be excluded (Rezec, 2004). Our setup addressed this issue, because the fixation was maintained steady during the experiment.

Conclusions
In this study a novel approach to study higher visual functions in the upper and lower VH was presented. The hemispherical screen allowed for a clear discrimination of stimuli location, and the fixation control was useful to avoid undesirable scanning paths that could mask the effects of an attentional bias. Attention seems to be mainly involved in differences between upper and lower VH. Nevertheless, the neuroanatomical structure of the visual cortex may also play a role in the lower VH advantage.

Acknowledgments
The authors would like to acknowledge all the participants who participated in this study.
Extended Automatic Analysis of Continuous ECG Monitoring (aCEM) Substantially Improves the Identification of Patients with Newly Diagnosed Atrial Fibrillation During Hospitalization for Acute Ischemic Stroke

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Aim
Atrial fibrillation accounts for approximately 20% of all ischemic strokes. Anticoagulation is highly effective in stroke prevention in these patients. However, early detection of AF after stroke remains challenging. Recent observational studies and RCTs promote prolonged ECG-monitoring for the detection of AF. The present study aimed at estimating the role of extended automatic analysis of continuous ECG monitoring (aCEM) for detecting AF already during hospitalization.

Methods
Six hundred and eighty consecutive patients with ischemic stroke or TIA admitted to our Stroke Center in 2014 were included in this analysis. Generally, they received an ECG on admission, followed by standard continuous ECG monitoring (CEM) during their stay on our stroke unit (SU), and finally portable aCEM (Apoplex medical, SRA clinic) on the early rehabilitation unit. Out of these 680 patients, 105 did not undergo CEM but received portable aCEM directly.

Results
A total of 151 patients were discharged with the diagnosis of AF, which was already known on admission in 97 (64%) and newly diagnosed in 54 (36%). From the latter group, ECG on admission identified 27 with AF (18% from total of 151). CEM 14 (9%) and portable aCEM detected an additional 11 patients (7%). One patient with an implanted ECG-recorder showed AF-episodes at read-out and another patient fainted during hospitalization and demonstrated AF on the concomittantly written ECG.

Conclusion
Portable aCEM considerably contributed to identifying stroke patients with paroxysmal AF, most likely due to an extended monitoring period. It might serve to reduce stroke recurrence by optimizing secondary stroke prevention.
P34
Mid-Regional Pro-Atrial Natriuretic Peptide as Independent Outcome and Aetiological Ischemic Stroke biomarker: Results from the CoRisk study

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Aim
Validated prognostic blood biomarkers may improve early risk stratification in acute stroke patients. We addressed the incremental value of midregional pro-Atrial Natriuretic Peptide (MR-proANP) in outcome prediction as compared to established clinical variables. Furthermore we analysed its significance in predicting cardioembolic (CE) stroke.

Method
In this prospective, multicenter cohort-study we measured MR-pro ANP of ischemic stroke patients within 24h of symptoms onset. Main primary endpoints were death and unfavorable functional outcome (modified-Rankin-Scale (mRS) from 3 to 6 points) within 90 days. Secondary endpoint was cardioembolic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

Results
Out of 786 patients, 783 completed their 90 days follow-up, 118 patients died. After full adjustment, higher MR-proANP levels were independently associated with mortality (adjusted odds ratio (adj.OR) 4.9 [95% CI, 1.78 – 13.50], p < 0.002, but not functional outcome (adj.OR 1.77 [95% CI, 0.85 – 3.68], p=0.12). Adding MR-proANP to the full regression model, the discriminatory accuracy improved significantly for mortality (Area under the receiver operating curve (AUC) without MR-proANP 0.86 [95% CI, 0.83 – 0.89]; AUC including MR-proANP 0.87 [95% CI, 0.84 – 0.90] p*<0.006). MR-proANP independently predicted CE stroke (adj.OR 2.27 [95% CI, 1.20 – 4.29], P < 0.01) and by adding MRproANP to the multivariate model the discrimination improved (from AUC 0.73 [95% CI, 0.69 – 0.76] to AUC 0.75 [95% CI, 0.71 – 0.79]p<0.001*).

Conclusions
MR-proANP is a newly validated blood biomarker adding prognostic information for mortality after stroke. Higher levels of MR-proANP were specifically associated with cardioembolic stroke risk.
Allergies and autoimmune comorbidities in narcolepsy

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Background and Objectives
Narcolepsy (N) and Narcolepsy with Cataplexy (NC) are chronic neurological disorders affecting approximately 0.02% of population worldwide. Due to the observations of involvement of DQB1*0606 receptor and linkage to CD4+T cells an immune mediated mechanism in NC is supposed to lead to the destruction of hypocretinergic neurons. In general population, allergies have a prevalence of 10-20% and 5-9% for autoimmune disorders. Little is known on the incidence of allergic predisposition and autoimmune disorders in patients suffering von N and NC. Here, we present an interim analysis of our study on this item.

Methods
We prospectively assessed out-patient N and NC individuals. Assessment was performed by clinical interview and questionnaires raising data to socio-demographic and clinical characteristics same as history and treatment. In concerned patients further information was assembled and diagnosis of autoimmune disorders was verified.

Results
103 narcoleptic patients (88 NC (85.4%)) aged between 10 and 77 years (63 women (61.1%)) were included. Allergic diseases were reported in 28/103 (27.1%): hay fever (n=12), allergic asthma (n=13) and food allergies (n=3). An autoimmune disorder was found in 19/103 patients (18.4%), 11 (57.9%) of them female. Autoimmune disorders included psoriasis (n=6), atopic dermatitis (n=5), Hashimoto’s thyroiditis (n=3), Crohn’s disease (n=2), alopecia areata (n=1), multiple sclerosis (n=1) and vitiligo (n=1).

Conclusion
In N/NC, coexisting allergies and in particular autoimmune disorders are frequent and higher than in the general population. Our preliminary finding strengthens the concept of autoimmunity in narcolepsy.
How to combine the paired-pulse paradigm stimulation technique with the quadropulse (QuadS) and quintopulse stimulation (QuintS)

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Background & Aim
Transcranial magnetic stimulation has advanced our knowledge of cortical physiology. Paired-pulse TMS allows explore intra-cortical facilitation (ICF), but the mechanism remains undetermined. Repetitive spinal motor neuron discharges (repMNDs) could contribute to ICF, which can be explored by the quadropulse (QuadS) and quintopulse stimulation (QuintS) technique. The objective was to establish a novel stimulation setup combining the paired-pulse stimulation paradigm with QuadS and QuintS. The ulterior objective is to explore the role of repMNDs in intracortical facilitation.

Methods
In our study we wanted to find a method to measure the repMNDs in intracortical facilitation (ICF) using the paired-pulse TMS paradigm. For this purpose, we combined the paired-pulse paradigm with the quadropulse and quintopulse stimulation techniques (QuadS and QuintS) to quantify the repMNDs. The challenge was to set up the stimulation protocol combining multiple stimulators in a predefined sequence order and to randomize the stimulation conditions. The major challenge arose from the technical specifics of the devices which had to be defined and occasionally explored to allow precise timing of the sequential stimuli.

Results
We chose Labview to trigger the stimulators according to the experimental conditions and to acquire the data for off-line analysis. For the stimulation, we used the Grass S88, the Digitimer DS7AH and the Magstim BiStim TMS devices, and the ENMG-VikingSelect instrument for the MEP recording. The Labview triggers in a sequential order the Magstim BiStim TMS device for the motor cortex stimulation, the Grass S88 for the ulnar nerve stimulation at the wrist and the Digitimer DS7AH for the brachial plexus stimulation at the Erb’s point. The stimulation of the ulnar nerve consists of one, two or three impulses at an interstimulus interval (ISI) of 3 ms in the TST, QuadS or QuintS respectively. The experimental stimulation conditions including single-pulse and paired-pulse TMS, TST, QuadS and QuintS can be randomly applied.

Conclusions
This novel stimulation protocol combines the paired-pulse stimulation and the TST, QuadS and QuintS to explore whether repMNDs contribute to the intracortical facilitation.

Reference
P37
EEG signal coupling measures as prognostic tool for survival in comatose patients

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Clinical assessment of comatose patients is a notoriously difficult, but essential task. Many multimodal algorithms combining clinical examination, EEG, SEP, VEP, and biomarkers have been proposed, aiming at improving prognostic indicators. In this retrospective study we evaluate the potential of quantitative EEG (qEEG) methods as novel complementary approaches. In 79 patients, general synchronization between EEG signals on the left-right (inter-hemispheric) axis and on the anterior-posterior (intra-hemispheric) axis was measured with four different signal coupling measures. The results were statistically different depending on the survival or death in the Intensive Care Unit for five of eight measures. One measure was also found to be different according to the etiology of coma. In combination, these synchronization measures reached very high predictive values for prognosis in coma (AUC of 0.875; 0.946 for post-anoxic encephalopathy). We conclude that EEG synchronization methods have the potential to become part of future multimodal algorithms for prognostication in coma.
Case Report: Carotid cavernous fistula as a rare cause of vision loss and gaze palsy

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A 58-year-old patient presented with diplopia in all directions of gaze for one week, disturbed vision and redness of his right eye as well as a bruit in his right ear for two days. Clinical examination revealed an incomplete oculomotor nerve palsy and decreased acuity of vision on his right eye. A pulsatile exophthalmus, conjunctival injections and chemosis of the right eye were seen (figure 1). CT angiography showed an enlarged superior ophthalmic vein (figure 2), the cerebral pan-angiography revealed an indirect carotid cavernous fistula (CCF) Barrow type D on the right side. The carotid cavernous fistula was successfully treated by coil embolisation. Afterwards the physical and functional signs resolved. Follow-up images showed no evidence of a persistent fistula.

**Conclusion**

CCF results from an abnormal communication between the arterial and venous systems within the cavernous sinus in the skull. The majority of CCF occurs after a trauma, as others can develop spontaneously as suspected in this case. It is a rare condition, but should be considered in differential diagnosis of acute vision loss and gaze palsy. Suggestive clinical findings can lead to the appropriate diagnosis.

![Figure 1](image1.jpg)

![Figure 2](image2.jpg)
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy with a highly variable clinical presentation. Hence, diagnosis is challenging and mostly relies on clinical suspicion. Various treatment approaches with different side effects and economical burden are available (steroids, IVIG, plasmapheresis). Retrospectively, we investigated a cohort of CIDP patients with the aim to disclose diagnostic and therapeutic challenges, which may have an impact in daily neurological practise.

Methods
We analysed clinical data, diagnostic workup and treatment of 18 adult patients with CIDP under intravenous immunoglobulin therapy (IVIG) from 2003-2014.

Results
We identified 15 men and 3 women with a mean symptom duration of 32 months before the diagnosis was made. Based on EFNS criteria clinical presentation was typical in 7 and atypical in 11 patients. Predominantly distal manifestation (DADS) was found in 1 patient, pure sensory symptoms in 9 patients and focal involvement of the brachial plexus in 1 patient. Just half of all patients fulfilled the electrophysiological criteria of prominent demyelinating features (EFNS/INCAT criteria for CIDP). Supportive laboratory features such as elevated CSF protein were found in 15/18 patients. Nerve biopsy was performed in selected patients and showed demyelination features in 3 out of 7 patients. In 1 patient MRI abnormalities of proximal nerve fascicles at the cervicobrachial plexus could be detected. 10 patients received additional immunosuppressive therapy beside immunoglobulins (prednisone, Aza, MMF or MTX). Interestingly, the IVIG-dose (between 0.4-1mg/kg/KG) and therapeutic interval (between 3-12 weeks) were highly variable. In 2 patients IVIG was stopped because of inefficacy or complete remissions.

Conclusions
In this retrospective cohort we illustrate the clinical, diagnostic and therapeutic variability in CIDP patients. Therefore, strict clinical and electrophysiological criteria of CIDP are less sensitive for daily routine, especially for atypical forms. Supportive criteria, especially elevated CSF protein, could be helpful to define the diagnosis. Due to a mild initial presentation and atypical presentation the time from first symptoms to definite diagnosis was rather long. Difference in IVIG-dose and interval as well as the use of concomitant immunosuppression were also highly variable which calls for individual treatment approaches rather than a standard treatment.
P40
Neurosonographic findings in non-systemic vasculitic neuropathy: an intriguing case report

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Aim
The value of ultrasound of peripheral nerves in acquired immune-mediated neuropathies has been recently reported. The impact of neurosonography in vasculitic neuropathy is yet to be defined. We report the correlation of electrophysiological and ultrasound studies in a patient with nonsystemic vasculitic neuropathy at first diagnosis and in response to immunosuppressive therapy.

Case Report
A 44-year-old female presented with neuropathic pain and allodynia at the scapula radiating along the dermatoms C8/Th1 on the right arm of 1 month duration. On follow-up, an electrifying pain was localised at the fingertips of the left hand and in the region of the right knee. Additionally, the patient complained about weakness of the right intrinsic hand muscles. Diagnostic workup: Electrodiagnostic studies of the median and ulnar nerve were consistent with axonal neuropathy in a multifocal pattern. Clinical, laboratory and radiology evidence of non-neuromuscular involvement and systemic rheumatological diseases were absent. On nerve ultrasound massive patchy swelling of the median and ulnar nerve were detected bilaterally. At the site of nerve enlargement compression was painful. Hence, the diagnosis of non-systemic vasculitic neuropathy was made by fulfilling 5 of 6 diagnostic criteria (Collins et al., Neurology 2003). Nerve biopsy was not feasible according to the affected sensorimotor nerves (i.e. median nerve). As high-dose steroids were insufficient we escalated treatment to monthly i.v. cyclophosphamide. After two months of treatment the nerve conduction studies as well as neurosonography improved. The enlargement of single nerve fascicles diminished but overall swelling of the affected nerves were still present.

Conclusions
Superficial peripheral nerves can be easily investigated by high-resolution neurosonography and provide an useful complementary tool to electrodiagnostic studies. Morphological analysis of nerves and changes due to therapy could be well visualized. Ultrasound studies in vasculitic neuropathy are rare, but might be an ancillary technique to guide non-invasive diagnosis. Additionally, neurosonography might be useful to target nerve biopsy and to monitor therapeutic efficacy.
Automatic event-detection for the neurophysiological evaluation of voluntary and involuntary movements

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Aims
Neurophysiological evaluation of voluntary and involuntary movements in various disorders such as Parkinson disease, myoclonus, psychogenic movement disorders includes the analysis of cerebral activity by means of electroencephalography (EEG). A way to perform this analysis is by averaging EEG signal relative to a voluntary or involuntary movement recorded through electromyography (EMG). This technique, termed back-averaging, identifies brain patterns related to a particular motor activity and may elucidate its neural basis. Typically, these EMG events (voluntary muscle activity, myoclonus, etc.) are manually labeled by expert clinicians in a time-consuming process. This project aims at creating a tool for automatic EMG event-detection to support clinicians in this process.

Methods
We developed a computer application that uses machine-learning methods to automatically detect EMG events and analyze their relation with cortical activity (i.e. EEG-EMG back-averaging). The application builds statistical models based on recordings already labeled by expert clinicians, and exploits them to speed up the event detection and analysis. We have explored the possibility of discriminating voluntary and involuntary movements using supervised machine learning methods. The performance of the system is being prospectively assessed by comparison with manual labeling of recordings involving both healthy subjects and patients with movement disorders.

Results
The application provides the visualization of the EEG/EMG recording –both in the temporal and spectral domain–, automatic detection of the EMG events and manual editing of such events. Automatic event detection showed high sensitivity with a low rate of false detections when compared to manually labeled events. Back-averaging of automatically detected voluntary movements in healthy subjects yielded the expected movement-related cortical potential (Bereitschaftspotential).

Conclusions
An automatic application has been developed for supporting the clinical evaluation of motor control and movement disorders. This tool provides automatic detection of EMG events based on statistical models. In turn, these models can be further refined by integrating knowledge from the clinical expert (e.g. using manually labeled samples from a subset of the data). Preliminary results on the discrimination of voluntary movements are encouraging, but further work is necessary to fully assess this approach for different movement disorders.
Headache in the patients with temporomandibular joint disorders

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Aim
Aim of this study was to compare the clinical characteristics of patients from the subgroup with osteoarthritis (G-1) and patients with disc displacement (DD) (G-2) of TMJ related types of headaches and with one-year-follow-up after treatment.

Methods
G-1 included 70 patients who were treated for signs and symptoms of OA of TMJ. Pain intensity (at first examination T0) in TMJ was shown on the visual-analogue scale (0, no pain; 10, the worst pain) as well as headaches. They were treated by an occlusal splint and/or physical therapy with a six-month (T1) and one-year (T2) follow-up. G-2 included 35 patients from a subgroup with DD. Definitive TMJ-diagnoses were confirmed by magnetic resonance imaging.

Results
There was a significant age difference (p<0.001) between the two subgroups of TMJ diagnoses, however there were no differences in pain during the follow-up period. In the beginning, the pain amounted to T0: G-1 6.5 / G-2 6.1 and at T2: G-1 1.6 / G-2 1.7. The applied treatment modalities at T1/T2 achieved TMJs without pain in 27.14%/64.29% of patients from G-1 and in 28.57%/57.15% of patients from G-2. There were equal shares of patients without headache (G-1 54.3%; G-2 48 %). The share of tension headaches was G-1 10%, G-2 11.4%, migraines G-1 15.2%, G-2 22.9%, TMJ-related headache G-1 4.3%, G-2 11.4% and cervicogenic headache G-1 15.7%, G-2 5.7%.

Conclusions
Pain intensity and treatment success do not vary within the observed groups. Migraine and TMJ-related headaches are more common in patients from G-2.

References
Türp JC. J Craniomandib Funct 2014;6:213;
Erratic movement disorders disclosing Grave's disease

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Background
Thyroid dysfunction can be associated to several neurologic symptoms. In particular, hyperthyroidism is often characterized by tremor, seizures, confusion, etc in addition to general symptoms directly related to excessive circulating thyroid hormones. Other involuntary movement disorders such as chorea, ballism have been rarely reported in the context of Grave’s disease. We report here a patient presenting with involuntary movements of which workup solely revealed hyperthyroidism due to Grave's disease and which dramatically improved as the disease was controlled.

Disclose Patient
This 60 year-old woman without relevant history of neurological or psychiatric disease, complained of imbalance associated with falls evolving for 5 years. Neurological examination found prominent, high amplitude, involuntary postural erratic and brisk limb movements predominating on the left side, more pronounced in the leg while walking, causing infrequent falls. Muscle strength was preserved as were sensory, cerebellar, inner ear and cognitive functions. Tachycardia and high blood pressure were also found, but no exophtalmia. The patient was highly anxious and complained of insomnia.

Results
A thorough workup including blood and CSF inflammatory, infectious, metabolic markers; brain, spinal cord imaging and EEG, was unremarkable except TSH concentrations below measurable threshold, high T3 and T4 levels. Complementary investigations found elevated anti thyroperoxydase, thyroglobulin and TSH receptors antibodies and thyroid scintigraphy highly evoking Grave's disease. The patient was accordingly treated with carbimazole that was stopped due to sever muscle pain (initially misdiagnosed as part of hyperthyroidism symptoms). Then with 131I radiotherapy was performed. Few weeks later, initial abnormal movement nearly disappeared, unveiling mild rapid and regular tremor which predominated in right limbs. The patient was now quiet and general hyperthyroidism symptoms were almost alleviated.

Discussion and conclusion
This patient presented with brisk and erratic limb movements, mixed with the more typical tremor in relation to Grave's disease. Despite temporal correlation with the disease evolution, the movement pattern was evocative of functional origin. We discuss that these intriguing movements were most likely superimposed to more common hyperthyroidism neurologic symptoms in the context of anxiety and social stigmatization.
P44
Glioblastoma multiforme: Chameleon of neurology – a case report

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Background
Multiple sclerosis is the most common neurological disease in young patients between 20 and 40 years. Since there is no pathognomonic finding for multiple sclerosis, autoimmune, infectious, malignant and vascular diseases should be taken into consideration for differential diagnosis. The radiological similarity of multiple sclerosis lesions and lesions of primary brain tumors is estimated to be approximately 1%.

Case report
We report the case of a 19 year old male who presented with a slowly, distal ascending, progressive right sided hemihypaesthesia since two weeks. The radiological findings (cMRI) showed multiple to 0.7 cm measured lesions which were located subcortical, periventricular, in the region of the thalamus and the pons. Considering the patient’s young age and the distribution of the cerebral lesions multiple sclerosis seemed to be likely. The spinal cord was without pathological findings. The analysis of the cerebrospinal fluid showed a normal cell count <1/µl and unremarkable other findings (normal protein, no evidence of oligoclonal bands, negative MRZ-reaction). The complementary laboratory-chemical examinations according to guidelines for possible differential diagnosis of multiple sclerosis were unremarkable. As a first therapy the patient received a high dose of intravenous corticosteroids. Two more cMRIs were performed in the following two months because of progressing symptoms. New lesions and expanded old lesions were found. Despite repeated double-dose, intravenous corticosteroids and finally five courses of plasmapheresis, neurological symptoms have progressed and intensified. We decided to take brain biopsy though most of the lesions were located in the left, eloquent hemisphere. The histological result revealed a glioblastoma multiforme (WHO grade 4) with negative prognostic molecular markers (unmethylated MGMT promoter, no IDH1/2 mutation).

Discussion and result
Magnetic resonance imaging is today one oft he most important paraclinical instruments for the diagnosis of diseases of the central nervous system. Tumor-like demyelinating brain lesions are also known and described as „tumefactive multiple sclerosis“: Greater demyelinating areas with mass effect, perifocal edema and ring enhancement can imitate brain tumors. There are just a few reports about the opposite case: Brain tumors imitating multiple sclerosis. The presence of multifocal lesions and the patient’s young age, which is untypical for glioblastoma multiforme, have aggravated the difference between radiological and clinical findings. In conclusion cases with progressing symptoms despite intense immunomodulatory therapy require histopathological diagnosis.
The Impact of Deep Brain Stimulation on Sleep-Wake Function in Patients with Parkinson's disease

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Aim
To determine the impact of both nucleus subthalamicus (STN) and globus pallidus internus (GPI) deep brain stimulation (DBS) on sleep-wake function in patients with Parkinson’s disease (PD) three and six months after DBS surgery.

Methods
A prospective observational study will be performed. Up to 40 adult participants with PD will undergo stereotactic implantation of DBS electrodes in the STN or GPI. A detailed assessment of sleep-wake function will be performed prior and at three and six months after DBS surgery. The assessment includes well-established measures, such as polysomnography, actigraphy, maintenance of wakefulness test and multiple sleep latency test, a detailed sleep history and a battery of validated self- and expert-rating questionnaires and scales, including Parkinson’s disease sleep scale (PDSS) and Epworth sleepiness scale (ESS).

Results
The current study seeks to further highlight risks and benefits of a DBS intervention in relation to the sleep-wake function in PD.

Conclusions
Our study will provide new evidence regarding the role of DBS in sleep-wake mechanisms in PD. The impact of DBS on sleep and wakefulness should be taken into account when choosing for patients with PD the best therapeutic option, including the best DBS target. The elucidation of the impact of medication, DBS and the disease itself on sleep and wakefulness will be of great value to the postoperative therapeutic equilibration.

Acknowledgments
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Comments:
The study design and the protocol of the prospective study is based on a currently ongoing retrospective analysis of pre- and post-DBS data from PD patients in our department.
Discovery of cerebrospinal fluid biomarkers for transition to secondary progressive multiple sclerosis by LC mass spectrometry

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Introduction
Multiple sclerosis (MS) is an exclusion diagnosis, established on the basis of clinical history and examination, supported by suggestive magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) oligoclonal bands. After an initial phase characterized clinically by the presence of relapses, most relapsing remitting MS (RRMS) patients undergo a transition towards secondary progressive MS (SPMS), the hallmark of which is progressive disability accumulation. The time from diagnosis to SPMS transition as well as the slope of progression during the SP phase is highly heterogeneous. Biomarkers discriminating RRMS and SPMS are lacking, and diagnosis is clinical. Yet accurately distinguishing these 2 phases of the disease is a cornerstone in the development of specific treatments for SPMS, during which most of the disability accumulation occurs.

Objective
The aim of the present study is to discover clinically relevant CSF protein biomarkers assisting the diagnosis of RRMS transition towards SPMS. Methods We used a high-throughput LC mass spectrometry method to compare the CSF proteome of RRMS patients versus SPMS, as well as versus a control group consisting of patients with other neurological diseases (OND). In the initial discovery phase of the project, CSF samples of 5 patients per group were analysed.

Preliminary Results
Out of a total of 925 detected peptides in CSF, 6 were differentially expressed between RRMS and SPMS, 17 between RRMS and OND, and 15 between SPMS and OND. Validation of ficolin-3 (FCN3), keratin-16 (KRT16), tenascin R (TNR), lactoferrin (LTF), junctional adhesion molecule 2 (JAM2) and secreted protein acidic and rich in cysteine like 1 (SPARC-like1) in a larger cohort (n=36) by ELISA and/or immunoblotting is currently underway.

Discussion
Using high-throughput body fluid profiling by LC mass spectrometry, small proteins and peptides were detected as promising candidate CSF biomarkers for diagnosis of RRMS transition towards SPMS. Validation in a larger cohort of RRMS and SPMS patients will hopefully lead to the discovery of clinically useful candidates.
Development and comparison of simulated driving setups

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Aim
Driving is a complex task that requires visual perception which relies on central and peripheral object detection. Previous research has shown that visual target detection depends on age, especially when peripheral objects need to be perceived[1]. Although simulation has been widely adopted for controlled driving evaluation, only a handful of studies have compared results between cross-platform simulators. Studying driving behavior across platforms is an important step towards understanding the findings of the various subtasks involved in Driving. Therefore, the aim of this project is to develop a hemisphere driving setup and compare it with the fixed frame simulated driving setup.

Methods
A hemisphere driving setup was developed involving the design of mechanical parts for a new steering wheel approach, software engineering and electronics design. A CAD software was used for the design of the steering wheel parts. The implementation of the distortion and the driving simulator was achieved using different tools such as programming on low level hardware access and with a high level 3D engine. Different distortion approaches and algorithms were implemented and compared for achieving the best possible image quality when projecting onto the hemisphere. The new projection hardware for the hemisphere projection was compared to the before used hardware in terms of contrast and achieved brightness. The complete setup was presented to different people. Based on their feedback, improvements have been made to the driving simulator setup. A system usability study is scheduled and aims to show the acceptance of the developed setup. Figure 1 shows the complete simulator setup.

Results
The new projection hardware showed increased brightness compared to earlier used hardware. The used distortion algorithms showed comparable results but with increased performance and software independent usage. Conclusions Hemispherical driving simulator setups show the immersion feeling and the realism grade of fixed frame driving setups combined with lower material costs and increased mobility. Acknowledgments Giuseppe Zito, for his help with the hemisphere projection and Urs Rohrer for his help in the design and production of the mechanical parts.

Reference
Predicting pure amnestic mild cognitive impairment conversion to Alzheimer’s disease using joint modeling of imaging and clinical data

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Aims
Predicting the conversion of amnestic mild cognitive impairment (aMCI) to Alzheimer’s disease (AD) is a challenging problem for which machine learning could be of great use. In this work, we aim at assessing the independent and joint value of imaging (structural MRI (sMRI), resting-state fMRI (rsfMRI)) and clinical data in classifying stable versus progressive aMCI patients.

Methods
We use baseline imaging and clinical data from 22 MCI, among whom 11 have converted to AD at follow up, and 11 have not. We extract both high and low dimensional features for imaging data: high dimensional features are the preprocessed images for sMRI, and connectivity vectors for rsfMRI. For low dimensional features, we compute singular value decomposition and select the first component. In order to combine modalities, we use the first component of each modality and concatenate them. A random forest classifier was deployed to discriminate between MCI converters and nonconverters.

Results
While baseline clinical data does not allow predicting conversion of aMCI to AD, rsfMRI yields accuracies of up to 82% (consistent across 2 atlases). These findings are extremely promising, considering that no previous studies have deployed pattern recognition tools on rsfMRI for conversion prediction. Using sMRI, we reach up to 77%; these results are in line with what is reported in the literature; however, it is important to note that most papers have used large datasets such as ADNI or AddNeuroMed. The use of joint imaging and clinical modalities yields up to 77% accuracy, with imaging data weighting more than clinical data in the classifier’s decision. The highest prediction accuracy that we reach is by combining both imaging modalities (86% accuracy, 91% specificity, 82% accuracy, p=0.001).

Conclusions
sMRI and rsfMRI were able to predict the future conversion of aMCI patients to AD, with accuracies of up to 86%.

Acknowledgments
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