Detection of Intact Borrelia garinii in a sural nerve biopsy

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Background
Mononeuropathy multiplex is a rare clinical manifestation of neuroborreliosis that is characterized by a multifocal axonal damage and painful sensations in the affected limb. The mechanism underlying these neuropathies remains still unclear, although interactions between anti-Borrelia antibodies and several peripheral nerve constituent molecules raise intriguing possibilities. Here, we present a patient in whom Borrelia garinii was immunohistochemically detected along the sural nerve.

Clinical Case
A 40-year-old male presented with a six-month history of B-symptoms and neuropathic pain of the right foot sole as well as tingling sensations of the back of his right foot. Neurologic examination revealed paretic flexors and extensors but also a paretic in-/eversion of his right foot, a reduced ankle jerk reflex, allodynia and a loss of touch sensations. Electrophysiologic studies yielded a predominantly axonal damage of the right peroneal, tibial, saphenous and sural nerve. MRI demonstrated inflammatory changes of the right ischiatic nerve. When CSF was investigated, lymphocytosis (126 cells/l), increased protein level (2.0 g/l) and intrathecal synthesis of IgM immunoglobulins were detected. Additional CSF analyses showed elevated CSF-serum indices for both, IgM as well as IgG, and to a lesser extent also increased HSV- and VZV-IgG indices. A biopsy of the affected right sural nerve showed extensive lymphocytic infiltrates and loosely distributed helical structures. Additional immunohistochemical investigations allowed to identify them as spirochetes. Using PCR of nerve tissue, these spirochetes could be assigned to borrelia garinii. Since a immunodeficiency was assumed as the underlying cause of this disease, a screening for malignancies and HIV was performed but have failed to identify a low immunity.

Conclusion
To the best of our knowledge, this is the first proof that B. garinii can infiltrate and persist in peripheral nerves in immunocompetent patients. Hence, local infection seems to be directly causal for nerve damage by triggering an excessive local immune response.
Disrupting myelin-specific Th17 cell trafficking to the gut dampens experimental autoimmune encephalomyelitis

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Background
Multiple sclerosis (MS) is a common autoimmune disease of the central nervous system (CNS). While an association between MS and inflammatory bowel diseases is observed, the link connecting intestinal immune responses and neuroinflammation remains unclear.

Aims
The aim of this study was to investigate the role of immune cell trafficking to the large intestine during experimental autoimmune encephalomyelitis (EAE), a murine model of MS, to assess their importance during neuroinflammation.

Methods
Active and adoptive transfer model of murine experimental autoimmune encephalomyelitis (EAE) were used. Immune cells isolated from the lamina propria of the large intestine were analyzed by flow cytometry and specific myelin reactive CD4+ T cells in the intestinal compartment were further evaluated ex vivo. Gene expression profiles of inflammatory markers were performed by RT-qPCR. Whole mount colonic analysis was performed to assess the localization of Th17 cells within the colon during EAE. Gut microbiota composition was evaluated by 16S rRNA gene sequencing.

Results
We observed that encephalitogenic Th17 cells infiltrate the colonic lamina propria before neurological symptom development using two murine MS models, the active and adoptive experimental autoimmune encephalomyelitis (EAE). Targeting specifically Th17 intestinal homing by blocking integrin α4β7-MAdCAM-1 pathway not only impaired T cell migration to the large intestine but further dampened EAE severity. Mechanistically myelin-specific Th17 cell proliferated in the colon and affected the gut microbiota composition. Finally, the beneficial effect of blocking the integrin α4β7-MAdCAM-1 pathway on EAE was interdependent of the gut microbiota.

Conclusion
Those results show that disrupting myelin-specific Th17 cell trafficking to the large intestine is sufficient to harness neuroinflammation and suggest that the gut environment and microbiota promote the activation of encephalitogenic Th17 cell. Blocking the migration of pro-inflammatory CD4+ T cells in the intestinal compartment alters the EAE disease course pointing towards a contribution of the gut-brain axis in EAE development. Although the link between gut immunity and MS has yet to be further clarified, a better understanding of how immune cells are generated and regulated in the intestine during neuroinflammation could support innovative approaches to dampen neuroinflammation by targeting the gut-brain axis.
Detection of novel CNS-specific antibodies using hiPSC-derived astrocytes and neurons: a pilot study on autoimmune-mediated neurological syndromes

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Aims
The last 10 years have seen a thrilling rise in the discovery of CNS-reactive auto-antibodies (Abs) involved in neurological disorders such as paraneoplastic syndromes (PNS), autoimmune encephalitis (AIE), neuromyelitis optica (NMO) or systemic lupus erythematosous (SLE). 7-11% of the patients developing auto-immune limbic encephalitis remain seronegative for all currently known neural antigens (Ag). This observation emphasizes the need for the development of new assays able to unravel the presence of yet unknown CNS-reactive Abs. We developed an innovative cell-based assay (CBA) using human-induced pluripotent stem cell (hiPSC)-derived neurons and astrocytes as a source of CNS Ag. We evaluated their capacity to detect auto-Abs in serum and cerebrospinal fluid (CSF) of patients with CNS diseases, the latter being likely due to auto-immune mechanisms but with negative routine antibody panel.

Methods
96-well plated hiPSC-derived astrocytes and neurons were incubated with paired serum/CSF of 109 patients suffering from inflammatory neurological diseases (IND) and 19 patients with non-inflammatory neurological diseases (NIND). IgG bound to CNS cells were detected using a combination of fluorescently labelled Ab. IgG-associated fluorescence intensity (FI) measure was semi-automated using a fluorescence plate reader. Serum or CSF were defined as positive using a ROUT test with a FDR at 2% on quantified FI. Each CBA well was also observed by fluorescence microscopy. To cross-validate the presence of CNS-reactive Ab, IgG reactivity was tested by flow cytometry using hiPSC-derived astrocytes and neurons exposed to the serum/CSF.

Results
Using our hiPSC-derived CBA, 20 patients (18 IND, 2 NIND) appeared positive on hiPSC-derived astrocytes/neurons including 5 patients previously diagnosed with auto-reactive Ab (3 NMO patients, one PNS and one SLE patient) and 15 with not-yet reported auto-reactive Ab. These results were confirmed by fluorescence microscopy and flow cytometry.

Conclusions
Our hiPSC-based CBA may allow discovering new CNS-reactive Abs. Such a potent tool opens new perspectives in understanding the mechanisms leading to autoimmune mediated neurological syndromes and may lead to improved diagnostic and therapeutic measures in patients with CNS autoimmune conditions.
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Comparison of recent pivotal recommendations for the diagnosis and treatment of late onset Pompe disease using diagnostic nodes

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Pompe disease is a rare autosomal-recessive disorder characterised by limb girdle myopathy and respiratory weakness in the late onset form (LOPD) and cardiomyopathy only in the early onset form. Various mutations in the acid alpha-glucosidase gene lead to toxic lysosomal and extra-lysosomal glycogen accumulation in all organs due to ineffective glycogen clearance by the encoded enzyme. Only one randomized trial demonstrated beneficial effects of respiratory function and meters walked in the 6-minute walking test with enzyme replacement therapy (ERT). These results were confirmed in several retrospective and prospective observations and in meta-analyses. Due to a potential life-long therapy, moderate efficacy and high treatment costs time of ERT initiation and cessation is an ongoing matter of debate. So far, several national and international recommendations have been published with different criteria concerning diagnosis, initiation and cessation of ERT in LOPD. We therefore formally analysed recent published recommendations and consensus statements of LOPD using diagnostic nodes (DODES) as a special software tool. With DODES, an objective analysis becomes possible if the content of the recommendations is represented as algorithms using cross-compatible elements. This analysis formally disclosed both, areas of great heterogeneity and concordance for the diagnosis and management of LOPD and paved the way for a Pompe disease burden scale focussing on ERT initiation. According to this investigation further clinical research should concentrate on ERT in pre-symptomatic and severely affected LOPD patients and on cessation criteria for ERT as these issues are areas of international uncertainty and discordance.
Small vessel disease is associated with an unfavorable outcome in stroke patients on oral anticoagulation

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Aims
Cerebral small vessel disease (SVD) is an important cause for both ischemic stroke (IS) and intracranial hemorrhage (ICH). To date, knowledge on the impact of SVD on the clinical course in stroke patients treated with oral anticoagulation (OAC) for atrial fibrillation (AF) is limited.

Methods
Registry-based prospective study of 320 patients (aged 78.2±9.2 years) treated with anticoagulation following AF-stroke. Patients underwent standardized magnetic-resonance-imaging assessing measures of SVD, including cerebral microbleeds (CMBs) and white matter lesions (WMLs). Median follow-up was 754 days. Using adjusted logistic and Cox regression we assessed the association of imaging measures with clinical outcome including recurrent IS, ICH and death and assessed disability.

Results
Recurrent IS was more common than ICH (22 versus 8, respectively). CMBs were related to an increased risk of the composite endpoint (IS, ICH, death: OR 2.05, 95%CI 1.27-3.31; p=0.003), as were WMLs (OR 2.00, 95%CI 1.23-3.27, p=0.005). This was also true in time-to-event analysis (CMBs: HR 9.17, 95%CI 1.39-3.52; p < 0.001; WMLs: HR 7.05, 95%CI 1.20-3.17; p=0.007). Both measures were associated with an increased risk for recurrent IS (CMBs: HR 4.4, 95%CI 1.07-18.2; p=0.04; WMLs: HR 5.27, 95%CI 1.08-25.79, p=0.04) and ICH (CMBs: HR 2.43, 95%CI 1.04-5.69; p=0.04; WMLs: HR 2.57, 95%CI 1.11-5.98, p=0.03). Furthermore, confluent WMLs were associated with increased disability (OR 4.03; 95%CI 2.16-7.52; p < 0.001) and mortality (HR 1.81, 95%CI 1.04-3.14, p=0.04).

Conclusions
In AF-stroke patients treated with oral anticoagulation, SVD is associated with an unfavorable outcome. The presence of microbleeds indicated a risk higher for recurrent ischemic stroke than for intracranial hemorrhage.
Do we have the appropriate tools for measuring cognitive decline in PD-MCI patients?

Aims
To explore cognitive, neuropsychological and daily functional-related cognitive deficits among PD patients, diagnosed with mild cognitive impairment (MCI). Level I diagnostic criteria for PD-MCI includes an abbreviated global cognitive assessment, and Level II requires at least two neuropsychological tests that assess cognitive functioning in 5 domains. PD-MCI is defined when performance is 1 to 2 standard deviations below cut-off norms scores, or significantly decline from estimated premorbid levels. Knowledge about cognitive deficits in the context of daily functioning in this population is scarce.

Methods
The study included 118 participants, ages 40-79, 77 diagnosed with PD who scored 22 to 25 on the global cognitive assessment Montreal Cognitive Assessment (MoCA). A control group included 41 healthy controls (HC) matched for gender, age, and education level, and scored 25 or higher on the MoCA. All participants achieved a score lower than 18 on the Beck Depression Inventory (BDI). Level II neuropsychological assessment tools were administered along with self-report questionnaires focused on participant’s daily function abilities, such as the Time Organization and Participation Scale (TOPS).

Results
No significant group differences were found for gender, age or education level. Most participants education level in both groups was academic (PD: 60%; HC: 70%). Analysis revealed a surprisingly low number of participants in the PD-MCI group with cognitive deficit, according to the neuropsychological tests cut-off scores (0-56.4%). The highest rates were identified by the Trail Making Test A (PD: 56.4%; HC: 19.5%), B (PD: 38.5%; HC: 22.0%), and the Rey-Osterrieth Complex Figure Test (copying PD: 25.6%; HC: 4.9%; delayed recall (PD: 24.4%; HC: 12.2%). The profiles exhibited higher mean scores and a different distribution curve to the norm. The TOPS revealed significant differences between the groups indicating deficient ability in timely organization of daily activities and consequent emotional frustration for the PD subjects.

Conclusion
These results support the ongoing discussion of the complexity of capturing PD-MCI, particularly among people with premorbid high education level. Considering the neuropsychological tests results, assessments which reflect these people’s real-life daily confrontations are warranted.
Impact of dietary factors and circadian rhythms on Fatigue in multiple sclerosis

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Background
Multiple sclerosis (MS) is a chronic inflammatory and autoimmune disease that affects the central nervous system. Fatigue is a common debilitating symptom experienced by patients with MS. However, it is a difficult symptom to treat efficiently. Recent studies suggest that food intake could impact fatigue. When assessing eating habits, researchers have classically focused on food content (i.e. calories and macronutrients intake), but for other diseases such as the metabolic syndrome, a new dimension is being explored, the timing of caloric intake. This increased interest in eating patterns, sometimes dubbed “chrononutrition”, with the underlying idea that the timing of caloric intake over the 24h cycle might interact with the circadian rhythm and have additional effects on metabolism.

Aims
The purpose of this pilot study was to assess the association between timing of food intake and fatigue among patients with MS and their caregivers as controls using questionnaires. Methods We set up a pilot survey of 33 patients with MS and 12 accompanying caregivers as control participants using an MS-specific and validated fatigue questionnaire in French (EMIF-SEP), which is composed of 40 items, as well as a questionnaire specifically addressing dietary timing developed by nutrition epidemiologists (currently in validation).

Results
Out of the 45 participants in the survey, 42 (93%) fully completed the EMIF-SEP and 45 (100%) the dietary rhythm questionnaires. Among the 41 women and 4 men, the mean age (± standard deviation) was 51 years (± 12) for the MS group and 53 years (± 13) in caregivers. MS patients were classified into relapsing-remitting (n = 19), secondary progressive and primary progressive (n = 8) and unspecified MS (n = 3). The mean EMIF-SEP score was 89 points (± 25) for the MS group and 83 (± 24) for the MS caregivers. The mean eating duration per 24h cycle was 12.7 h. (± 2) for the MS group versus 12.5 h. (± 1.6) for the MS caregivers during weekdays and 10.8 hours (± 2.2) and 11.1 (±1) respectively during weekends. Correlations between fatigue score and eating duration will be presented.

Conclusions
This pilot survey indicates that it is feasible to address the timing of caloric intake using a new questionnaire in MS patients and to correlate timing of food intake with fatigue. This study has led to the start of a larger study at the Lausanne University Hospital to evaluate the link between chrononutrition and fatigue in MS.
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Acute Ischemic Stroke, Atrial Fibrillation and Early DOAC-Treatment: 30-Day Risk of Recurrent Ischemic Stroke, Intracranial Haemorrhage in a Multi-Centre Individual Patient Data Meta-Analysis

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Aim
We aimed to investigate recurrent ischaemic stroke (IS) and symptomatic intracranial haemorrhage (ICH) early after a recent cerebral ischaemia in patients with atrial fibrillation (AF) and their time course in relation to the initiation of direct oral anticoagulants (DOACs).

Patient & Methods
International, individual patient data meta-analysis from 8 cohort studies. We included patients with acute IS or TIA, non-valvular AF, and a DOAC within 30 days. We excluded patients with symptomatic intracranial haemorrhage (ICH) within 24 hours of endovascular recanalization therapy (n=2), or not started on a DOAC within 30 days. The endpoints were recurrent IS (re-IS) and ICH within 30 days.

Results
We included 2555 patients (median age: 77 years, IQR 70-84), of which 2460 had IS (96.5%). The median NIHSS was 5 (IQR 2-10). DOAC were started after a median of 5 days (IQR 2-10). Re-IS occurred, after a median of 6 days (IQR 2-15), in 37 patients (1.4%); 16 of these re-IS (43%) occurred prior to DOAC-start. ICH occurred, after a median of 10 days (IQR 7.5-14), in 11 patients (0.4%); 6 of these ICH (55%) occurred after DOAC-start.

Conclusions
Among patients with acute IS and AF, nearly half of the re-IS occurred prior to DOAC-start, i.e. were potentially preventable. The number of ICH potentially attributable to early start of DOAC was very low. Ongoing randomized clinical trials will show whether an earlier DOAC-start can further reduce the risk of re-IS while keeping the risk of ICH low.
Tacrolimus in a patient with anti-HMGCR antibody-associated necrotizing autoimmune myopathy

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Background
Statins are among the most frequently prescribed drugs for the treatment of dyslipidemia and for risk reduction in cardiovascular disease. However, they can cause a wide spectrum of muscular adverse effects, from asymptomatic elevations of creatin kinase (CK) and myalgia to toxic necrotizing myopathy. While these effects are usually self-limiting upon discontinuation of the offending medication, in some instances statins trigger a severe autoimmune myopathy with antibodies that recognise 3-Hydroxy-2-methylglutaryl-coenzyme A reductase (HMGCR) that does not resolve when statin therapy is stopped. Recognition of statin-associated autoimmune myopathy is important as patients require immunosuppressive therapy to prevent progressive weakness.

Case Report
We present the case of a patient with statin-associated autoimmune myopathy that demonstrates the challenging management of this entity. The patient was initially treated with intravenous immunoglobulin (IVIg), which resulted in clinical improvement. However, CK levels remained above 6000 IU/L, requiring escalation of therapy. Add-on steroids coincided with aggravation of weakness. Despite an increase in the dose and frequency of IVIg, she experienced recurrent relapses. Rituximab was not effective, and the use of other immune-modulating agents, such as methotrexate and cyclophosphamide, was limited due to the presence of various comorbidities (liver disease, history of breast cancer). Therefore, tacrolimus was started as rescue therapy in combination with IVIg and steroids, which permitted clinical remission. The patient has remained stable with maintenance therapy consisting of tacrolimus and very-low-dose prednisone.

Conclusion
Statin-associated autoimmune myopathy is responsive to immunosuppressive therapy, however, as this case report illustrates, achieving clinical remission may be difficult and require the use of multiple immunotherapeutic agents. To our knowledge, this is the first report describing the successful use of tacrolimus in treating anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Tacrolimus may be effective for treatment and prevention of relapses in patients with statin-associated autoimmune myopathy.
80Hz vs. 130Hz: Differential effect STN DBS frequency on Oculomotor vs. Stroop task performance: an exploratory, double blind study

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Objectives
Deep Brain Stimulation of the subthalamic nucleus (STN-DBS) is an effective treatment for patients with advanced Parkinson’s disease (PD). The role of the frequency of stimulation is not fully understood. We compared the effect of 80 Hz and 130 Hz on functions mediated by the associative and oculomotor fronto-striatal loops by assessing several oculomotor tasks and a cognitive test (the Stroop test), in a randomised double blind design.

Methods
After overnight withdrawal of dopaminergic medication, 20 patients received 80Hz and 130 Hz stimulation in a randomised order during 24 hours. The amplitude of stimulation was adjusted to keep the energy delivered stable. The assessments included: Unified PD Rating Scale motor score (UPDRS-III), pro-saccade (S) and anti-saccades (AS) task and Stroop test. Horizontal eye movements were collected using an eye-tracking system consisting of an infrared camera and padded helmet (Mobile EBTH, e(ye)BRAIN. 24 horizontal saccades across 3 visual angles (5°, 10°,20°) were registered for both S and AS.

Results
Motor scores were similar between the two frequencies, tremor did not deteriorate. The saccade latencies and gain were similar for the two frequencies of stimulation during the S task. However, for AS, the error rate (10.2±6.3 vs. 12.2±5.73, p=0.02) and the latencies (326.0±101.6 ms vs. 381±135 ms, p= 0.03) were higher at 80Hz. The Stroop test revealed less errors in the more complex task at 80Hz (2.5±3.1 vs. 1.1±1.4 p=0.02).

Conclusions
The acute change of frequencies did not affect the clinical benefit measured with UPDRS III. However, antisaccade performance was superior at 130Hz stimulation, while performance on the complex Stroop task was comparatively better at 80Hz. This discrepancy might be related to interference with neural circuits differentially involved in lower-order oculomotor function versus higher-order cognitive tasks.
First ever treatment in Multiple Sclerosis: Fingolimod vs dimethyl fumarate - The Lausanne real life experience

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Background
Because patients with Multiple Sclerosis (MS) are now treated as early as possible after disease onset, the current MS treated population is much different from the patients included in the randomized clinical trials for disease modifying drugs: younger age, shorter disease duration, lower clinical and radiological disease activity. Objective: To study the efficacy and tolerance of fingolimod (FGL) and dimethyl-fumarate (DMF) in early treated, treatment-naive patients with relapsing-remitting MS.

Methods
From the Lausanne observational MS registry of 1616 patients, we retrospectively collected clinical and radiological data of the 82 patients fulfilling the following inclusion criteria: (i) first line treatment with FGL or DMF, (ii) initiation of treatment within 36 months after disease onset, (iii) minimal treatment duration of 12 m.

Results
There were 61 patients on FGL and 21 on DMF. Mean disease duration prior to treatment initiation was 14 m. Demographics and MRI characteristics at baseline were not significantly different in both groups, but patients on FGL had higher pre-treatment clinical activity (mean relapses 1.97, SD 0.98 vs 1.43, SD 1.17, p=0.04). Almost 20% of the patients in both groups had highly active disease (≥2 relapses/year prior to treatment initiation and ≥1 Gd-enhancing T1 lesion at treatment onset). At last follow-up (median 43 m, range 16-133), 53.3% of FGL and 66.7% of DMF patients reached NEDA 3 status (p=0.258), and median EDSS score remained stable in both groups. Both treatments significantly decreased the occurrence of new T1 Gd-enhancing lesions (FGL median number of lesions at onset 1.0, range 0-26, at last follow up 0, range 0-2, RR 0.31, 95% CI 0.168 – 0.577, p < 0.001, DMF at onset 1.0, range 0-8, at last follow up 0, range 0-5, RR 0.18, 95% CI 0.061 – 0.52, p < 0.001). Retention tended to be better in the DMF group (81% of the DMF patients versus 62.3% on FGL, p=0.2). The main reason for discontinuation was disease activity. No severe side effects occurred on both treatments.

Discussion
Our findings support both efficacy and tolerance of FGL and DMF in early treated, treatment naive MS patients. In Lausanne, FGL was more frequently prescribed than DMF (ratio 3:1), especially in patients with evidence of higher clinical disease activity. Despite the higher pre-treatment clinical activity in the FGL group, the majority of patients were free of disease activity at last follow-up.
Transcriptomic analysis of reactive human iPSC-derived astrocytes induced by neuroinflammatory cytokines

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Aims
Astrocytes occupy a central place in neuroinflammatory diseases, such as multiple sclerosis (MS). Recent studies in mice have identified two clear states of astrocyte reactivity, A1 and A2, respectively induced by neuroinflammation and transient ischemia. However, due to the difficulty in obtaining human astrocytes, validity of these data in a human context remains to be established. Here, we aimed at better characterizing human astrocyte reactivity in different neuroinflammatory conditions. To address this issue, we took advantage of our recently published serum-free technique to obtain resting astrocytes from human induced pluripotent stem cells (hiPSCs).

Methods
We generated hiPSC-derived astrocytes from healthy donors and MS patients and stimulated them with major neuroinflammatory cytokines (IL-6, IL-1β and/or TNFα) to assess their transcriptomic profile in response to these stimuli.

Results
Transcriptomic analysis of reactive astrocytes showed first that each of these three cytokines leads to the modulation of a specific set of genes, triggering a unique activation profile of astrocytes. Second, gene ontology analysis revealed that IL-6 triggered the upregulation of genes mainly involved in cell adhesion, CNS development and ion transport while IL-1β and TNFα led to the upregulation of genes mainly involved in the inflammatory response, interferon signaling and defense against viruses.

Conclusion
In conclusion, our study reveals specific activation states of astrocytes in response to neuroinflammatory cues, suggesting distinct functionalities in different inflammatory contexts. As each neuroinflammatory disease is associated to a different inflammatory CNS milieu, our data call for a more precise characterization of reactive astrocytes in a given disease to decipher their role in such conditions. Better understanding of these reactive states would lead to a better understanding of astrocyte roles in neuroinflammatory diseases and may allow identifying new therapeutic targets.
P20
Subdural versus subgaleal drainage for chronic subdural hematomas – a post hoc analysis of the TOSCAN trial

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Object
The use of subdural drains after surgical evacuation of chronic subdural hematoma decreases the risk of recurrence and has become the standard of care. Halfway through the highly controlled, randomized TOSCAN trial, our institutional guidelines changed to recommend subgaleal instead of subdural drainage. We report a post hoc analysis on the influence of drain location in patients participating in the TOSCAN trial.

Methods
We studied 361 patients enrolled in the TOSCAN trial. The patients were stratified according to whether they received surgery before (cohort A) or after (cohort B) the change in institutional protocol. We performed an intention-to-treat analysis with surgery for recurrence as the primary endpoint. Secondary endpoints were: outcome based on modified Rankin scale, seizures, infections, parenchymal brain injuries, and hematoma diameter.

Results
Of the 361 patients included in the analysis, 214 were stratified into cohort A (subdural drainage recommended), while 147 were stratified into cohort B (subgaleal drainage recommended). There was a 31.78% rate of cross-over from the subdural to the subgaleal drainage insertion site due to technical or anatomical difficulties. No differences in the rates of re-operation (21.5 vs 25.17%, p=0.415), infections (0.47 vs. 2.04%), seizures (3.27 vs 2.72%) or the rate of favorable outcomes at 1 and 6 months (91.26 vs 96.43%; 89.90 vs 91.55%) were noted between the two cohorts. Postoperatively, patients in cohort A had more frequent parenchymal brain tissue injuries (2.8 vs 0%). Postoperative absolute and relative hematoma reduction was similar irrespective of the location of the drain.

Conclusion
Subgaleal rather than subdural placement of the drain did not increase the risk for re-operation for recurrence of chronic subdural hematomas, nor did it have a negative impact on clinical or radiological outcome. The intention to place a subdural drain was associated with a higher rate of parenchymal injuries.
P21
Pituitary function and endocrinological outcome of transsphenoidal surgery with respect to Shape-grade - a SwissPit study

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Aim
Transsphenoidal surgery may lead to restoration but also to new deficiencies of pituitary function. The Shape-classification has been introduced to systematically describe different growth patterns of pituitary tumors. In nonfunctioning adenoma (NFA) it was shown, that the higher the Shape-grade, the less likely a total resection and decompression of the optic chiasm and pituitary stalk was possible. The aim of this retrospective study is to describe the correlation between Sahpe-grades and the endocrinological outcome in NFA.

Methods
Patients suffering from NFA treated by transsphenoidal surgery at the authors’ institution 2005-2017 were eligible for inclusion. Gross total resection (GTR), preoperative tumor and remnant volume, Knosp grades, decompression of the pituitary stalk, pre- and postoperative pituitary function were assessed with respect to the individual Shape-grade. Based on the maximum coronar and sagittal tumor diameters and the relation to surrounding structures the following grades are distinguished: I) round appearance; IIA) oval shape without CS invasion; IIB) oval with CS invasion; III) dumbbell-shaped with narrowing at sphenoidal plane; IV) mushroom-shaped; V) polyllobulated.

Results
189 patients (Shape-I, n=28 (15%); Shape-IIA, n=66 (35%); Shape-IIB, n=25 (13%); Shape-III, n=37 (19%); Shape-IV, n=12 (6%); Shape-V, n=21 (11%)) were included. The GTR and pituitary stalk decompression rates varied significantly between the different Shape-grades with higher grades being less likely to be totally resected and the pituitary stalk decompressed. Hypopituitarism was more prevalent in higher shape grades pre- and postoperatively (e.g. Shape I, 53%/21%; Shape V, 81%/56%). The likelihood for endocrinological recovery was higher in lower Shape-grades, whereas the risk for new hormonal deficiencies rose in higher Shape-grades.

Conclusion
The pituitary function as well as the endocrinological outcome of transsphenoidal surgery for NFA is influenced by the shape of a pituitary adenoma. The Shape-classification offers a standardized grading system to assess the different tumor shapes.
P22
Current patterns of practice in spinal Fusion for chronic Low Back Pain – Results from a Survey at the German Spine Societies' Annual Congress 2018

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Background
The indication for lumbar spine fusion as well as the preoperative selection criteria for patients suffering from chronic lower back pain (CLBP) and corresponding degenerative changes but without nerve root compression or neurogenic claudication are under debate. In such patients, literature suggests minimal improvement after surgical treatment, however for many it remains a last solution after all conservative treatments have failed. The aim of this study was to examine and compare patterns found in current practice.

Method
A total of 143 printed questionnaires containing 51 questions were distributed at the German Spine Societies' annual congress 6-8 December 2018.

Results
127 (89%) surveys were returned by 64 orthopaedic surgeons and 63 neurosurgeons, 29 working at a university hospital, 57 in a non-university public hospital and 41 in a private hospital or practice. Thirty-one were chairmen of their clinic, 62 consultants and 20 board certified surgeons. The mean experience of respondents was 14.5±8.1 years. The majority of 41 surgeons (32.3%) answered to perform 1-10 lumbar fusion procedures for patients with CLBP per year, 20 perform 11-20, 10 perform 21-30 and 17 answered to performing more than 50. 28 (22%) perform none. The majority of 42.5% of surgeons treats their patients for at least 6-12 months conservatively before considering surgery. Thirty-six (28.3%) respondents would each consider a postoperative pain reduction of 50-60% or 60-70% a treatment success. When asked for an estimate of the percentage of patients with good surgical results after fusion for CLBP 45 (38.4%) respondents think that less than 50% exhibit good results and only 17 (13.4%) think that 70% or more exhibit good results. Orthopaedic surgeons perform more lumbar fusion surgeries than neurosurgeons (p=0.04*), fuse more lumbar segments than neurosurgeons (p= 0.03*), are more likely to order their CLBP patients to cease smoking preoperatively (p=0.02*) and are satisfied with a lesser pain reduction postoperatively (p=0.01*) than neurosurgeons.

Conclusions
Despite the discouraging evidence in literature, the majority of respondents still perform fusion surgery in CLBP- patients. Orthopaedic surgeons appear to be slightly more optimistic with surgical results but as it appears had a lower threshold on what to consider a surgical success.
P23 Reduction of external ventricular drain associated infections after introduction of a chlorhexidine containing dressing

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Background
Dressings containing chlorhexidine (CHX) lower the incidence of external ventricular drain (EVD)-associated infections (EVDAIs). In a previous prospective randomized trial (RCT) at the University Hospital Basel (NCT02078830), a significant reduction in bacterial cutaneous and catheter colonization was detected. However, the study was underpowered to demonstrate an effect on the incidence of EVDAI.

Methods
Retrospective (2009-2013) and prospective (2014-2017) review of patients undergoing EVD-insertion at the University Hospital Basel. The control group consisted of patients from January 2009 to October 2013, where the CHX-dressings were not in use. The study group consisted of patients between February 2016 and December 2017, where CHX-dressing was standard of care. Comparisons were made using the Chi-squared test. Primary endpoint was the diagnosis of EVDAI. Statistical significance was set at P ≤ .05.

Results
224 out of 306 (73.2%) patients were eligible for analysis. 79 out of 224 (35.3%) were assigned to the control group, 55 out of 224 (24.6%) to the RCT-group and 90 out of 224 (40.2%) to the study group. During the whole study period, 118 out of 224 (52.7%) received a CHX-dressing while 106 out of 224 (47.3%) did not. The rate of EVDAI was substantially lower after the introduction of the CHX-dressing as a standard of care with 7 out of 90 (7.8%) when compared to 13 out of 79 (16.4%) patients in the control group. The difference did not reach statistical significance (p=.083). However, the cumulative incidence (4.1 vs. 7.7) and the prevalence (8 vs. 16 per 100 persons) nearly halved respectively. A significant decrease in EVDAI of approximately 8% was observed, when a CHX-dressing was used. In detail, 12 out of 118 (10.2%) in the CHX compared to 19 out of 106 (17.9%) in the Non-CHX-group developed EVDAI (p=.036).

Conclusion
CHX-containing dressings as a standard of care for the exit site of EVD effectively reduce the incidence of EVDAI.
Angiographic Analyses of natural anastomoses between the posterior and anterior cerebral arteries in Moyamoya disease

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Background and Purpose
Moyamoya disease is a chronic neurovascular steno-occlusive disease of the internal carotid artery and its main branches, associated with the development of compensatory vascular collaterals. A detailed description of collateral circles in literature is lacking. Generally, the posterior circulation is less affected by the pathology and its vascular flow could compensate the hypoperfusion of the ICA territories. The aim of this study is to describe these connections between the posterior cerebral artery and the anterior cerebral artery necessary to compensate the ACA territories hypoperfusion in Moyamoya population.

Materials and Methods
All patients treated for Moyamoya disease from 2004 to 2018 in 4 neurosurgical centers with available cerebral digital subtraction angiography were included. 40 patients (80 hemispheres) with the diagnosis of Moyamoya disease were evaluated. The presence of anastomoses between the PCA and the ACA was found in 31 hemispheres.

Results
31 hemispheres (38.75 %) presented a collateral circle between the PCA and the ACA. The most frequently encountered collaterals were branches from the posterior callosal artery (20 % of cases), and from the posterior choroidal arteries (20 % of cases). Other connections found were pio-pial anastomosis between cortical branches of the PCA and the ACA (15 %). We also proposed a four-grade classification based on the competence of these anastomoses to supply retrogradely ACA’s territories.

Conclusion
We found three different types of anastomoses between the anterior and posterior circulation, with different ability to compensate the anterior circulation. Their development depends on the perfusion needs of the anterior cerebral artery territories and can provide to the retrograde refilling of the ACA branches.
P25
Chemosensory function in posttraumatic patients: the role of olfactory distortions

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Background
The chemical senses comprise smell, taste and intranasal trigeminal function. These systems allow humans to detect their molecular environment. After traumatic head injury chemosensory functions are often impaired. Patients complain not only about quantitative loss (anosmia/hyposmia), but also qualitative impairment, such as parosmia (distorted perception of odors) or phantosmia (odor hallucination). The origin and clinical significance of these olfactory distortions are poorly understood. We aimed to establish the chemosensory characteristics (smell, taste, trigeminal) of posttraumatic patients (PP) and analyzed whether olfactory distortions influence the degree of chemosensory impairment.

Methods
We performed a retrospective study based on 75 patients with olfactory complaints following head trauma. We assessed their chemosensory function with Sniffin’ Sticks (olfaction), lateralization test (trigeminal), and taste strips (taste). Demographics, test and CT scan/MRI results were reported in a database. Data were analyzed with unpaired t-test with Welch’s correction, Mann-Whitney test, and Fischer’s exact test. Statistical significance was reached when p< 0.05.

Results
Besides olfaction, taste and trigeminal function were also slightly below normal values in PP. The mean identification test score (+/-SD) was higher in the group with distortions (7.1+/-2.6; n=34) compared to the group without (5.6+/-3.2; n=41; p< 0.05). Regarding the percentage of subjects with cerebral abnormalities, gender and results of other chemosensory tests, there was no significant difference between the two groups.

Conclusion
We found that patients with qualitative dysfunction have better odor identification test scores compared to those without qualitative dysfunction. It may support the hypothesis that parosmia or phantosmia may be a sign of olfactory neuroregeneration. A longitudinal study is needed to further assess whether these symptoms may be a useful prognostic factor for olfactory recovery after head injury.
P26  
Prehemorrhage antiplatelet use in aneurysmal subarachnoid haemorrhage and its impact on clinical outcome

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Aim
The aim of this study was to investigate whether the rebleed rate and rate of poor outcome were influenced by the use of antiplatelet agents before aneurysmal subarachnoid hemorrhage (aSAH).

Methods
Patients were collected from prospective databases of two tertiary referral centers for aSAH patients. Patients were divided into “antiplatelet user” and “nonuser” according to their use of antiplatelet agents before the initial hemorrhage. With multivariate analyses we assessed the use of antiplatelets regarding rebleed rate and poor outcome, defined as Glasgow outcome Scale 1-3 at 6 months follow-up. In the antiplatelet user group, the impact of thrombocyte transfusion on rebleed rate and poor outcome was calculated.

Results
A total of 1,134 patients were included (15.2% antiplatelet users). Patients in the antiplatelet user group were significantly older with higher incidence of hypertension, diabetes and hypercholesterinemia. Antiplatelet users showed both a significant increase in in-hospital mortality (25.4% vs. 17.0%, p = 0.031) as well as poor outcome (57.4% vs. 43.3%, p=0.003). No difference in rebleed rates was seen. In multivariate analysis, antiplatelet use remained associated with poor outcome (OR 1.83, 95% CI 1.22-2.74; p = 0.04). Thrombocyte transfusion did not lead to a significant change in rebleed rate or poor outcome (transfusion vs. no transfusion: 11.1% vs. 16.0%, p = 0.37 and 59.6% vs. 59.1%, p = 0.96, respectively).

Conclusion
In this multicenter study the use of antiplatelet agents before aSAH was associated with increased risk of poor outcome at 6 months without significant increase in rebleed rate. Thrombocyte transfusion had no impact on rebleed or outcome.
Intravenous Thrombolysis versus Endovascular Therapy in Acute Middle Cerebral Artery M2-Segment Occlusion: A Monocenter Cohort Study

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Introduction
Since the endovascular milestone stroke trials there is striking evidence for endovascular treatment in acute stroke patients with proximal vessel occlusion of the anterior cerebral circulation. However, there is limited evidence available for endovascular treatment in acute stroke patients with M2-segment occlusion of the middle cerebral artery. Recent data shows that endovascular treatment (EVT) might be also beneficial in selected patients with acute M2 occlusions (1). Thus, we aimed to compare the safety and effectiveness of EVT versus intravenous thrombolysis with recombinant tissue plasminogen activator (iv-rtPA) in M2-occlusions.

Method
Retrospective, monocenter, cohort-study of 120 stroke patients with acute M2-occlusion and complete follow-up from a comprehensive stroke center between 2014 and 2018, of whom 24 (20%) patients received iv-rtPA and 61 patients (51%) were treated with EVT. Epidemiological, clinical and radiological data were statistically analyzed.

Results
The median NIHSS on admission was similar for both groups (EVT group = 10; iv-rtPA= 8; p=0.83). The rate of good clinical outcome (modified Rankin Scale (mRS) ≤2) was significantly higher in the EVT group (75%) compared to the iv-rtPA group (46%) (p=0.009), whereas the mortality rate was significantly higher in the iv-rtPA group (29%) compared to the EVT group (10%) (p=0.026). The intracranial hemorrhage rate was similar for both groups (13% vs. 5%, p=0.2).

Conclusion
This retrospective cohort-study suggests that endovascular treatment of acute stroke patients with M2 occlusion might be beneficial compared to iv-thrombolysis only.
P28
Build-Up Effect of Motor Evoked Potentials

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Background and Objective
Interpretation of MEPs during intraoperative neurophysiological monitoring is a debated issue. Warning criteria vary among centers: Presence and absence of myogenic responses, increase in stimulus threshold and decrease in response amplitudes, which may carry different meanings for monitoring of brain, brainstem, or spinal cord surgery. The phenomenon of increase of MEP amplitudes during rapid sequences of stimuli has been described usually when stimulations are done at frequencies of 1 or 2 Hz. So far it is unknown, whether or not the presence or magnitude of this build-up effect correlates to clinical findings, or if it can be used intraoperatively to assess reversible damage to the motor system.

Methods
Muscle MEPs from upper and or lower extremity muscles were recorded during surgeries for spinal or intracranial pathologies in 50 patients with and without neurological dysfunction. All MEP amplitudes of ten subsequent responses were recorded at baseline and closing at stimulus intensities 10% above motor threshold using stimulus rates of 1 Hz and 2 Hz. MEP-amplitudes were plotted against the number of stimulations. Presence of build-up was noted with subsequent increase of amplitudes by at least 30% from the first response of ten. The clinical status was recorded before and after surgery using the NIHSS and the MRC muscle strength (0-5). Presence and absence of a build-up effect was correlated to the presence or absence of motor deficits.

Results
MEP amplitude build-up was noted to be present in 46%, and absent in 54%. Patients without build-up had a higher likelihood of having motor deficits. The majority of those patients with motor deficits and without build-up at baseline showed appearance of a build-up after tumor removal or neural decompression.

Conclusion
Presence of MEP amplitude build-up effect seemed to be associated with intact motor function and loss of the effect with motor impairment. Further studies are needed to elucidate this relation.
P29
Combating Glioblastoma: Activation of microglia by targeting CD47 and Siglecs

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Aims
Instead of targeting the tumor cells directly, modulation of the tumor microenvironment (TME) has gained more attention. Microglia (MG), the most prevalent cell type of the GBM-TME, represents a promising cell population for modulation. Here we aim at defining the role of inhibitory CD33-related Siglecs on MG, in particular Siglec-9, in GBM progression, and as an additional target to CD47-Sirpa disruption for MG specific immunotherapy in GBM patients.

Methods
To gather information about the expression and prognostic implication of Siglecs in GBM-associated MG, human MG are directly sorted from resected tumors by flow cytometry using a MG specific marker panel and subjected to RNAseq analysis. Mouse MG are sorted from MG reporter mice. Sorted human/mouse MG are co-cultured in vitro with respective tumor cells, and anti-Siglec-9 and/or anti-CD47 antibodies are administered to assess tumor cell phagocytosis by flow cytometry and time-lapse imaging.

Results
Flow-cytometric characterization revealed high expression of Siglec-9 on human GBM-associated MG and a gradient from the tumor center to periphery (51.2% center vs. 29.2% periphery). Phagocytosis assays with human PBMC-derived macrophages (M0) co-cultured with GBM-cell lines showed a significant increase in tumor-phagocytizing M0 in the combination treatment compared to control or anti-CD47 alone (1.46% control vs 8.46% combination, p = 0.001; 5.87% anti-CD47 vs 8.46% combination, p = 0.007). We did not see a significant increase with anti-Siglec-9 alone. However, after enzymatic removal of sialic acid on the tumor cells by treatment with sialidase and therefore targeting not only Siglec-9 but all the Siglec receptors, we observed a significant increase in phagocytosis (1.08% control vs 14.85% desialylation, p < 0.001) which could be even boosted by adding anti-CD47 (14.85% desialylation vs 21.8% desialylation + anti-CD47, p < 0.05). Phagocytosis assays performed with mouse MG showed as well a significant increase in GBM-cell phagocytosis in the combination treatment compared to control (1.36% control vs 6.62% combination, p < 0.05).

Conclusion
Taken together our findings implicate the sialic acid-Siglec pathway as a potential ‘don’t eat me signal’ in M0 and MG. But to fully restore the phagocytic capacity, combination with other ‘don’t eat me signals’ like CD47 and/or inhibition of several Siglecs by targeting their ligand seems to be a promising approach, which we will confirm in-vivo.
P30
Radiomics-based thrombus features predict the number of passes for arterial recanalization in patients with acute ischemic stroke

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Aims
Stentretriever-based mechanical thrombectomy (MTB) is a reference treatment for acute ischemic stroke (AIS) due to large artery occlusion, but the more attempts to retrieve the occluding thrombus, the worse the clinical outcome. Thrombus radiomics features (RF) are predictive of recanalization with IV alteplase and may help predict the number of passes needed for successful recanalization with MTB.

Methods
Intracranial thrombi of 47 patients with AIS due to anterior circulation large-vessel occlusion were segmented. 1477 RF were extracted from non-contrast CT scan (NCCT). A linear regression analysis was applied to select RF most strongly associated with the number of passes for complete recanalization. These RF were then used to train a support-vector regression machine-learning classifier. The machine-learning classifier was finally tested on an independent consecutive cohort of 15 patient.

Results
Selected thrombus radiomics features computed from NCCT are predictive of the number of passes with MTB for successful arterial recanalization (R-squared: 0.663, p < 0.05; on the independent testing cohort). Notably, our machine-learning model performed better than thrombus length, volume, mean or maximal attenuation coefficient (all p < 0.05).

Conclusions
Radiomics-based intracranial thrombus features accurately predict the number of attempts to retrieve the occluding thrombus in acute ischemic stroke.
Brain functional connectivity predicts outcome in comatose patients after cardiac arrest

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Clinical outcome prognostication in comatose patients following cardiac arrest is currently based on multimodal assessments of clinical and electrophysiological markers. This requires the intervention of trained experts and lacks standardization. Quantitative Electroencephalography (EEG) analysis could provide complementary and unbiased information about patients’ chances of recovery. Here we investigate the properties of EEG-based functional brain networks in comatose patients and their predictive power regarding patient’s outcome. During the first day of coma, we used 63 channel EEG to prospectively record resting state activity in comatose patients after cardiac arrest. Of the 92 patients included in our study, 55 survived beyond unresponsive wakefulness. Functional networks were based on the ‘debiased weighted phase lag index’ computed over epochs of five seconds. We derived topological features, including clustering coefficient, path length, modularity and participation coefficient. For all topological measures, we investigated their variance over time and computed predictive values for patients’ outcome by splitting the sample in training and test datasets. Group-level analysis revealed significantly different network organization during the first day in survivors and non-survivors. Time variance of path length provided the best test set prediction of good outcome on the first day of coma (PPV:.85, CI:.55-.98, Specificity:.89, 95% CI:.65-.99). Excluding patients with epileptiform activity would have eliminated all false positive predictions. Overall, the time variance of path length in functional connectivity is highly informative of patients’ outcome as survivors exhibit a richer repertoire of path length than non-survivors during the first day.
P32 MRI-EEG correlation for outcome prediction in post-anoxic myoclonus, a multicenter study

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Aims
Post-anoxic myoclonus (PAM) is historically considered a strong predictor of poor prognostic after cardiac arrest (CA). Although recent studies suggested that a subset of these patients may improve towards a good outcome, identifying these patients has been difficult. We examined the prognostic ability of EEG and MRI in combination to identify patients with good outcome in a multi-centric retrospective study.

Methods
Adults with PAM who had an MRI within 20 days after CA were identified in four prospective CA registries. The primary outcome measure was coma recovery to following commands by hospital discharge. Clinical exam included brainstem reflexes and motor activity. EEG was assessed by local certified neurophysiologists for best background continuity, reactivity, presence of epileptiform activity, and burst suppression with identical bursts (BSIB). MRI was examined by local neuroradiologists for presence of diffusion restriction and/or FLAIR changes consistent with anoxic brain injury. A prediction model was developed using optimal combination of variables.

Results
Among 78 patients (median 56 years; 37% women) 11 (14.1 %) followed commands at discharge, 7 (9 %) had good outcome (CPC<3) at three months and 61 (78%) died. Patients who followed commands were more likely to have pupillary and corneal reflexes, motor response of flexion or better, EEG continuity and reactivity, no BSIB and no anoxic injury on MRI. EEG was continuous in 23 patients (29%), reactive in 18 (23%), and in 73 (94%) showed epileptiform patterns. In patients who followed commands, EEG was continuous in all, reactive in 8 (72.7%), and epileptiform in 9 (81.8%); no patients showed BSIB. In patients who did not follow commands, EEG was continuous in 12 (18%, p<0.001 as compared to following commands), reactive in 10 (15%, p<0.001), epileptiform in 65 (95.5%, p=0.093), and had BSIB in 38 (57%, p=0.001). MRI revealed anoxic brain injury in 61 patients (78%). In patients who followed commands, anoxic injury was present in 1, with subtle changes in the corona radiata. In patients who did not recover to follow commands, anoxic changes were seen in 60 (89%, p<0.001). The combined EEG/MRI variable of continuous background and no anoxic changes on MRI was associated coma recovery at hospital discharge with sensitivity 91% (95%CI:0.59-1.00), specificity 99% (95%CI:0.92-1.00), positive predictive value 91% (95%CI:0.59-1.00), and negative predictive value 99% (95%CI:0.92-1.00).

Conclusions
EEG and MRI are complementary and identifies both good and poor outcome in patients with PAM with high accuracy. An MRI should be considered in patients with continuous or reactive EEGs.
A score to identify patients with good outcome after early epileptiform EEG following cardiac arrest

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Aims
Epileptiform patterns, occurring in about 1/3 of comatose patients after cardiac arrest (CA), are often but not invariably associated with poor outcome (1, 2). Our aim is to explore whether a combination of particular EEG patterns among those with epileptiform activity may identify patients with favourable outcome.

Methods
We retrospectively analysed a registry of comatose post-CA patients with epileptiform EEG within 3 days, admitted at two centres (CHUV, Sion Hospital; January 2013 - February 2019). EEGs at 12-36h and 36-72h from CA were scored with the ACNS nomenclature (3) (background, reactivity, status epilepticus, seizures). EEG features were compared according to outcome (CPC 1-3 vs 4-5) at three months. Significant EEG variables were combined in a score assessed with ROC curves; its correlation with serum neuron-specific enolase (NSE) was tested. Validation was obtained on an external independent cohort (BWH, Boston, USA).

Results
Among 488 patients, 107 had early epileptiform EEG. CPC 1-3, reached in 18 (17%), was associated with absence of epileptiform abnormalities and background continuity ≥ 50% at 12-36h (p < 0.00001 each), reactivity at 12-36h and 36-72h (p < 0.0001 each), normal background amplitude (p = 0.0004) and SIRPs at 36-72h (p = 0.0001). A 6-points score including these variables with a cut-off of ≥ 2 had sensitivity of 100% and specificity of 70% for CPC 1-3 (AUC = 0.98, 95% CI 0.94-1). A robust negative correlation was found between increasing EEG score and NSE peak values (r = -0.46, p = 0.0001). In the validation cohort, score ≥ 2 was 100% sensitive and 88% specific for Best CPC 1-3 (AUC = 0.96, 95% CI 0.91-1).
Correlation of somatosensory evoked potentials amplitude after cardiac arrest with other outcome prognosticators

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Aims

In comatose patients after cardiac arrest (CA), bilateral absence of cortical somato-sensory evoked potentials (SSEPs) responses is considered a specific poor outcome predictor. Recent studies 1,2 suggest that their amplitude may bear additional prognostic information. Our aim is to explore the SSEP amplitude relationship with other known prognosticators.

Methods

Cortical SSEPs amplitudes were measured (N20/P25 peak-to-peak, Fz reference)1,2 in consecutive patients of the Lausanne CA registry. We assessed their correlation with pupillary light reflex (PLR), motor response at 72h, EEG reactivity and absence of epileptiform features, and serum NSE peak. An amplitude cut-off was sought; its added value predicting poor prognosis (CPC 4-5 within 3 months) in addition to other tests was explored using ROC curves.

Results

Among 158 patients, 114 (72%) men, aged 62.5y (± 14.6), 86 (54%) awakened within three months. Mean SSEPs amplitude was 3.08 (2.03) in awakeners vs 1.25 (1.71) uV in the others (p < 0.0001). SSEP amplitudes were negatively correlated with serum NSE (r = -0.379; p < 0.0001), positively with both EEG at 12-36h and 36-72h components (respectively, r = 0.462, p < 0.0001; r = 0.448; p < 0.0001), and positively with present motor response and PLR (both p < 0 .0001). A SSEP amplitude ≤ 0.41 uV was 100% specific (95% CI, 96-100%), and 47 % sensitive (95% CI, 35-59%) for CPC 4-5 (AUC = 0.802, 95%CI, 0.730- 0.874). A score including EEG (reactivity, epileptiform features at 12-36h), clinical (presence of myoclonus, absence of PLR) and biochemical parameters (peak NSE) was 100% specific (95%CI, 96-100%) and 38% sensitive (95%CI, 26-51%) for CPC 4-5, with an AUC = 0.889 (95%CI 0.831-0.947). Adding SSEPs ≤ 0.41 uV, sensitivity was 44% (95%CI, 32-57%), and AUC=0.839 (95% CI 0.768-0.910). This difference was not statistically significant (p = 0.13).

Conclusion

Even if SSEPs amplitudes correlate with clinical outcome and other recognized prognostic variables, adding them to a multimodal prognostication including EEG, clinical and biochemical variables does not enhance poor outcome prediction, suggesting that SSEP are redundant in clinical practice if considering others predictors.
High-density ECoG improves the detection of high frequency oscillations that predict seizure outcome

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Objectives
Residual fast ripples (FR) in the intraoperative ECoG are highly specific predictors of postsurgical seizure recurrence. However, a FR is generated by a small patch of cortical tissue. Spatial sampling with standard electrodes may thus miss clinically relevant information.

Methods
We analyzed FR rates in the intraoperative ECoG of 22 patients that underwent resective epilepsy surgery. We used standard electrodes with 10 mm inter-contact spacing (standard ECoG) in 14 surgeries and high-density grid electrodes with 5 mm spacing (hd-ECoG) in 8 surgeries. We detected FR using a previously validated automatic detector.

Results
Postoperative seizure freedom was achieved in 13/22 (59%) cases. Across all 42 ECoG recordings, FR rates were higher for hd-ECoG than for standard ECoG. In the 13 seizure free patients (ILAE 1), no residual FR were detected (specificity = 100%). In the 10 patients with seizure recurrence (ILAE > 1), residual FR were detected in 2/2 hd-ECoG and 1/8 standard ECoG (Accuracy ACCstandard ECoG = 50%, CI [23% 77%], ACChd-ECoG = 100%, CI [63% 100%]).

Conclusion
Denser spatial sampling by hd-ECoG improved FR detection and thus seizure outcome prediction compared to standard ECoG. Significance: Hd-ECoG may advance seizure freedom after epilepsy surgery.
High-Frequency oscillations in scalp EEG mirror seizure frequency in pediatric focal epilepsy

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Objective
High-frequency oscillations (HFO) are promising EEG biomarkers of epileptogenicity. While the evidence supporting their significance derives mainly from invasive recordings, recent studies have extended these observations to HFO recorded in the widely accessible scalp EEG. Here, we investigated whether scalp HFO in drug-resistant focal epilepsy correspond to epilepsy severity, if they are related to invasive HFO and how they are affected by surgical therapy.

Methods
In 11 children with drug-resistant focal epilepsy that underwent epilepsy surgery, we recorded pre- and postsurgical scalp EEG with a custom-made low-noise amplifier (LNA), in addition to a commercial device (CD). In four of these children, we also recorded intraoperative electrocorticography (ECoG). To detect clinically relevant HFO in both scalp EEG and ECoG, we applied a previously validated automated detector in the time-frequency domain. We compared the scalp HFO rates with the seizure frequency and the HFO location between scalp EEG and ECoG.

Results
Scalp HFO rates showed a significant positive correlation with seizure frequency (R² = 0.84, p < 0.001). Overall, scalp HFO rates were higher in patients with active epilepsy (17 recordings, p = 0.006, PPV = 93%, NPV = 100%, accuracy = 94% CI [71% 100%]) and decreased following successful epilepsy surgery. Higher scalp HFO rates were detected with the LNA compared to the CD (p < 0.001). The location of the highest HFO rates in scalp EEG matched the location of the highest HFO rates in ECoG.

Significance
HFO in scalp EEG mirror seizure frequency, and thus disease severity, in children with drug-resistant focal epilepsy. The LNA considerably improves detectability, and the automated detector ensures a prospective, bias-free definition of clinically relevant HFO in scalp EEG. This study is the first step towards using non-invasively recorded scalp HFO for therapy monitoring in patients affected by epilepsy.
Brain-computer interfaces based on cortical source activity during attempted movements reconstructed from high-density EEG in patients with amyotrophic lateral sclerosis

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Aims
For people with motor neuron diseases, such as amyotrophic lateral sclerosis (ALS), a brain-computer interface (BCI) may be the only way to provide a means of communication. Bypassing any muscular output function, a BCI directly translates brain patterns into control signals for communication and environmental control. To this end, we studied the brain patterns in response to different movement attempts in healthy subjects and in five people with ALS with different severity of paralysis, ranging from partial paralysis to complete locked-in syndrome.

Methods
The subjects performed a delayed instructed movement task with a range of movements. Movement instructions were presented on a screen or as spoken words from a loudspeaker, and were followed after two seconds by a go cue. As the subjects performed the task, we recorded high-density electroencephalogram (EEG), electrooculogram, and electromyogram using a 128-channel recording system (ANT Neuro). We co-registered the EEG electrode positions with the structural magnetic resonance imaging scans to accurately reconstruct the sources of cortical activity. We then calibrated a regularized linear discriminant analysis decoder on movement-related cortical potentials (MRCPs) and event-related desynchronization and synchronization (ERDS) responses in the beta frequency bands.

Results
We characterized the subjects’ motor-evoked responses, even in the absence of any actual movements. We found preparatory responses and MRCPs in the low-frequency range, as well as ERDS responses present in different frequency bands for different subjects. Surprisingly, these responses could be identified in single trials. Our decoder successfully detected feet, wrist and finger movements in an asynchronous test scenario.

Conclusion
These results demonstrate the potential to develop an effective communication BCI based on high-density EEG cortical source reconstruction for people with locked-in syndrome.
Decoding gait events from high density EEG in healthy volunteers as preliminary step towards brain-controlled neuromodulation in people with paraplegia

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Accurate decoding of gait events from electroencephalographic (EEG) recordings would provide the optimal information to trigger spinal cord stimulation in order to alleviate gait deficits and promote functional recovery in people with paraplegia. As a preliminary step towards this goal, we investigated cortical dynamics reconstructed from high-density EEG recordings (128 electrodes) during walking on a treadmill and overground in ten healthy volunteers. In order to track and study gait, we recorded bilateral electromyographic (EMG) activity from seven lower extremity muscles, and used a motion capture system to acquire three-dimensional kinematics during walking. We identified key gait events (foot strike and foot off) by analysis of EMG signals and kinematic parameters. We reconstructed cortical dynamics using EEG source imaging based on individual anatomy derived from structural magnetic resonance imaging scans. In accordance with previous literature, we found low gamma (28-40 Hz) amplitude modulations related to gait phases that occurred specifically in the leg motor cortical areas. Surprisingly, we also found that these gait-related amplitude modulations were detectable at a single trial level, which is a prerequisite for accurate decoding of gait events. We then calibrated a decoder that detected gait events from the reconstructed activity of cortical sources. Here, we present the first results of this non-invasive gait event decoding strategy.
Repetitive Ocular Vestibular Evoked Myogenic Potential (RoVEMP) Stimulation For Diagnosis of Myasthenia Gravis: Optimization Of Stimulation Parameters

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INTRODUCTION
Early and accurate diagnosis is of great importance for the course and outcome of myasthenia gravis (MG). Recently, repetitive ocular vestibular evoked myogenic potential (RoVEMP) stimulation has been developed as a novel diagnostic tool for MG. Quantification of extraocular muscle response decrement after repetitive stimulation facilitates the often challenging diagnosis of MG. Comparison of different stimulation paradigms is needed to determine the most sensitive and specific parameters for detecting the characteristic RoVEMP decrement.

METHODS
Repetitive bone-conducted oVEMPs were elicited in 18 MG patients and 20 healthy subjects. To determine the most sensitive and specific RoVEMP paradigm for decrement detection, we compared four different repetition rates (20Hz, 30Hz, 40Hz, 50Hz). In addition to the inferior oblique muscles, we recorded oVEMPs from the lateral rectus muscles.

RESULTS
Repetitive stimulation at all tested repetition rates with recordings from inferior oblique muscles allowed for effective differentiation between MG patients and healthy subjects. Among all repetition rates, 30Hz showed a trend towards superiority, with a sensitivity of 71% and a specificity of 94% (area under the curve (AUC) 0.88) when using the smaller decrement of the two eyes and -10% as cutoff. Considering the larger decrement for analysis (-9% as cutoff), sensitivity increased to 82%, but specificity decreased to 78% (AUC 0.81).

CONCLUSIONS
Our study suggests 30Hz repetitive oVEMP stimulation from the inferior oblique muscles as the most effective stimulation paradigm. Repetitive oVEMP stimulation with optimal parameters facilitates early and accurate diagnosis of ocular MG.
P40
Characteristics of acute MRI examinations in focal non-convulsive status epilepticus – a retrospective analysis

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Introduction
The mechanisms involved in the propagation and persistence of epileptic activity during status epilepticus (SE) are largely unclear. Proposed mechanisms include cortico-subcortical interactions resulting in a hyperactive wide-spread epileptogenic network. In this study, we set out to determine characteristic magnetic resonance imaging (MRI) findings during SE to identify affected brain structures during SE.

Materials and Methods
We retrospectively analyzed 641 consecutive patients with diagnoses of EEG-documented nonconvulsive SE according to Salzburg consensus criteria between March 15th 2001 and October 31st 2018. Inclusion criteria for MRI imaging were (I) MRI examination on the same day of the EEG or (II) between two consecutive EEG examinations in SE.

Results
We found 77 cases with acute MRI examinations in SE fulfilling the inclusion criteria. In 50 cases MRI and EEG were performed on the same day. DWI-restrictions were found in 92.2% of all cases. Neocortical, hippocampal (with or without involvement of the amygdala) and thalamic alterations occurred in 64.9%, 81.8% and 55.8% of the patients, respectively. The lateralization of the electroencephalographic focus was identified correctly in the MRI in 80%, 71.4% and 79.1% of the cases. We found overlapping signals between the EEG discharges and the cortical DWI-restrictions in 96% of all cases. In 88.4% of the patients with thalamic DWI restrictions, the dorso-medial thalamus was affected.

Conclusion
Acute, reversible DWI restrictions in MRI are common during focal SE und reflect the localization of the epileptic focus in the EEG. Moreover, the MRI findings suggest the activation of subcortical structures, in particular the dorso-medial thalamus, suggesting a pathophysiological activation of a wide-spread epileptogenic network in SE.
Multi-modal intraoperative electrophysiological mapping of the anterior nucleus of the thalamus in refractory epilepsy

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Purpose
Deep brain stimulation (DBS) in the anterior nucleus of the thalamus (ANT) has been shown to be effective in reducing seizure frequency in focal epilepsy. However, treatment response varies considerably on an individual level. Previous studies showed that the anti-epileptic effect of anterior thalamic DBS may be dependent on the stimulation site within the ANT and functional connectivity from imaging data showed differences in the default network in ANT DBS responders as compared to non-responders.

Method
In this pilot study we aim to implement a multimodal mapping of the anterior nucleus of the thalamus based on intra-operative monitoring. We recorded intraoperatively 16-channel surface EEG, local field potentials (LFP), and micro-electrode signals along the implantation trajectory. Data post-processing included spike-frequency analysis, spectral analysis of local field potentials and cortico-subcortical coherence. Here we present intra-operative data from 6 DBS trajectories in 3 patients.

Results
Upon entry in the anterior nucleus of the thalamus, we observed increased theta band (4-8 Hz) LFP activity within the first 4.5mm after entry in the anterior thalamus (entry was predicted based on direct MRI-targeting). Spectral coherence analysis revealed increased theta band coupling between the LFP and ipsilateral temporal EEG electrodes with maximal coherence between 3 and 7mm after entry. MER recordings did not reveal a consistent pattern to delineate the target region.

Conclusion
LFP theta activity and LFP-EEG coherence between the ANT and temporal surface EEG showed a consistent pattern to delineate the anterior nucleus of the thalamus. This pilot data corroborates the feasibility to use intra-operative electrophysiological monitoring for mapping the ANT. These observations could be used in future studies as potential biomarkers to determine the stimulation site within the ANT and to enhance treatment response after DBS implantation.
The Swiss Narcolepsy Scale (SNS) and its Short Form (sSNS) for the discrimination of narcolepsy in patients with hypersomnolence: A cohort study based on the Bern Sleep-Wake Database

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Background/Aims
Previous studies reported high sensitivity and specificity of the Swiss Narcolepsy Scale (SNS) for the diagnosis of narcolepsy type 1. We used data from the Bern Sleep-Wake Database to investigate the discriminating capacity of both the SNS and the Epworth Sleepiness Scale (ESS) to identify narcolepsy type 1 and type 2 in patients with central disorders of hypersomnolence (CDH) or sleepy patients with obstructive sleep apnea (OSA). In addition, we aimed to develop a simplified version of the SNS.

Methods
We used data from the Bern Sleep-Wake Database. The validation of the diagnoses was based on the third edition of the International Classification of Sleep Disorders (ICSD-3). We created the two-item short-form SNS (sSNS), based on the discriminative capability of the models including all possible combinations of the five questions of the SNS.

Results
Using the previously published co-efficiencies, we confirmed the high capacity of the SNS in identifying narcolepsy type 1. The updated SNS (based on new co-efficiencies and cut-off) and the sSNS showed high capacity and were both superior to ESS in identifying narcolepsy type 1. The sSNS correlated significantly with the SNS (r = -0.897, p < 0.001). No scale showed sufficient discrimination for narcolepsy type 2.

Conclusions This is the largest cohort study that confirms the discriminating power of SNS for narcolepsy type 1 in patients with hypersomnolence and the first study to assess its discriminative power for narcolepsy type 2. The easy-to-use and easy-to-calculate short-form scale has a high discriminating power for narcolepsy type 1 and may be used as screening tool, especially among general practitioners, to identify patients and accelerate their referral to a center of expertise.
NAD+/NADH dysregulation revealed by 31P-MRS in the Gclm KO mouse

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Schizophrenia (SZ), a major psychiatric disease, is a developmental syndrome involving decreased connectivity deriving from both genetic and environmental factors. The reciprocal interaction of oxidative stress and NMDAR hypofunction leading to impairment of inhibitory interneurons and neural synchronization may represent one core pathophysiology. Nicotinamide Adenine dinucleotide NADH (reduced form) and NAD+ (oxidized form) are cofactors of energy producing pathways. Their ratio RX (NAD+/NADH) reflects the cellular oxidoreductive state. Oxidative stress and redox dysregulation have been suggested in various neurological diseases including Schizophrenia, Parkinson’s and Alzheimer’s diseases as well as aging. The in vivo measurement of redox state and NAD contents has recently been available and demonstrated in cat and human brains by 31P-MRS. We previously demonstrated the feasibility of such measurement in mouse brain, however in vivo measurement of these indices during brain development has never been attempted. With the aim to identify biomarkers for early detection of SZ, we investigated in vivo the redox and glutamate (Glu) systems during neurodevelopment in the glutathione (GSH) deficient gclm-KO mice. The NAD+/NADH (RX) and the neurochemical profile were determined using 31P- and 1H-MRS respectively. In wild type (WT) mice, an increase of RX was observed from postnatal day P20 to P250, due to an increase of [NAD+] and a decrease of [NADH]. Gclm-KO mice showed a much more pronounced increase of RX during development which was significantly higher as compared to WT at P90. Consistently high redox-ratio, reflecting high frontal oxidative status was associated with low GSH level in gclm-KO mice. Glutamine/Glutamate ratio was negatively correlated with GABA in WT animals at P90 while the correlation was disrupted in gclm-KO. Moreover at P40 low GABA was associated with low NADH in gclm-KO. This may reflect an impairment of the inhibitory circuitry. In this study we demonstrated first: the feasibility of longitudinal measurement of NAD+, NADH and RX in mice brains during development at 14.1T which opens widely the prospect of studying longitudinally the energy metabolism and redox dysfunction in mouse models of brain pathologies. Secondly we are on the good way to identify molecular mechanism affecting brain development and regulation in the gclm-KO mice, which could be relevant for the pathophysiology of schizophrenia.
Mitochondrial dysfunction in Early Psychosis Patients: a translational study

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Aims
Mitochondria play a pivotal role in regulating cellular functions including bioenergetics, calcium homeostasis, redox signaling, and apoptotic cell death, all crucial for neuronal activity, sprouting, development and survival. Impairments in mitochondrial structure, network dynamics, electron transport system activity, transcriptome, proteome and in sequence of mitochondrial-relevant genes both in brain and in peripheral cells are implicated in schizophrenia (SZ). As oxidative stress appears as a common hub in SZ pathophysiology, it is vital to understand the interplay between mitochondrial dysfunction and redox impairment, and to clarify if redox susceptibility confers a predisposition to mitochondrial impairments in SZ patients. Here we investigated (1) oxidative stress impact on mitochondrial integrity in the redox dysregulated Gclm-KO mice (70% decrease in glutathione level and oxidative stress from juvenile stage until adulthood); (2) mitochondrial response to stress in early psychosis patients (EPP); (3) impact of redox susceptibility (GCLC high-risk genotypes) on mitochondrial markers.

Methods
Effect of oxidative stress on mitochondrial morphology: ultrastructural changes in mPFC of Gclm-KO mice characterized by electron microscopy. Fibroblasts from EPP and healthy controls were used to assess mitochondrial characteristics (complex 1 subunit alterations, fusion/fission and pro-/anti-apoptotic markers) in basal and oxidative stress conditions.

Results
We found an increased of mitochondrial damage in Gclm-KO mice compared to wild-type mice in parallel to oxidative stress, suggesting impaired energy production and ROS generation. Profiling of mitochondrial response to oxidative stress in EPP fibroblasts showed altered levels of mitochondrial markers. Discriminant analysis revealed that the response to oxidative stress of mitochondrial markers efficiently separate EPP from controls and individuals with different redox susceptibility (i.e. different polymorphism in GCLC gene). Mitochondria profiling in patients’ fibroblasts thus appears as a powerful approach for patients’ stratification.

Conclusion
These results indicate that mitochondrial abnormalities as observed in SZ mouse model and patients may result from a redox dysregulation. These abnormalities may enhance ROS production, impair mitochondria clearance and motility and altogether lower energy production at sites with high energetic demand (e.g. at synapses or in parvalbumin interneurons).
N-acetyl-cysteine treatment and environmental enrichment reversed the long-lasting effect of oxidative stress on PVI circuitry: relevance for schizophrenia

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A hallmark of the pathophysiology of schizophrenia is a dysfunction of parvalbumin-expressing fast-spiking interneurons (PVI), which are essential for neuronal synchrony during sensory and cognitive processing. Oxidative stress and inflammation, as observed in schizophrenia, affects the highly metabolically active PVI. Some schizophrenia patients have decreased brain glutathione (GSH) levels due to genetic and functional origin. GSH dysregulation, by increasing vulnerability to oxidative stress and inflammation during early development leads to impaired cortical circuitry, specifically the PVI and the perineuronal nets (PNN) that surround them. We tested whether a combined treatment of N-acetyl-cysteine (NAC) and enriched environment (EE), during adolescent, prevents the deleterious effect of oxidative insult on PVI and PNN. We used a transgenic mouse model with GSH deficit (GCLM KO) that shows SZ related phenotype, increased oxidative stress and microglia activation. GCLM KO and WT mice were treated with a dopamine reuptake inhibitor, the GBR-12909 dihydrochloride (GBR), to induce an additional oxidative stress, from postnatal day (PND) 10 to 20. Then, GBR-injected mice were subjected to NAC and EE during adolescent period. Finally, morphological and functional analysis were conducted on adult animals. Here, we confirmed previous findings that an additional oxidative stress (GBR) in early postnatal days (P10-20) led to long-lasting effects in adult GCLM KO: increase in oxidative stress, activation of microglia, increase in MMP9-IR, and PVI and PNN impairment. These effects were completely reversed by the combination of NAC treatment (given between P21-35) and EE (during P35-56). Interestingly, MMP9-IR was also reversed by NAC treatment alone. The fast rhythmic oscillations reflecting neuronal synchronization of PVI was decreased in the GBR-treated GCLM KO, and recovered by NAC/EE. Thus, an early oxidative insult induces long-lasting effects on PVI and PNN, which can be reversed by a combined NAC and EE, even after the challenge. In analogy, individuals carrying genetic risks to redox dysregulation potentially vulnerable to early-life insults could benefit from a combined pharmacological and psycho-social therapy.
Correlation of microglial activation with white matter changes in dementia with Lewy bodies

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Dementia with Lewy bodies (DLB) is the second-leading degenerative dementia after Alzheimer’s disease. Neuropathologically, it is characterized by alpha-synuclein protein deposition with variable degree of concurrent Alzheimer’s pathology. Neuroinflammation is also increasingly recognized as a significant contributor to degeneration.

Objective
to examine the relationship between microglial activation as measured with [11C]-PK11195 brain PET and MR diffusion tensor imaging (DTI) in DLB.

Methods
Nineteen clinically probable DLB and 20 similarly aged controls underwent 3T structural MRI (T1-weighted) and DTI. Eighteen DLB subjects also underwent [11C]-PK11195 PET imaging. Tract-Based Spatial Statistics (TBSS) were performed to compare DTI parameters in DLB relative to controls and identify associations of [11C]-PK11195 binding with white matter integrity and cognitive score in DLB patients.

Results
TBSS showed widespread changes in DLB for all DTI parameters (reduced fractional anisotropy, increased diffusivity), including the corpus callosum, corona radiata and superior longitudinal fasciculus (family-wise error (FWE)-corrected p<0.05). Higher [11C]-PK11195 binding in parietal cortices correlated with widespread lower mean and radial diffusivity in DLB patients (FWE-corrected p < 0.05). Furthermore, preserved cognition in DLB (higher Addenbrookes Cognitive Evaluation revised score) correlated with higher [11C]-PK11195 binding in frontal, temporal, and occipital lobes.

Conclusion
Our study demonstrates that higher PK11195 binding is associated with a relative preservation of white matter and cognition in DLB, positioning neuroinflammation as a potential early marker of DLB etiopathogenesis.
P47
Slow wave promotes sleep-dependent plasticity during stroke recovery

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Aim
Clinical and experimental studies suggest a positive role for sleep in brain plasticity during stroke recovery. Here, we investigate the role of Slow Wave (SW) oscillations during sleep on motor recovery following ischemic stroke using optogenetic techniques and in vivo electrophysiology in mice.

Methods
Ischemic stroke was caused in wild type mice using middle cerebral artery occlusion (MCAo). Following injections of CamkII-ChR2-EYFP (ChR2), CamkII-ArchT-EYFP (ArchT) and CamkII-mCherry (control) adeno-associated viruses (AAV) within the peri-lesional primary somatosensory forelimb (S1FL) cortex, SW-like oscillations were induced by optic stimulation of transfected pyramidal neurons. Randomly distributed single light pulses were delivered for 2 h sessions from post-stroke day 5, and consecutively every day until post-stroke day 15. Behavioural tests at post-stroke days 4, 7, 10 and 15 were used to assess the effect of optogenetically evoked SW on motor outcomes. The presence of puncta positive for the pre-synaptic marker vesicular glutamate transporter type 1 (Vglut1) and the post-synaptic density marker 95 (PSD-95) as a measure of axonal sprouting following MCAo and optogenetic SW-like oscillations induction.

Results
We showed that MCAo induced an increased amount of NREM sleep following ischemic stroke, where spontaneous ipsilesional SW where decreased in amplitude and positive slope compared to control animals. During optogenetic sessions, both ChR2 and ArchT stimulations of S1FL pyramidal neurons successfully induced SW sleep-like responses in ipsilateral and contralateral electroencephalography (EEG) traces. Behavioural testing showed that optogenetically-evoked SW significantly improved the recovery of fine motor movement as compared to control mice. Finally, SWs like evoked brain oscillations during NREM sleep induced increased axonal sprouting within both ipsilateral and contralateral hemispheres.

Conclusion
In line with the literature, our results suggest a positive role of sleep in motor recovery following ischemic stroke. Moreover, optogenetically-evoked SW sleep-like oscillations, targeting the activity of pyramidal neurons in the peri-lesional cortex, significantly promote functional outcomes after stroke and induced axonal sprouting in the ipsilateral as well as in the contralateral hemispheres.
Prediction of long-term outcomes in early psychosis: a new approach from topology

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Clinical and biological markers that quantify disease course or response to medication play a crucial role in treatment decision. The clinical heterogeneity of patients in the early phase of psychosis hampers the identification of such markers. Stratification is therefore a key step to tailor intervention and to improve functional deficits which critically contribute to long-term quality of life. Topological data analysis (TDA) is a powerful approach to studying the shape of biological datasets. We applied TDA to stratify early psychosis patients according to their symptoms and assessed the predictive power of this stratification for long-term outcomes. We then searched for a biosignature of the groups, focusing on redox markers to as redox dysregulation/oxidative stress is proposed as a pathophysiological hub in schizophrenia.

Methods
• Subjects: early psychosis patients (mean age 25y) recruited from the Lausanne “Treatment and early intervention program”; test cohort, n=101; replication cohort, n=93.
• Stratification: the TDA algorithm Mapper was applied to the 30 item scores of the Positive And Negative Syndrome Scale.
• Outcomes after 3-year follow-up: scores of global or social and occupational functioning, the percentage of patients in symptomatic remission, working, or living independently.
• Metabolic profiling: blood levels of 29 amino acids and derivatives; activity of 3 antioxidant enzymes.

Results
Three groups of patients were identified by TDA: group A, characterized by an overall low level of symptom, group B, by high positive and negative symptoms, and group C, by high negative symptoms. Importantly, group A had a high predictive value for good outcomes: patients in this group functioned better at follow-up than those from group B and C. We confirmed these results in the replication cohort. The metabolic biosignature suggests a better regulation of the anti-oxidant defenses in patients with better outcome (group A) and a deficient redox homeostasis in groups B and C.

Conclusion
Unsupervised data-driven topological analysis allowed patients’ stratification into clinically relevant subgroups and the detection of patients at risk for poor functional outcomes. This stratification was robust and its predictive power surpassed the one obtained with a standard clustering method. This approach, combined with mechanism based metabolic profile, should pave the way to personalized functional-disability preventive strategies at early stages of the disease.
Amnestic syndrome in idiopathic Normal Pressure Hydrocephalus

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Background
Executive functions are classically impaired in idiopathic Normal Pressure Hydrocephalus (iNPH); however, some iNPH patients are also presenting with an amnestic syndrome of the hippocampal type similar to Alzheimer’s disease (AD). This study aims to disentangle the predictive factors of this amnestic syndrome in iNPH, especially the association with abnormal CSF biomarkers for AD.

Methods
One hundred consecutive iNPH patients (77.0 ± 6.6 years; 38% female, 12.0 ± 3.5 education years) assessed in the Division of Neurology, Geneva University Hospitals from 2011 to 2019 were included in this cross-sectional study. Episodic memory was evaluated with the Free and Cued Selective Recall Test (FCSRT) before CSF tap test. The main outcome was the sum of total recall scores on the FCSRT, with a value of < 40/48 indicating the presence of an amnestic syndrome of the hippocampal type. Independent samples t-tests or Pearson’s Chi-squared tests, as appropriate, were used to compare patients with and without an amnestic syndrome. Predictors of the memory profile were examined using post-imputation linear regressions.

Results
Thirty-eight iNPH patients (38%) were classified as amnestic (FCSRT sum of total recalls < 40/48). The amnestic iNPH patients were significantly less educated (10.2 ± 3.5 versus 13.1 ± 3.0 years, p-value < 0.001) and presented a more severe cognitive impairment (MMSE: 22.6 ± 3.3 versus 25.8 ± 2.8; p-value < 0.001) than the non-amnestic patients; they had a similar disease duration, white matter abnormalities and CSF biomarkers levels for AD. The level of education was associated with the FCSRT sum of total recalls in the multivariate model (β = 0.63; 95% CI [0.15;1.12]; p = 0.011), as well as the MMSE (β = 0.93; 95% CI [0.35;1.52]; p = 0.002), but not CSF biomarkers for AD.

Conclusions
Education and global cognition, but not a comorbid AD pathology, are associated with an amnestic syndrome of the hippocampal type in iNPH. These findings suggest that amnestic syndrome in iNPH does not reflect an underlying AD comorbidity that is frequent in patients with iNPH.
Systemic and CNS neuroinflammation is associated with neuropsychiatric symptoms

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AIMS
Systemic and CNS inflammation are linked to neuropsychiatric symptoms (NPS). Neuroinflammation is also associated with cerebrovascular and neurodegeneration processes and cognitive decline. Here, we sought to identify cerebrospinal fluid (CSF) and peripheral blood serum inflammation marker signatures associated with NPS in older subjects while taking into account cognitive impairment and core Alzheimer’s disease (AD) pathology. Associations between identified markers and structural imaging data were also assessed to establish their link with regional neurodegeneration.

METHODS
We administered the neuropsychiatric inventory (NPI-Q) questionnaire and quantified a panel of 28 neuroinflammatory markers and albumin using sandwich immunoassays in both CSF and serum as well as the levels of AD CSF biomarkers Aβ1-42, tau and p-tau181 in 87 older community-dwelling subjects with normal cognition or with cognitive impairment. Additionally, morphometric data was obtained from magnetic resonance imaging scans in the same cohort. Regression models selected molecules associated with NPI-Q scores.

RESULTS
Mean age was 70 years, MMSE score 27, and NPI-Q score 2.5. The occurrence of NPS was associated with a specific combination of inflammatory markers in CSF independently of cognitive status: soluble intracellular adhesion molecule-1, C-reactive protein and IFN-γ induced 10kDa protein. This signature interacts with AD pathology at the level of soluble intracellular adhesion molecule-1 only. Severity of NPS was associated with thymus and activation-regulated chemokine. In serum, a distinct combination of markers including interleukin-6 and C-reactive protein are associated with NPS. Correcting these models for the CSF/serum albumin ratio, considered here as a marker of blood-brain barrier permeability, indicated that these signatures originate in the CNS. Specific inflammatory markers are also associated with individual NPI-Q categories. Furthermore, soluble intracellular adhesion molecule-1 was robustly associated with volumetric changes in hippocampus and the third ventricle. Interestingly, volume changes in these two areas are also associated with the occurrence of NPS.

CONCLUSION
This study shows that specific CSF and serum inflammatory marker signatures are associated with NPS. These signatures are independent of cognitive status, originate in the CNS and can be considered potential biomarkers of NPS and the underlying cerebral pathology.
P51
ICH volume, hematoma expansion and 3-month-mortality in patients on antiplatelet therapy. A systematic review and meta-analysis

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Background
Data on the influence of prior antiplatelet therapy (APT) on intracerebral haemorrhage (ICH) are conflicting. We aimed to summarize and meta-analyse the association of prior APT on characteristics of ICH and outcome.

Methods
We performed a systematic review and meta-analysis of all studies published on PubMed comparing ICH outcomes of patients on APT (APT-ICH) with patients not taking APT (non-APT-ICH). Primary outcomes were haematoma volume on admission (mean difference and 95%-CI), secondary haematoma expansion (HE), short-term- and 3-month mortality. Odds ratios (OR) were calculated with Mantel-Hanszel random-effects method and 95%-CI.

Results
Out of 1205 identified studies, 28 on 31063 patients with APT-ICH and 62789 patients with non-APT-ICH matched our in- and exclusion criteria. Patients on APT were older (mean age difference 6.8 years, 95%-CI 5.71 - 7.90, p < 0.00001; I² = 69%, p < 0.00001), had larger haematoma volume (mean difference 3.6 ml, 95% - CI 1.43 - 5.28, p = 0.0006; I² = 60%, p < 0.0009), but there was no statistically significant difference in secondary haematoma expansion (OR 1.26, 95%-CI 0.83 - 1.91, p = 0.27; I² = 65%, p = 0.001). Mortality in patients with ATP-ICH was higher at short-term- (OR 2.02, 95%-CI 1.41 - 2.90, p = 0.001; I² = 76%, p < 0.00001) and 3-month (OR 1.5, 95%-CI 1.24 - 1.81; p < 0.0001, I²= 70%, p < 0.001). We found insufficient data for functional outcome and comparison of single vs dual APT-ICH.

Discussion
Prior APT is associated with predictors of poor outcome and mortality. Data on functional outcome and differences in single and dual APT-ICH are scarce and warrant further investigation along with the individual impact of APT therapy in the context of competing other predictors of poor outcome (i.e. age).
Role of Caveolin-1 in neovascularization and astrogliosis after stroke and effects of cavtratin as a neuroprotectant

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Background
Complex cellular and molecular events occur in the neurovascular unit after stroke and contribute to neuronal death, neurological deterioration and mortality. In the CNS, Caveolin-1 (Cav-1) is present in brain endothelial cells and astrocyte cultures. Cav-1 has a dual mode of action. On one hand, Cav-1 is associated with caveolae formation involved in endocytosis and transcytosis. On the other hand, Cav-1 can act through a scaffolding domain to modulate signaling pathways (1). Therefore, Cav-1 is likely to be an important player in the context of NVU dysfunction. However, its role after stroke is still controversial and the effect of Cavtratin, a cell-permeable peptide containing the scaffolding domain of Cav-1 has never been investigated (2).

Aims
The goal of the study was to investigate the role of Cav-1 in the acute phase after stroke and evaluate the potential neuroprotective effect of the Cavtratin peptide.

Methods
We first compared wild type (WT) and genetically modified Cav-1 knock-out (KO) mice in an ischemia-reperfusion model using transient Middle Cerebral Artery Occlusion (tMCAO). Outcome measures including lesion volume, behavioral tests, and immunofluorescence staining were collected at various time-points and up to 7 days after injury. We then performed blinded and randomized IP injections of Cavtratin or control scrambled peptide (dose 2.5 mg/kg) 3 hours after the reperfusion and evaluated the same outcome measures as above.

Results
After tMCAO, Cav-1 expression was increased in new blood vessels within the lesion and we showed for the first time its presence in reactive astrocytes in the peri-lesion. Cav-1 KO mice displayed a more severe post-stroke outcome with larger lesions and worse behavioural scores than WT mice in all tests. Cav-1 KO mice exhibited reduced neovascularization and modified astrogliosis compared to WT mice 3 days post injury associated with aggravated functional deficits. Preliminary results of the outcomes after Cavtratin or control peptide injection show that mice injected with Cavtratin perform better in behavioral tests and display some features of neuroprotection.

Conclusion
Altogether, these results point towards a protective role of endogenous Cav-1 in the first days after ischemia by promoting both neovascularization and astrogliosis (3), and single injection of Cavtratin may facilitate the recovery post-stroke.
Background and purpose

To assess the spectrum of genetic anomalies in a cohort of children presenting at least one cerebral or spinal pial arteriovenous fistula (pial AVF) or a vein of Galen malformation (VGAM). Materials and Methods: We conducted a retrospective analysis in 94 children known to have either with a pial AVF (n=43) or a VGAM (n=51), who were previously screened for Hemorrhagic Hereditary Telangiectasia (HHT) disease (ENG, ACVRL1 and SMAD4 mutations), Capillary malformation – arteriovenous malformation (CM-AVM) syndrome type 1 due to RASA1 mutation and type 2 due to EPHB4 mutation. The type of the shunt was thoroughly evaluated and then classified (pial AVF or VGAM). Arteriovenous shunts through the vein of Galen were classified as true VGAM only if the deep cerebral system was not draining together with the shunt but rather through an alternative venous pathway. Shunts that drained together with normal brain venous outflow through the vein of Galen were classified as pial AVF and not VGAM.

Results

We identified a germline mutation in 28 probands. EPHB4 mutation was identified only in 5 of the 51 patients with VGAM. Hemorrhagic Hereditary Telangiectasia disease or RASA1 mutation were identified only in 23 of the 43 pial AVFs: eight mutations in ENG and one in ACVRL1 leading to a diagnosis of HHT and 14 in RASA1 leading to a diagnosis of CM-AVM1.

Conclusion

These results highlight the importance of genetic testing in this setting because of the high frequency of gene mutations in pediatric patients with cerebrospinal arteriovenous fistulas. EPHB4 mutation appears associated with true VAGM whereas HHT disease and RASA1 mutation appear associated with pial fistulas. More comprehensive studies are required to demonstrate a causal relationship.
Flashing light therapy against photophobia in migraine – an fMRI study

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Objective
Photophobia is the most prevalent accompanying symptom of migraine. Patients often tend to avoid bright light exposure as it can trigger or worsen a migraine attack. However, a recent study from Australia suggests that avoidance of aversive light stimulus may potentiate photophobia, whereas systematic exposure might induce better coping with the aversive stimulus, possibly due to a habituation mechanism [1]. This led us to the hypothesis that photophobia might be treated in some migraine patients using prolonged exposure to flickering light stimulus. Despite behavioral indications for a possible benefit thereof [2], neurophysiological studies using EEG and fMRI have mostly shown a deficient interictal habituation to repeated sensory stimuli in migraine patients [3]. The current study was set up to test repeated exposure to flashing light as a therapeutic intervention against photophobia in migraine patients.

Methods
Neuroimaging: The scans consisted of 10 subsequent runs, each one including 7 alternating blocks of flashing light (8 Hz) and darkness for 140 sec. The subjects were asked to fix their gaze to a cross that was present throughout the runs. fMRI data were collected using a 3T SIEMENS PRISMA system with a 64 channel head coil and dedicated head fixation. Images were analyzed using SPM12. We performed the within-subject contrast based on the acquired data in the fMRI sessions following the Flash (“PostFlash”) and the Dark ("PostDark") interventions.

Results
Based on FWE < 0.05 correction 2 types of visual cortex activity patterns were found: -Habituation to “Flash”: This was found in 6 out of 11 healthy subjects and 2 out of 9 patients. -No habituation to “Flash”: This was found in 3/9 patients in line with the previously reported habituation deficit in many migraine patients.[4] Other participants showed no significant differences in the visual cortex between conditions.

Conclusion
Our initial results were in line with the neurophysiological studies reporting deficient interictal habituation in migraine patients and also revealed migraine patients demonstrating an activation drop in the visual cortex following the “Flash”. Previous literature suggests the existence of two subgroups of migraine patients, with and without habituation to sensory stimulation, which lends credibility to the observed intragroup variability. The intragroup variability observed underlines the necessity to analyze data individually in clinical studies.[5]
Rare genetic variants in patients with cervical artery dissection

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Introduction
To identify pathogenic genetic variants associated with cervical artery dissection (CeAD). Patients and methods: CeAD-patients with either a family history of CeAD (f-CeAD) or recurrent CeAD (r-CeAD) from the CeAD-databases of two experienced stroke centers were analyzed by whole exome sequencing. Variants with allele frequency < 0.05 and classified as pathogenic by predicting algorithms (SIFT or Polyphen-2) or the ClinVar database were explored. First, we analyzed a panel of 30 candidate genes associated with arterial dissection (any site) or aneurysm according the OMIM (online Mendelian Inheritance of Men) database. Second, we performed a genome-wide search for pathogenic variants causing other vascular phenotypes possibly related to CeAD. Findings were classified as CeAD-causing (pathogenic variants in genes from the arterial dissection or aneurysm panel) or suggestive (pathogenic variants in genes associated with other vascular phenotypes and variants of unknown significance in genes from the arterial dissection or aneurysm panel). All other variants were classified as benign/uncertain.

Results
Among 43 CeAD-patients, 28 patients (17 pedigrees) had f-CeAD and 15 had r-CeAD. No CeAD-causing variants were identified in r-CeAD patients. Among f-CeAD-patients, 5/17 pedigrees carried CeAD-causing variants in COL3A1, COL4A1, COL4A3, COL4A4, COL5A1, COL5A2 and FBN1. Suggestive variants in ABCC6, COL3A1, COL5A2, COL5A2, MEF2A, and RNF213 were detected in three pedigrees with f-CeAD and six patients with r-CeAD.

Discussion and Conclusion
CeAD-causing variants were rare and exclusively found in f-CeAD-patients, suggesting differences between the genetic architectures of f-CeAD and r-CeAD. The identified variants indicate a high genetic heterogeneity of the study sample.
Enlarging the Transient Global Amnesia Spectrum: Vascular and other atypical triggers and manifestations

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Aims
Transient global amnesia (TGA) represents a benign syndrome usually easily distinguishable from stroke. It is often accompanied by an isolated hippocampus punctate lesion on diffusion-weighted imaging (HPDL). We report 13 unusual “TGA” cases associated with unusual triggers (such as acute strokes) or clinical aspects (such as focal neurological signs, or absence of amnestic manifestations).

Methods
Over 12-years, our comprehensive stroke center prospectively collected patients with clinically and/or radiologically defined TGA with A) acute vascular lesions, B) other neurological triggers, and C) unusual neurological manifestations. They were analyzed and grouped to redefine an enlarged “TGA spectrum”.

Results
We identified in group A) 5 patients with typical TGA (4 with HPDL) and radiological evidence of recent ischemic or hemorrhagic brain lesions (acute convexity subarachnoid hemorrhage, lenticular hemorrhage, 3 ischemic strokes in the middle cerebral artery territory), B) 4 patients with typical TGA (3 with HPDL) plus other transient neurological signs (aphasia, behavioral problems, minor lateralizing sensory-motor deficits), and C) 4 patients with HPDL but without clinical amnesia (but acute aphasia, minor lateralizing sensory-motor deficit, focal seizures with loss of awareness from anti-CASPR-2 encephalitis, and convulsive peri-coital syncope).

Conclusions
TGA can be triggered by acute vascular and other neurological events. Furthermore, TGA may present with additional focal neurological signs, or as HPDL with a non-amnestic syndrome. Therefore, TGA may better be considered as a “TGA spectrum”, with clinical and/or radiological manifestations being the common expression of acute stress to the brain.
Serum neurofilament light chain predicts brain volume loss in patients with atrial fibrillation

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Background and Aims
There is emerging evidence that atrial fibrillation (AF) is associated with cognitive dysfunction, increased risk for dementia and reduced brain volume independent of stroke, but the underlying mechanisms of these associations remain unclear. Here, we investigated the association of serum neurofilament light chain (sNfL), a neuroaxonal injury biomarker, with brain atrophy in AF patients.

Methods
Explorative analysis from the prospective observational Swiss-AF cohort study (NCT02105844), which recruited AF patients aged ≥ 65 years without recent stroke. We measured sNfL concentrations in duplicate at baseline using a single molecule array (SIMOA) assay. Brain MRI was obtained at baseline and after two years using a standardized protocol. This included a 3D T1-weighted MPRAGE sequence, on which we applied Structural Image Evaluation using Normalization of Atrophy (SIENA) with optimized parameters for brain extraction to calculate the two-year percentage whole brain volume change (PBVC). We further assessed the normalized brain volume using Sienax, presence and volume of ischemic infarcts and white matter hyperintensities and count of microbleeds on appropriate sequences on the baseline MRI. We excluded patients with acute infarcts.

Results
We included 232 consecutive Swiss-AF patients (median age 73, 75% male) for whom pilot data were available. In a simple linear regression model, baseline sNfL was significantly associated with two-year PBVC, with a 0.13% whole brain volume decrease per 10 pg/ml higher sNfL levels (95% CI [0.07, 0.19], p < .001). This association remained significant after adjustment for clinical parameters (age, sex, AF type, history of stroke and other vascular risk factors) and baseline MRI variables (aforementioned vascular brain lesions and normalized brain volume).

Conclusion
In AF patients, baseline sNfL was predictive of brain atrophy at two years independent of stroke history, cerebral infarcts and MRI markers of small vessel disease. This association might reflect a chronic neurodegenerative process in AF.
Migraine and cervicogenic headache: analysis of pathogenic interaction

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The main currently considered theory of migraine pathophysiology is trigeminovascular theory, in which the leading role was given to CGRP (calcitonin-gene related peptide), contained in the endings of trigeminal nerve and released intracranially during a migraine attack. In 2013 M. Schuelera et al pointed out the possible effect of pathological impulses from extracranial tissues to the onset of a migraine attack (Markus Schuelera et al. PAIN 2013:154: 1622-1631). According to their data it’s possible to suggest that therapy of cervical structures pathology in patients with migraine may favorably affect headache’s course and the effectiveness of treatment. Aim of the study is to evaluate the effect of the treatment of pathological impulses from cervical anatomical structures on the course of migraine and describe the effect of dimethylsulfoxide on the meningeal fibers of the trigeminal nerve on the model of migraine in rats.

Methods
Clinical part: Patients with cervicalgia and migraine were diagnosed by MRI of the cervical spine, history taking and neurological examination. After this they were treated by Comprehensive treatment received by patients includes: manual therapy, novocainic infiltration of the neck muscles, DMSO applications, triptans during migraine attack. Experimental part: as an object of study in vitro was used an isolated rat skull preparation. Under visual control, the peripheral process of the trigeminal nerve was drawn into the glass electrode. Application of 0.1%, 1%, 10% of DMSO is carried out in the region of divergence of the middle meningeal artery. Application of 0.1%, 1%, 10% of DMSO is carried out in the region of divergence of the middle meningeal artery.

Results
1. In 61% of patients after the complex treatment described above, the intensity of migraine decreased (from 8.4 to 6.1 points VAS); 2. 69% of respondents noted a decrease of migraine attacks frequency (from 3.5 to 1.3 per month); 3. 82% noted an improvement in mood and quality of life in general. 4. 10% DMSO caused a dramatic change in the frequency of action potential from the first minutes of its presence in the solution (from 2.75 ± 0.76 s⁻¹ to 16.57 ± 2.33 s⁻¹) with next denervation.

Conclusion
the results of this study confirm the mutual influence of cervicogenic headache and migraine when they are combined in a patient. We noted the positive dynamics of the migraine course in patients during therapy aimed to eliminating of pathological impulses from cervical spine and dramatic action of 10% DMSO exposure to trigeminal nerve fibers with their subsequent denervation.
Effect of a motor-cognitive dual-task training for MS-related fatigue

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Aim of the study
To assess the effect of dual task training on MS-related fatigue. Background: Fatigue is one of the most common symptoms in people with MS (PwMS) where it represents the most impairing symptom for about 40% of them. Fatigue is now recognized as caused by a connectivity impairment in frontal and prefrontal areas, which results in increased activation. Dual tasks exercises are the best training to stimulate at the same time different cerebral areas and some studies found a correlation between dual tasks activities and fatigue onset in PwMS. Until now, the effect of dual task exercises on postural stability has been studied in stroke patients, Parkinson and MS patients but the effect of a dual task training on fatigue has never been explored.

Materials and Methods
We enrolled 11 patients (8F, 3M) with a mean age of 53 years in this single group open label study. Inclusion criteria were: Diagnosis of MS (any clinical course) EDSS ≤ 6.5 Fatigue defined as cognitive and/or motor score in FSMC ≥ 22. All patients performed a 2 weeks training program with 10 dual task exercise sessions in addition to the usual rehabilitative treatment in an in-patient clinical setting. Each session lasted 20 minutes and included the combination of cycling and cognitive tasks focusing on working memory. Outcome measures were: FSMC (total, cognitive and motor) as main outcome 6MWT 12MSWS TUG (single and dual task) HADS

Results & Discussion
The positive predictive value for modifications in the final FSMC total score is the initial FSMC motor score (p < 0.05); the complete statistical analysis showed that after the dual task training we didn’t reach a significant improvement neither for the main and secondary outcome measures. These preliminary data showed that motor FSMC score predicted the improvement of final global FSMC score, even if the global improvement on fatigue didn’t reach the statistically significance. This may be explained by motor planning role of prefrontal region trained by cognitive training in the dual task exercise resulting in a better motor planning strategy which compensate functional disconnection due to MS probably responsible for fatigue in PwMS. Another easier explanation is that the aerobic exercise overwhelm the cognitive training of the dual task. To verify these discordant explanations, it will be necessary to investigate a larger sample population, where dual task training would be compared with simple aerobic exercise.
Multimodal improvements after apomorphine treatment for chronic disorders of consciousness: preliminary results

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Aims
Treatment with apomorphine, a dopamine agonist, has exhibited behavioral effects on the recovery of patients with disorders of consciousness (DOC)[1,2], but its action on brain activity remains unknown. We report the preliminary results of a prospective open-label study using multimodal assessment methods, which aims to confirm the efficacy and investigate the mechanism of apomorphine treatment among post-coma patients.

Methods
Three patients with chronic DOC (1 female, 2 males; 47, 34 and 23 years old; 1 hemorrhage, 2 traumatic; 3.5, 4.5 and 3 months since onset) were administered subcutaneous apomorphine for 30 days. They were followed 30 days before initiation, during treatment and 30 days after withdrawal. Outcome measures included Coma Recovery Scale – Revised (CRS-R)[3], positron emission tomography (PET)[4,5] and electroencephalography-based (EEG) measures such as functional connectivity[6] and multivariate machine-learning classification[7,8].

Results
At baseline, patients 1 and 2 were diagnosed with the CRS-R as minimally conscious state (MCS) minus[9,10] (language-independent signs of consciousness), and patient 3 as MCS plus (language-related signs of consciousness). After the initiation of apomorphine, patient 1 improved to MCS plus, patient 2 remained in MCS minus but showed a new sign of consciousness and more consistent behaviors, and patient 3 emerged from the MCS. PET revealed an improvement of global brain metabolism after compared to before apomorphine treatment for all three patients (difference of +43%, +26%, and +4% for patient 1, 2, and 3 respectively). Functional connectivity measured by EEG network centrality also increased after treatment for all patients in the alpha frequency bands. EEG multivariate classifier improved after treatment for two patients (difference of +25%, +20%, -1% for patient 1, 2, and 3 respectively) with significant increase in most individual EEG markers.

Conclusion
After treatment, patients showed multimodal improvements with more frequent conscious behaviors and increased brain activity measures compared to baseline observations. These results suggest that the action of apomorphine on the recovery of DOC patients may be associated with measurable neuroimaging changes. Additional results from the subsequent placebo-controlled randomized controlled trial[11] will be necessary to confirm the efficacy and further define the neural effects of apomorphine treatment in severely brain-injured patients.
P62
Treatment of therapy refractory chronic cluster headache with the CGRP antibody erenumab – A case report

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Background
Cluster headache (CH) is a rare but severe headache disorder characterized by repeated unilateral head pain attacks accompanied by ipsilateral autonomic features. A minority of CH patients have the chronic form, without pain–free intervals between the headache attacks. Chronic CH is very disabling and the treatment is challenging. A recent study could show that Calcitonin gene-related peptide provokes cluster headache attacks in chronic cluster headache1. These results suggest that anti-CGRP drugs may be effective in cluster headache management. However evidence from clinical trials for anti-CGRP drugs in chronic CH is lacking. We report a case of a 36 year old female with chronic CH, who failed to respond to first, second, and third line therapies including also as well invasive treatment like sphenocath, nervous occipitalis infiltration and an implantation of a bilateral nervous occipitalis nerve stimulator. Under this treatment, she still had on average 4-5 attacks per day with intensities around the maximum mark on the visual-analogue-scale (VAS 8-10). We assessed her to a off-label treatment with erenumab.

Method
We used a patient headache diary to assess the CH attacks frequency, intensity, duration and the medication use two months prior and four months after initiation of treatment.

Results
After 2 months, Erenumab showed a marked reduction in cluster attack Intensity, duration and number of attacks per day. Furthermore, there was a drastic reduction in triptane and benzodiazepine use for acute attack treatment. After 4 month of treatment the effect was still present. Up to the present, no adverse effects of the erenumab treatment were observed.

Conclusion
These results suggest that anti-CGRP drugs might be effective in cluster headache management, however more reliable evidence is still lacking.
Case series of diastematomyelia, technical report

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Objective
The aim of this study is to show a case series of Split Cord Malformations (SCMs) in our department with relevant video and illustrations of the surgical procedure.

Introduction
SCMs are rare congenital forms of occult spinal dysraphism in which the spinal cord is divided over a portion of its length by a bone or fibrous spur. They derive from error in gastrulation during the embryonic stages of spinal development. Two types of SCM are described. We report four cases of SCM type I and two cases of SCM type II with clinical history, its management and surgical treatment.

Observations
Six patients with SCMs were followed and/or treated in our institution between January 2017 and January 2019. Five patients were females and one was male with a mean age of 8.8 years. Two patients were followed up and four patients underwent surgery. Indications to surgery were: prophylactic untethering prior to scoliosis surgery and slow onset of neurogenic bladder in one patient. The site of SCMs was at thoracic and/or lumbar levels. In patient with SCM II a unique dural sac containing both hemicords was found intraoperatively. All surgeries were realised with motor and sensory evoked potentials. One patient had new neurological deficit postoperatively, which improved. Two patients had no new neurological deficit and in one patient urodynamic studies improved postoperatively. One patient had CSF leak postoperatively. The mean of follow-up was 8 months (range 2-15 months).

Conclusion
SCMs are rare, their natural history is poorly understood. They can cause neurological deficits, possibly contribute to scoliosis onset or stay asymptomatic. When surgical correction for the scoliosis is indicated, even in absence of neurological deficit, prophylactic untethering with resection of the tethering structure should be considered. This condition requires close follow up by a multidisciplinary team including at least neurosurgeons, urologists, and orthopedic surgeons.
V02
Differential diagnosis of myotonia: Is temperature the key?

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A man in his early 30s complains since the early adolescence about muscle stiffness of his legs, which spread over the years also onto his arms and face and which increases with warmth and decreases when exposed to the cold. The clinical findings showed a slight distal tetraparesis with myotonic reaction with prolonged muscle relaxation while opening the fist or opening the eyes, slight Facies myopathica with ptosis, bald forehead, and high arched palate). However, percussion myotonia was not detected. Due to the clinical presentation, a needle electromyography was preformed, which showed myotonic discharges. The initial hypothesis was primarily a myotonic dystrophy type 1 (Curshmann Steinert) or typ II (PROMM). A genetic test for MD type I and II was initiated and returned negative. Therefore, more electrophysiological testing was performed, including a “short exercise and cold test”: recording electrodes where placed on right M. abductor digiti minimi (ADM) with stimulation of the right N. ulnaris at the wrist. The first stimulation was done at room temperature for a baseline of the compound muscle action potential (CMAP). Afterwards the hand was cooled with cold packs for 10 minutes and the patient was asked to do an isometric contraction of the ADM for 15 seconds for 3 times with afterwards measurement of the CMAP every 15 seconds during one minute. After cooling, a reduction of the CMAP was found, improving with each trial of muscle exercise, corresponding to an electrodiagnostic Pattern II as described by Fournier et al. 2004 for ion channel myotonia. Genetic testing confirmed a mutation in the CLCN1 gene, encoding for the chloride channel, resulting in congenital myotonia.
Summary
We present a protocol to efficiently evaluate aneurysm perfusion and vessel patency of sidewall aneurysm in rats and rabbits, using fluorescein-based fluorescence video angiography (FVA). With a positive predictive value of 92.6%, it is a simple but very effective and economical method with no special equipment required.

Abstract
Brain aneurysm treatment focuses on achieving complete occlusion, as well as preserving blood flow in the parent artery. Fluorescein sodium and indocyanine green are used to enable the observation of blood flow and vessel perfusion status, respectively. The aim of this study is to apply FVA to verify real-time blood flow, vessel perfusion status and occlusion of aneurysms after induction of sidewall aneurysms in rabbits and rats, as well as to validate the procedure in these species. Twenty sidewall aneurysms were created in 10 rabbits by suturing a decellularized arterial vessel pouch on the carotid artery of a donor rabbit. In addition, 48 microsurgical sidewall aneurysms were created in 48 rats. During follow-up at one month after creation, the parent artery/aneurysm complex was dissected and FVA was performed using an intravenous fluorescein (10%, 1 mL) injection via an ear vein catheterization in rabbits and a femoral vein catheterization in rats. Aneurysms were then harvested, and patency was evaluated macroscopically. Macroscopically, 14 out of 16 aneurysms in rabbits indicated no residual parent artery perfusion with totally occluded luminae, however 11 (79%) were detected by FVA. Four aneurysms were excluded due to technical problems. In rats, residual aneurysm perfusion was macroscopically observed in 25 out of 48 cases. Of the 23 without macroscopic evidence of perfusion, FVA confirmed the incidence of 22 aneurysms (96%). There were no adverse events associated with FVA. Fluorescein is easily applicable and no special equipment is needed. It is a safe and extremely effective method for evaluating parent artery integrity and aneurysm patency/residual perfusion in an experimental setting with rabbits and rats. FVA using fluorescein as a contrast agent appears to be effective in controlling patency of aneurysms and the underlying vessel and can even be adapted to bypass surgery.
A 16 month old girl was referred with seeming regression of gross motor skills. After reaching motor milestones with delay, she progressively wouldn't want to sit anymore; instead, she reflectively became opisthotonic when put to sit. Additionally, she presented with significant hyperreflexia. We show a short video sequence that catches this movement of sudden axial hyperextension without loss of consciousness resembling the truncal extension associated with hyperekplexia. Exome sequencing revealed that the girl carries a de novo mutation in GRIN2B, coding for the 2B subunit of the NMDA type glutamate ionotropic receptor, found at excitatory synapses throughout the brain. It is one of the increasing number of genes associated with developmental delay and epileptic encephalopathy. The girl has not suffered any obvious epileptic seizure so far. Although, the EEG exhibits pathologic activity (spike waves exclusively in sleep), her muscle hyperextension is not epileptic in nature. Her clinical course over 4 months indicates that she might experience a mild type of GRIN2B encephalopathy. In contrast to her, the majority of affected children develop an epileptic encephalopathy within the first weeks or months of life. The particular episodic movement we show in our video might help to think of the diagnosis of GRIN2B encephalopathy even in the absence of epileptic seizures.
P63
Serum neurofilament light chain is associated with progressive cerebral small vessel disease

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Background and purpose
Serum neurofilament-light-chain (NfL) is a circulating marker for neuroaxonal injury and was shown to be associated with severity of cerebral small vessel disease (SVD). Here we explored the association of serum-NfL with imaging and cognitive measures in SVD longitudinally.

Methods
From 503 subjects with SVD, baseline and follow-up MR-imaging was available for 264 participants (follow-up 8.7±0.2 years). Baseline serum-NfL was measured by an ultrasensitive single-molecule assay. MRI-markers of SVD including white matter hyperintensity (WMH) volume, lacunes, microbleeds and mean diffusivity (MD) were assessed at both timepoints. Cognitive testing was performed in 336 participants and included performance of global cognition, memory and processing speed. Associations with NfL were assessed using linear regression analyses and ANCOVA. Dementia status at follow-up was examined for all 503 participants.

Results
Serum-NfL was associated with baseline WMH-volume, MD-values as well as with presence of lacunes and microbleeds, after correction for age. Furthermore, NfL-levels were associated with future MRI markers of SVD (WMH: β=0.173; 95%CI[0.062, 0.327]; p=0.004; MD: β=0.165; 95%CI[0.048, 0.334]; p=0.009). In addition, NfL-levels were higher in subjects with lacunes and associated with incident lacunes. NfL-levels were associated with future cognitive impairment, including processing speed and memory at follow-up (β=-0.135; 95%CI [-0.226, -0.039]; p=0.005 and -0.116 [-0.199; -0.022]; p=0.015, respectively). Risk of developing dementia increased with higher NfL-levels (HR: 5.0; 95%CI2.6-9.4; p < 0.001), however without significance after adjusting for age.

Conclusions
Serum-Nfl is associated with markers of SVD and cognitive decline. Nfl may thus potentially serve as a marker for disease monitoring and outcome in SVD and potentially capture both vascular as well as neurodegenerative processes in the elderly.
Relapsing lymphopenia after dimethyl fumarate discontinuation: an observational study in the Lausanne MS cohort.

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Aims
Dimethyl fumarate (DMF) is a disease-modifying therapy (DMT) for relapsing-remitting multiple sclerosis (RRMS) which mechanism of actions remains incompletely understood. Early lymphopenia is a known side effect, and is associated with increased risk of progressive multifocal leukoencephalopathy (PML). The purpose of this observational study was to evaluate the number of patients who presented with late and persistant lymphopenia under DMF and after its discontinuation in the multiple sclerosis cohort of Lausanne.

Methods
From the 119 consecutive RRMS patients treated with DMF in our cohort, 11 patients (6 women and 5 men) discontinued DMF for severe and/or prolonged lymphopenia (grade 2-3, > 6 months). We here reviewed their clinical characteristics, lymphocyte counts during and after DMF interruption as well as after the introduction of a new DMT. Blood lymphocyte subsets were assessed by flow cytometry in a selected group of patients after the introduction of a new DMT.

Results
Severe and/or prolonged lymphopenia developed within 12 [3–37] months (mean [range]) after DMF introduction in 11 patients (9.2%). Their mean age was 55 years old [37-75], EDSS score 2 (1.5-3.5), disease duration 13 years [4-38]. Three patients (2.5%) developed severe lymphopenia more than 2 years after DMF introduction. In 8/11 (72.7%) patients, a new DMT was introduced after lymphocyte counts rose > 800/μl, according to disease activity. In 5/8 (62,5%) patients, lymphopenia (grade 2-3) relapsed after introduction of Interferon beta, Teriflunomide or Ocrelizumab. Blood leukocyte subset study showed that 4/5 (80%) patients had predominantly CD8+ T cell decrease or a disproportioned high CD4+/CD8+ ratio.

Conclusion
We here show that sustained severe lymphocyte modifications can be a late DMF side effect that persist despite its discontinuation and further relapse after switching to another DMT. Lymphopenia induced by DMF is mainly driven by CD8+ T cells that are involved in antiviral immunity. Sustained reduction in CD8+ T cells associated with DMF that can persist despite its discontinuation may thus increase PML risk. Neurologists should pay close attention to lymphocyte counts even several months after DMF discontinuation or when switching to a DMT not associated with lymphopenia.
Diagnosis of iNPH only through longterm drainage of spinal fluid. A case report.

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Background
Idiopathic normal pressure hydrocephalus (iNPH) features the classical triad consisting of gait disorder, urinary incontinence and cognitive decline along with a disproportionate ventricle enlargement. Autopsy studies revealed progressive supranuclear palsy (PSP) or Alzheimer pathology in a higher proportion of patients who were clinically diagnosed with iNPH during lifetime. Some of these patients even responded to a cerebral spine fluid (CSF) tap test.

Objective
To report the outcome of prolonged CSF drainage in a patient who presented clinically with a PSP-Corticobasal-syndrome-like overlap phenotype and radiological features suggestive of iNPH. Methods: This 80-year old female presented with a 6-months history of progressive gait disorder, cognitive decline, urinary incontinence, limb bradykinesia, apraxia and saccade abnormalities. An MRI scan revealed radiological features compatible with iNPH. A DATscan did not show a dopaminergic deficit. The iNPH score, based on a standardized assessment including a standardized walking test, neuropsychological test battery and quantification of urinary incontinence, was calculated before and after a single CSF tap test and prolonged drainage over 3 days, respectively.

Results
After the initial CSF tap test the iNPH score even dropped from 41 to 30 points indicating clinical deterioration. CSF drainage of cumulative 720ml over 3 days, however, led to significant subjective and objective improvement (iNPH score: 57 points).

Conclusion
A single CSF tap test may not be sufficient to determine treatment response to this test, but prolonged CSF drainage may provide additional information. Furthermore patients with clinical features suggesting atypical parkinsonism, but iNPH typical ventricle enlargement should be considered for CSF drainage.
Recurrence of multiple sclerosis activity after fingolimod discontinuation is not rare in older patients previously stable on treatment.

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Background
Growing evidence from post-marketing studies suggest that recurrence of disease activity (RDA) and even rebound activity after fingolimod (FGL) discontinuation are not rare.

Methods
From the 255 Relapsing Remitting Multiple Sclerosis patients who initiated FGL in the Lausanne MS clinic, 79 discontinued the medication. We retrospectively reviewed patient demographics, reason for discontinuation, type of Disease Modifying Drug (DMD) prescribed, clinical and MRI outcome after discontinuation. RDA was defined as either clinical and/or MRI activity and rebound was considered when disease activity after discontinuation was much higher than before FGL onset.

Results
Mean FGL treatment duration was 41±27.7 months. 31 (39.2 %) patients were on FGL as a first line therapy, 45.6% had switched from Interferon (IFN), 10.1% from natalizumab (NTZ) and 5.1% from other DMDs. Reasons for FGL discontinuation were: (i) lack of efficacy (n=28, 35.4 %), patients were then mostly switched to NTZ or anti-CD20 therapy), (ii) estimated high risk of PML (positive JCV status, age > 45 yo and treatment duration >2 years) (n=26, 32.9 %), patients were then mostly switched to teriflunomide (TRF) (n=16, 61.5 %) (iii) pregnancy planning (n=11, 13.9 %), (iv) side effects (n=7, 8.9 %) and (v) patients’ convenience (n=7, 8.9 %). RDA occurred in 30 patients (38.5%). From the 22 patients who experienced clinical relapses within 6 months (median 1, 1-5), 16 (72.7 %) had no clinical activity on FGL. 19 (79.2%) had MRI activity (median 3 new T2 lesions per patient, range 1-11). Seven patients experienced a rebound activity with a median of 8 new T2 lesions (2-11) and 1 relapse (0-3) per patient. Four of those patients had no DMD at time of rebound, 2 were on (TRF) and 1 on ocrelizumab. 7/26 patients (26.9%) switched for PML risk showed RDA and one severe rebound activity despite no evidence of disease activity during FGL treatment. Among those patients, younger age strongly correlated with RDA (p=0.003), while initial EDSS (p=0.297), clinical (p=0.339) or MRI activity (p=0.475) did not reach statistical significance.

Conclusion
RDA occurred in almost 40 % of our patients and 10 % had a severe rebound activity. Absence of treatment after FGL discontinuation was the main risk factor for rebound. Surprisingly, 25% of the older patients, who were expected to have a less active disease given their age and the absence of activity for several years on FGL experienced RDA.
Comparative outcomes after cerebrovascular accidents from atherosclerosis versus dissection of extracranial and intracranial arteries at 90 days

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OBJECTIVE
We compared the morbidity and mortality at 90 days in this retrospective study in patients with stroke from non-traumatic dissection of extracranial and intracranial arteries versus stroke from atherosclerosis.

METHODS
We retrospectively evaluated for the last 5 years patients who were admitted with a diagnosis of cerebrovascular accident. We divided these patients into those who suffered a stroke from atherosclerosis versus dissection of extracranial and intracranial arteries. We also performed a comparative analysis of the National Institute of Health Stroke Scale (NIHSS) score on admission, at the time of discharge and modified ranking score (MRS) at 3 months in these groups. We found 56 patients with dissection of extracranial or intracranial arteries. Of that, 32 had extracranial dissection and 24 patients had intracranial arterial dissection. NIHSS score in both groups, on admission, varied between 8 to 20 and we compared these patients in both the atherosclerotic group and arterial dissection groups. The total number of patients we evaluated in the atherosclerosis group was 500. We also evaluated the comorbidities associated in both groups that included hypertension, diabetes, history of atherosclerosis, cardiac disorders. In both groups, the standard treatment included neurological evaluation, angiography, Magnetic Resonance (MR) Brain studies, medical treatment with antiplatelet drugs, anticoagulants and follow up as needed. The age group overall was 65 +/-12 years in both groups. In conclusion, we found that at 3 months morbidity and mortality were similar in both groups. In arterial dissection group, the mortality varied between 3% to 6% whereas in the atherosclerotic group it varied between 3% to 5%. At 3 months, in the arterial dissection group, the modified ranking score was 1 to 2 in 78% of patients, 3 to 4 in 14% and 5 to 6 in 8%. The modified ranking score in the group with stroke due to atherosclerosis was 1 to 2 in 82%, 3 to 4 in 13% and 5 to 6 in 5% of patients.
Age at disease onset and clinical outcomes in patients with multiple sclerosis on immunomodulatory treatment

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Introduction
Pediatric-onset multiple sclerosis (MS) patients have higher relapse rates than adult-onset patients and an initially slower disability progression rate. However, less is known about the relation of age at disease onset and clinical outcomes across the full disease trajectory from childhood to older ages in MS patients on disease-modifying therapy (DMT).

Methods
We made use of the Swiss association for joint tasks of health insurers database which contains data from 14,718 MS patients who initiated their first DMT between 1995 and 2017 (69% women; 85% relapsing-remitting (RR)MS; mean age 39±11.5 years; disease duration 6±8 years). Patients were eligible for this analysis when they had a clinically isolated syndrome or RRMS, were on DMT for at least one year between 1995 and 2017 and had a MS diagnosis in or after the year 1993. Disability was assessed by the Expanded Disability Status Scale (EDSS) score. Age at disease onset was transformed into cubic splines to illustrate age-related event risks. The influence of age at disease onset on future relapses and disability progression were explored by multivariable Cox proportional hazard regression models.

Results
Data from 9,705 MS patients were eligible for this analysis. The association between age at disease onset and EDSS progression had a sigmoid shape. EDSS progression hazards remained stable in patients with disease onset from early childhood to about 32 years, then increased sharply around the age of 45 years there off remaining stable at a relatively high level. In contrast, the association between age at disease onset and relapses was almost linear. The risk for relapses was highest at younger ages and decreased continuously from childhood to around 35 years of age. A 20 years old patient with first symptoms of MS had a 1.5fold higher risk for a relapse on DMT than a 38 years old fellow adjusted for gender, relapse activity before DMT initiation, EDSS, pyramidal functional system score and the MS severity score. The hazard for relapses remained constant for a decade and then continuously decreased from age 45 on.

Conclusions
Age is an important factor affecting clinical outcomes in MS. The age of 35 seems to be critical with regard to the compensation of CNS damage caused by MS. Patients with disease onset later 40 years have a higher risk for disability progression independent of other disease characteristics. This should be considered when designing clinical trials or choosing DMT.
Higher serum neurofilament light chain levels are associated with lower self-reported quality of life in the Swiss MS Registry and the Swiss MS Cohort-Study

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Aims
Serum neurofilament light chain (sNfL) is a promising biomarker in multiple sclerosis (MS) associated with disease activity, treatment response and future disease course. Next to the prediction of clinical features, sNfL might also play a role in predicting the health-related quality of life (HRQoL) of persons with MS (PwMS). Therefore, our aim was to assess if sNfL levels could cross-sectionally predict self-reported HRQoL in a uni- as well as multivariable fashion.

Methods
This exploratory, ongoing, cross-sectional study combined self-reported data of the Swiss MS registry (SMSR) with clinical data and sNfL measurements of the Swiss MS cohort study (SMSC) for 66 PwMS participating in both studies (as of March 2019). HRQoL was measured using the French EuroQol 5-dimensions (EQ-5D) health status index value set (worst -0.53, best 1) of the EQ-5D 5-Level instrument and then rescaled (worst 0, best 100) for better interpretability. sNfL levels were measured using a SIMOA assay. First, the spearman correlation between HRQoL and sNfL levels was assessed. Second, we dichotomized the sNfL levels each at age-specific 90th, 95th, 97.5th percentiles of healthy controls (Barro et al., 2018). With these as predictor, a uni- and a multivariable (adjusted for Expanded Disability Status Scale (EDSS) and age) median regression model with HRQoL as the outcome was fitted.

Results
The correlation (rho = -0.454) indicated higher sNfL values with lower HRQoL. In the univariable analysis, PwMS above the 90th (n = 14), 95th (n = 10) and 97.5th (n = 6) percentiles of healthy controls had -17% [95% confidence interval: -29%; -4%], -16% [-34%; 1%] and -16% [-35%; -4%] lower EQ-5D index scores, respectively. In the multivariable analysis, PwMS with sNfL above versus below the 90th-percentile had 8% [-20%; -1%] lower EQ-5D scores. This was more pronounced for PwMS above versus below the 95th and 97.5th percentiles (95th: -15% [-24%; -7%]; 97.5th: -19% [-26%; -12%].
Conclusions
Higher sNfL measurements are associated with decreasing HRQoL, even after adjustment for EDSS and age. The effect sizes were substantial and exceeded the previously reported, strongest negative effect of individual symptoms on HRQoL (Barin et al., 2018). These preliminary results support the potential of sNfL being a valid new blood biomarker in MS and provide the rationale for the ongoing efforts to increase sample size in this study.
Factors influencing patient satisfaction with the first diagnostic consultation in multiple sclerosis: a Swiss Multiple Sclerosis Registry (SMSR) study

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Background
Patient satisfaction is predictive of adherence, malpractice litigation, and doctor-switching. Satisfaction with the first diagnostic consultation (FDC) in persons with multiple sclerosis (PwMS) has rarely been studied. We therefore investigated which factors of the FDC influence patient satisfaction and which topics PwMS thought were missing.

Methods
Using retrospective patient-reported data of the Swiss Multiple Sclerosis (MS) Registry from PwMS with relapsing disease onset, we fitted ordered logistic regression models on satisfaction with FDC, with socio-demographic and FDC features as explanatory factors.

Results
386 PwMS diagnosed after 1995 were included. 54% of participants were satisfied with the FDC, 22% were neutral, and 24% were not satisfied. In multivariable ordered logistic regression, good satisfaction with the FDC was associated with a conversation of at least 20 minutes (multivariable Odds Ratio [95% confidence interval 3.9 [2.42;6.27]), covering many MS relevant topics (1.35 [1.19;1.54] per additional topic), the presence of a close relative or a significant other (1.74 [1.03;2.94]), and shared decision making with regard to future DMT (3.39 [1.74;6.59]). By contrast, not receiving a specific diagnosis was a main driver for low patient satisfaction with the FDC (0.29 [0.15;0.55]). Main missing topics concerned life consequences (reported by 6.7%), psychological aspects (6.2%), how to obtain support and further information regarding therapies and prognosis of MS (5.2%).

Conclusions
A conversation of more than 20 minutes covering many MS relevant topics, a clear communication of the diagnosis, the presence of a close relative or a significant other, as well as shared decision making enhanced patient satisfaction with the FDC in PwMS.
**P71**

**Long-term Effect of Fingolimod in Reducing Blood Neurofilament Light Levels in Patients with Relapsing-remitting Multiple Sclerosis**

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**Aims**

To assess the effect of long-term treatment with fingolimod on blood neurofilament light chain (NfL) levels in patients with relapsing-remitting multiple sclerosis (RRMS).

**Background**

NfL, a cytoskeleton protein, is elevated in blood upon neuroaxonal damage. Blood NfL is a promising biomarker for monitoring disease activity, treatment response, and prognosis in MS.

**Methods**

This post hoc analysis was based on data from patients who received fingolimod 0.5 mg once daily or placebo/interferon β-1a (IFN) 30 μg once weekly in pivotal studies (24-month FREEDOMS/12-month TRANSFORMS), and then fingolimod in the open-label LONGTERMS extension study for up to 10 years. The analysis included a subset of patients who had blood NfL assessments at baseline, end of core (EoC) in pivotal studies, and end of study (EoS) in LONGTERMS. Patients were categorized into two groups: a continuous group (n = 37) who received fingolimod throughout the studies and a switched group (n = 42) who transitioned from placebo/IFN group to fingolimod in the LONGTERMS. NfL was measured using Single Molecule Array (SIMOATM) immunoassay. The geometric mean change in NfL levels from baseline to EoS was analyzed using Wilcoxon signed-rank test.

**Results**

The mean exposure to fingolimod was 3483 days in the continuous group and 2822 days in the switched group. In the continuous group, baseline NfL levels of 33 pg/mL were significantly reduced by approximately 40% at both EoC and EoS (20 pg/mL; P < 0.0001 and P = 0.0002, respectively). In the switched group, baseline NfL levels of 29 pg/mL were reduced by 15% at EoC (25 pg/mL, P > 0.44) and 41% at EoS (17 pg/mL, P < 0.0001).

**Conclusion**

Fingolimod 0.5 mg significantly reduced blood NfL, maintaining its low levels with continuous treatment for up to 10 years. NfL levels were reduced to a lesser extent during treatment with IFN but decreased further with switch to fingolimod, demonstrating the greater impact of highly effective therapy in RRMS.
P72
Accuracy of the pupillary unrest index for assessing fitness to drive

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Background
Sleepiness contributes to around 20% of motor vehicle accidents in industrialised countries. Due to the rapid fluctuations of sleepiness, its quantification remains challenging. Assessment methods that are reliable, cheap, and practical are urgently sought. Whether sleepy patients are fit to drive or not is still a clinical decision, but a battery of sleep and vigilance tests supports the clinician in the decision. Nevertheless, the relevance and accuracy of these tests has to be clarified. This study aimed to determine the accuracy of the pupillary unrest index (PUI) as a screening measure for fitness to drive in sleepy patients.

Methods
We retrospectively analysed data from the Bern Sleep Database (1997 - 2016) of untreated patients with narcolepsy-cataplexy (NC = 30), narcolepsy without cataplexy (N = 28), idiopathic hypersomnia (IH = 47), non-organic hypersomnia (NOH = 103), fatigue syndromes (FS = 94), and insufficient sleep syndromes (ISS = 53). All patients underwent pupillography and the maintenance of wakefulness test (MWT). We used the mean sleep latency in the MWT (MWT-SL) as the gold standard and the PUI as testing variable. We created a private (PRIV-M) and a professional driver model (PROF-M). For fitness to drive, the MWT-SL and PUI were defined as ≥ 20 min and < 9.80 for the PRIV-M, and ≥ 34 min and < 6.64 for the PROF-M. Cut-off values were derived from published norm values but we also analysed the accuracy of different PUI cut-off values in relation to the MWT-SL using ROC curves.

Results
The PUI in the PRIV-M or PROF-M reached a sensitivity of 0.52 or 0.63, specificity = 0.80 or 0.58, positive predictive value (PPV) = 0.51 or 0.69, negative predictive value (NPV) = 0.8 or 0.52. With respect to the diagnosis, predictive values > 0.8 were reached in the PRIV-M for N (PPV = 0.94) and NOH/FS/ISS patients (NPV = 0.8-0.98), and in the PROF-M for NC/N (PPV > 0.95) patients. According to ROC-curves, PUI values ranging from 6.64 - 9.8 were within the optimal sensitivity-specificity ratio.

Conclusion
The PUI was more accurate in the PRIV-M, however, 20% of the patients with an ‘acceptable’ PUI were not able to stay awake for 20 min in the MWT on average. Therefore, our data suggest that the PUI should not be used as a screening measure to exclude significant sleepiness relevant for driving, although autonomic dysfunctions might affect PUI values in patients.
**P73**

**Head to head comparison of clinical efficacy of dimethyl fumarate versus fingolimod in different pretreatment situations: A retrospective European real world study**

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**Introduction**

Despite fingolimod (FTY) and dimethyl fumarate (DMF) have been introduced to the market since several years, efficacy data concerning previous immunotherapy is still missing.

**Methods**

Patients from the participating centers were followed until 1st relapse after treatment start or in terms of relapse free survival for a maximum of 2 years. For the retrospective analysis, cox regression analyses adjusted for gender and disease duration were performed for the following pre-treatments: without DMT/Injectables/natalizumab/DMF or FTY.

**Results**

In total data from 732 relapsing MS patients (female: male=2.6:1.0) were analysed (DMF n=409, FTY n=323). In the follow-up time of 24 months relapse occurred in 180/732 patients. Focussing on the outcome “occurrence of MS relapse”, DMF treatment was associated with a significant higher aHR of 1.53 (95% CI 1.14 - 2.11, p < 0.005, n=732) compared to FTY treatment. Stratification into the predefined pre-treatment groups unmasked an increased relapse free survival in FTY treated patients pre-treated with natalizumab (aHR 4.10, 95%CI 1.72-9.76, p < 0.001, n=122) or without DMT (aHR 2.00; 95%CI 1.11-3.64, p=0.02, n=230). In contrast, no difference was observed in patients pre-treated with injectables or the respective other oral drug (injectables: p > 0.05, n=341; other oral: p > 0.05, n=39).

**Discussion**

FTY treatment was associated with lower clinical disease activity compared to DMF treatment. A subgroup analysis suggested a better efficacy of FTY over DMF in patients without DMT as well as patients pre-treated with natalizumab.
P74 Sleep-wake disturbances after ischemic stroke or transient ischemic attacks as predictors of new cardio-cerebro-vascular events and outcome

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Background and aims
Sleep-wake disturbances (SWD) are associated with increased cardio-cerebrovascular morbidity and mortality. Observations suggest that SWD are frequent in stroke and detrimental for its outcome. The aim of this study is to assess whether scores capturing the overall burden of sleep-wake disorders are predictive for 1) new cardio-cerebro-vascular events (CCVE) and 2) stroke outcome up to two years post-stroke (modified Rankin Scale, mRS).

Methods
We recruited 438 patients with TIA or ischemic stroke. Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) at hospital admission. Sleep disordered breathing (SBD) was assessed during the acute phase using respirography and insomnia, restless legs syndrome (RLS) and sleep duration about one and 3 months following the event by questionnaires and telephone interviews. Based on the severity of individual SWDs we created two sleep burden combined indices (A: based on a sum score; B: based on z-values). These indices were evaluated in multiple regression models as predictors of new CCVE occurring after 3 months up to two 2 years following stroke/TIA and in stroke patients only (N = 367) as predictors of mRS about 1 year post-stroke. Models were adjusted for baseline NIHSS, age and sex. We performed this preliminary analysis after all active patients (76% of recruited patients) have reached the year 1 visit and two-thirds thereof year 2 visit.

Results
Index A (M = 2.79, SD = 1.46) ranged from 0 to 9 and B from -0.89 to 3.24 (M = 0.00, SD = 0.55), with higher values indicating higher severity of combined SWD. Both sleep burden indices predicted new CCVE in TIA/stroke patients and functional stroke outcomes. Odds ratios for Index A respectively B for new CCVE were 1.21 (95% CI: 1.00-1.47, p = 0.053) and 1.84 (95% CI: 1.12-3.02- , p = 0.016). The coefficients in the linear regression models for mRS 1 year post-stroke were 0.152 (p < 0.001) and 0.519 (p < 0.001) for Index A and B, respectively.

Conclusions
Preliminary results of this ongoing study suggest that a high cumulative burden of different SWDs constitutes a risk for new cardio-cerebro-vascular events within the first two years following TIA/stroke and for worse stroke outcome after the first year of stroke. Despite small effects, these results support the need for interventional trials of SWD treatment in stroke.
New or enlarging T2 weighted lesions in the white matter near to the ventricle wall and thalamic atrophy are independently associated with lateral ventricular enlargement in multiple sclerosis

Introduction
Brain ventricular enlargement (VE) in multiple sclerosis (MS) is faster than whole brain atrophy (WBA) indicating that VE is not merely the reciprocal of WBA. However, the factors driving VE in MS are not fully understood. Inflammatory processes in white matter lesions (WMLs) close to the ventricle and deep grey matter (DGM) atrophy might play an important role.

Objective
To investigate the association between new/enlarging periventricular WMLs near to the brain ventricular system, DGM atrophy and lateral (Lat)VE in MS. Methods: Patients derived from the Genetic Multiple Sclerosis Associations study. LatVs and DGM were segmented fully automated at baseline and 5 years follow-up using ALVIN (Automatic Lateral Ventricle Delineation) and MAGeT (Multiple Automatically Generated Templates Brain Segmentation Algorithm), respectively. WMLs were segmented manually. To assess the distance from WMLs to the LatV, we parcellated the WM into concentric bands using FMRIB Software Library. WBA was measured using SIENA (Structural Image Evaluation Using Normalization of Atrophy). Associations between LatVV, clinical and MRI parameters were assessed in linear models using generalized estimating equations for repeated measures and validated using visual inspection of the residuals and Q-Q plots.

Results
We studied 127 MS patients (mean age 44±11, disease duration 12.9±9 years; 20% progressive MS; median EDSS 3.0). Mean LatVV at baseline was 29.7±14.2 mL. Crosssectionally, both T2wLV and thalamic volume were associated with the LatVV (p < 0.001). Each mL lower thalamic volume was associated with a 3 mL larger LatVV (adjusted for age, gender and T2wLV; p= 0.002). LatV enlarged on average by 2.4%/year and 41% of the patients had an increase in T2wLV during follow-up. Patients with new/enlarging T2w WMLs had accelerated LatVE compared with patients without (3.1±2.5 vs. 1.9±2.6%/year) independent of age and WBA (p = 0.002). Every mL T2wLV increase over five years was associated with a LatVE of 0.4%/year. New/enlarging in the first periventricular WM band had the strongest association to LatVE (p < 0.001). Moreover, DGM atrophy was associated with LatVE (p < 0.001) and this was statistically independent of WMLs. The association between DGM atrophy and LatVE was driven by thalamic atrophy in a multivariable linear model (p < 0.001).

Conclusion
New/enlarging T2w lesions near to the ventricle system and thalamic atrophy are independently associated with LatVE in MS.
Progression Independent of Relapse Activity (Pira) in relapsing-remitting multiple sclerosis patients on first-line immunomodulatory treatment with fingolimod vs. platform injectables

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Introduction
Disability progression independent of relapse activity (PIRA) has been described as a frequent phenomenon in patients classified as relapsing-remitting multiple sclerosis (RRMS). Objective: To compare relapse-associated progression of disability (RAP) and PIRA between interferon-beta/glartiramer acetate (IFN/GA) and fingolimod (FTY) in a real-world setting.

Methods
Based on data from the Swiss association for joint tasks of health insurers (n=14718 patients), we investigated whether confirmed disability worsening (CDW) was preceded by relapses (RAP) or occurred independent of relapse activity (PIRA). CDW was defined as an EDSS increase by 1 step (0.5 step, if previous EDSS was ≥ 5.5; 1.5 step if previous EDSS was 0) compared to the year before and confirmed one year later. PIRA was defined as no relapses since disease modifying therapy (DMT) initiation. Study inclusion was restricted to RRMS patients starting IFN / GA or FTY between 2010 and 2017 and > 2 years of follow-up. Time to first occurrence of RAP or PIRA was compared between IFN / GA vs. FTY using multivariable Cox regression with confounder adjustment for age, gender, relapses within 24 months prior to DMT initiation, EDSS, and year of DMT start.

Results
We included 1640 patients [1048 (64%) IFN/GA, 592 (36%) FTY, median (interquartile range) age 37 years (29;46); 70% female; median baseline EDSS = 2 (1.5;2.5); mean follow-up 3±2.1 and 3.7±1.6 years in the IFN/GA and FTY group, respectively]. DMT groups were well balanced with regard to potential confounders. In total, 792 / 1640 patients had at least one relapse during follow up. CDW was observed in 137 patients (8.4%): 92 patients (8.8%) in the IFN/GA and 45 (7.6%) in the FTY group, of which 32 (34.8%) and 24 (53.3%) were PIRA, respectively. Overall, PIRA was observed in 3.1% of the IFN/GA and 4.1% of the FTY group. Adjusted regression analysis indicated a less frequent occurrence of RAP in FTY (Hazard Ratio 0.63 [95% confidence interval: 0.42 ; 0.96]), but not PIRA (0.89 [0.48 ; 1.66]). Among patients without relapses (32 / 464 (6.9 %), IFN / GA; 24 / 384 (6.3%) FTY), the occurrence of PIRA did not differ significantly between IFN / GA and FTY groups (0.71 [0.38;1.31]).

Conclusion
Even with only annual EDSS assessments, a relevant proportion of CDW in RRMS seems to be not relapse-associated. Among patients without any relapses on DMT, the rate of disability progression was similar in IFN/GA and FTY treated patients.
P77 Improvements in balance control for multiple sclerosis patients with vibro-tactile biofeedback of trunk sway

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Introduction

Balance deficits are frequent in multiple sclerosis (MS). Previous studies have shown that vibrotactile feedback (VTf) of trunk sway improves MS patients' balance control compared to training without VTf. Objective: To determine how much VTf training is needed to obtain the best results with VTf. Moreover, we sought to investigate how long the carry-over benefit lasts once VTf training terminates and whether the benefit is similar for stance and gait tasks.

Methods

We included 14 MS patients with balance deficits: 4 male, 3/14 progressive MS, mean age 53.8±7.5, disease duration 10.5±12.6 years; median EDSS 3.0. Patients trained stance and gait tasks 2x per week with VTf for 4 weeks to determine when balance control with and without VTf no longer improved. The VTf thresholds were based on 90% ranges of trunk sway amplitudes and velocities for stance and gait tasks, respectively, measured before each week’s training sessions. Patients were then assessed weekly without VTf for another 4 weeks and 6 months later to determine when retention of improvement ended. The difference in trunk sway between the very first assessment and subsequent assessments was used to measure improvement. Balance was measured with gyroscopes mounted at the lower trunk. The gyroscope signals drove directionally active VTf in a head-band.

Results

VTf showed a 25% decrease in a global combined balance control index (BCI) of all tasks and measures (p < 0.004) for each of the 4 weeks of VTf training. The improvement was to within the range of healthy controls, and slightly less without VTf (p < 0.01). After cessation of training, the BCI showed an average 21% carry-over effect each week (p < 0.02) lasting over 1 month. At 6 months, the carry-over effect was not present anymore. Improvement was present for both stance and gait tasks. For example, VTf improved trunk roll by 26% during walking with head extension-flexion movements (p < 0.02) and increased gait speed (30%) without an increase in trunk sway velocity.

Conclusions

VTf training yields clinically relevant reductions (to within normal limits) in sway during stance and gait, and improved gait speed. This research provides guidelines for the practical application of VTf for improved balance control in MS patients. The reduction of retained improvement 2-6 months after training is an estimate of the time when patients need to return to the clinic to receive VTf training again, but needs precise definition.
Atrophy of the Lateral Geniculate Nucleus after Optic Neuritis in Neuromyelitis Optica Spectrum Disorders: a longitudinal study

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Introduction
Cross-sectional studies showed smaller volumes of the lateral geniculate nucleus (LGN) in patients with neuromyelitis optica spectrum disorders (NMOSD) and previous optic neuritis (ON), suggesting anterograde trans-synaptic degeneration. However, longitudinal data to confirm and quantify this process over time, are lacking.

Aim
To study the longitudinal course of LGN volume in patients with NMOSD.

Methods
Twenty-nine AQP4-IgG seropositive patients (age at baseline: 47.8 ± 14.6 years (y), F:M=27:2, disease duration: 5.9 ± 6.1y, 17/29 with prior ON, time since last ON: 4.6 ± 3.4y) and 18 healthy controls (HC; age at baseline: 39.3 ± 15.8y; F:M=13:5) were included. Mean follow-up time was 3.7 ± 1 y for patients and 1.7 ± 0.7 y for HC. LGN volume was measured using a multi-atlas-based approach of automated segmentation on T1-weighted magnetic resonance images. Linear mixed effect models and paired samples t-test were used in the statistical analysis.

Results
At baseline, patients with prior ON (NMO-ON) had lower LGN volumes compared to patients without ON (NMO-NON) (197.7 ± 24.5 mm³ vs. 225.4 ± 27.8; B= -30.1, SE= 10.9, p= 0.011) and to HC (197.7 ± 24.5 mm³ vs. 222.2 ± 30.8; B= -28.1, SE= 9.8, p= 0.007). After exclusion of four patients that had new ON during follow-up, there was no change in LGN volume, neither in the entire patient group (B= -0.92, SE= 0.58, p= 0.116), nor in the NMO-ON subgroup (B= -0.98, SE= 0.72, p= 0.186). Moreover, there was no group effect on the longitudinal evolution of LGN volume, neither between NMO-ON and NMO-NON (B= -0.21, SE= 1.20, p= 0.859), nor between NMO-ON and HC (B= 0.57, SE= 1.79, p= 0.753). In the four patients with new ON during follow-up, mean LGN volume was 185.5 ± 27.9 mm³ at the last visit before new ON (V0) and 175.9 ± 26.3 mm³ at the last available visit (V2; mean time since ON: 2.7 ± 0.9 y, range: 1.8-3.9 y). The difference between LGN volume at V2 and V0 was significant (mean difference= -9.6 mm³, with 95% CI: -17.9 to -1.2, t= -3.7, p= 0.036).
Conclusion
In this longitudinal analysis, we found evidence of LGN atrophy in four NMOSD patients with new ON during follow-up. In contrast, there was no subsequent LGN volume loss in the NMO-ON cohort without new ON. These findings suggest that LGN atrophy due to trans-synaptic degeneration occurs during the first four years after ON, but is not progressive over long-term follow-up.
A framework for estimating the burden of chronic diseases: Design and application in the context of multiple sclerosis

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Aim
When population-based databases are unavailable, nationwide assessments of the disease burden of multiple sclerosis (MS) resort to clinical, administrative or convenience-sampled data sources, which may produce results of limited external validity. Our aim was to develop a framework for estimating measures of occurrence of chronic diseases, and more broadly disease burden, that mitigate these limitations and to apply this framework to estimate the prevalence of multiple sclerosis (MS) in Switzerland.

Methods
We developed a 7-step framework which implements the combination of several data sources together with a resampling and critical appraisal approach. The framework was applied to estimate the MS prevalence for 2016 in Switzerland, for which four distinct data sources (Swiss MS registry, Swiss national MS treatment registry, MediService database and Swiss MS cohort study) were combined. Results were reviewed by disease experts and compared to earlier Swiss estimates and current prevalence estimates from other countries.

Results
We estimate that in the year 2016 between 14’700 and 15’750 persons with MS have been living in Switzerland, yielding a period prevalence of 174-187 / 100’000 inhabitants. Compared to the last estimate in 1986, we detected a substantial increase of MS diagnoses which coincides with a higher number of diagnoses in women below the age of 65.

Conclusions
Internationally, Switzerland is a high-prevalence country for MS, although estimates were somewhat lower than recent evaluations of Northern European countries. In addition, we corroborate previous reports that the prevalence increase coincides with a higher number of MS diagnoses among women. The proposed framework has wide applicability and the potential to place estimates of disease occurrence and burden with imperfect data availability on more solid grounds.
Ageing with Multiple Sclerosis: The role of calendar age and disease duration for disease outcomes and co-morbidity occurrence in the Swiss Multiple Sclerosis Registry

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Background
Older age impacts Multiple Sclerosis (MS) disease course and pathology. With rising age, the risk of comorbidities exerting reinforcing effects on pre-existing MS symptoms increases. Objectives: To study independent influences of “ageing” and “MS disease duration” (since first symptom onset) on disability burden.

Methods
Using data from 1.134 persons with MS (PwMS) from the Swiss MS Registry, distribution of disability milestones (having reached expanded disability status scale (EDSS) of 3.5-6.5, n=251 (22.1%); or EDSS>6.5, n=104 (9.2%)) and self-reported occurrence of co-morbidity (cancer, n=26 (2.2%); hypertension; n=145 (12.8%); diabetes type 2, n=35 (3.0%); cardiovascular problems, n=40 (3.5%)) was compared in two dimensions across six age decades (18-29, 30-39, 40-49, 50-59, 60-69, 70+) and four MS duration strata (0-9, 10-19, 20-29, 30+ years). Multivariable logistic regression models adjusted for sex, MS subtype at diagnosis, body mass index, smoking status (never, previously, current), and current disease-modifying treatment were applied. Age and MS duration groups were included jointly as linear variables.

Results
73.7% were female and median [interquartile range] age was 49 years [39-58]. Achieving disability milestones was independently and positively associated with age and disease duration. The frequency of an EDSS between 3.5 and 6.5 increased by 4% per age category (Odds Ratio (OR) 1.04 [95% confidence interval 1.03;1.06]) and by 4% (OR 1.04 [1.02;1.05]) per disease duration category. The frequency of having an EDSS>6.5 also independently increased by 2% (OR 1.02 [1.00;1.05]) per age category and by 8% (OR 1.08 [1.05;1.10]) per disease duration category. By contrast, age was the main driver for cardiovascular problems with 5% (OR 1.05 [1.01;1.09]), hypertension with 8% (OR 1.08 [1.06;1.11]), diabetes with 7% (OR 1.07 [1.03;1.11]), and cancer with 5% (OR 1.05 [1.00;1.09]) frequency increase per category, respectively, whereas point estimates for MS duration did not reach statistical significance.

Conclusion
Reaching specific EDSS milestones was associated with both calendar age and disease duration. The occurrence of four major co-morbidities was mainly associated with calendar age, but not with MS disease duration. With the increased life expectancy of PwMS, this harbors implications for both prevention and treatment strategies of co-morbidities in PwMS, for instance to avoid polypharmacy.
Ocrelizumab Treatment Effect on Upper Limb Function in PPMS Patients with Disability: Subgroup Results of the ORATORIO Study to Inform the ORATORIO-HAND Study Design

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Aim
Ocrelizumab demonstrated efficacy versus placebo in reducing upper limb dysfunction (9-Hole Peg Test [9HPT]) in ORATORIO (Expanded Disability Status Scale [EDSS] ≤ 6.5). Ocrelizumab benefit in more disabled PPMS patients ineligible for inclusion in ORATORIO would fulfill an unmet need. The objective was to assess ocrelizumab efficacy on upper limb function in more disabled/older patients with primary progressive multiple sclerosis (PPMS) from the Phase III ORATORIO study (NCT01194570) to inform the design of the Phase IIIb ORATORIO-HAND study.

Methods
ORATORIO PPMS patients (N=732; EDSS 3.0-6.5; age 18-55 years) were randomized (2:1) to ocrelizumab or placebo for ≥120 weeks and until a pre-specified number of EDSS progression events occurred. Efficacy of ocrelizumab in preventing progression of upper limb function as measured by 12-week confirmed 20% worsening in 9HPT (average of both hands) was investigated in baseline subgroups: EDSS ≥ 6.0 (N=220), age > 45 years (N=384), and 9HPT time > 25 seconds (N=434).

Results
Ocrelizumab reduced upper limb disability progression in more disabled/older PPMS patients. Risk reductions versus placebo in 9HPT progression were similar in patients with baseline EDSS score < 6.0 and ≥ 6.0 (40% versus 38%, p=0.92), and baseline 9HPT time ≤ 25s and > 25s (49% versus 44%, p=0.82). Progression events mainly occurred in patients with 9HPT > 25s versus ≤ 25s (placebo: 34.3% vs 17.8%; ocrelizumab: 21.5% vs 9.9%); a weak trend for greater efficacy in patients ≤ 45 years versus > 45 years was observed (p=0.29).
Conclusions
ORATORIO-HAND is designed to further investigate the efficacy of ocrelizumab on upper limb function. Based on the 9HPT progression rates observed in ORATORIO, 1,000 eligible patients (EDSS 3.0-8.0, age 18-65 years, 9HPT > 25s), randomized (1:1) to ocrelizumab or placebo for ≥ 120 weeks (until a pre-specified number of progression events occur) will enable the assessment of ocrelizumab efficacy on confirmed 9HPT progression (primary endpoint). Screening will begin Q1 2019.
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Atypical Anti-MOG syndrome with a pseudotumor cerebri-like presentation – a case report

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Aims
To describe an atypical case with Anti-MOG antibody related demyelinating syndrome.

Method
Case report.

Results
The anti-MOG antibody syndrome is an autoantibody-mediated disease that induces inflammatory demyelinating lesions in the central nervous system. The clinical manifestations include typically those of optic neuritis, encephalitis, or myelitis. We present a patient with anti-MOG antibodies who had an atypical clinical presentation: headache and a significantly elevated intracranial pressure, which is a rarely reported finding in anti-MOG syndromes so far. Our 67-year old female patient had a 3-week history of blurred vision and bilateral papilledema. She was initially diagnosed with pseudotumor cerebri syndrome. The clinical examination showed furthermore a gait ataxia. Due to a diagnosed Crohn’s Disease a regular medication with Azathioprin and Sulfasalazin was already introduced. The MRI brain scan revealed multiple supra- and infratentorial T2-weighted hyperintense lesions with Gadolinium enhancement. An extended laboratory analysis revealed no hints of infection. The lumbar puncture revealed an elevated opening pressure of 31 cmH20 and otherwise a normal cell count with a mildly elevated protein synthesis. A CSF flow cytometry and CSF pathology analysis did not show any signs of malignant disease. Serology for Anti-MOG Ab was positive and AQP4 Ab negative. After the verification of the Anti-MOG Ab we initiated a plasmapheresis followed by i.v. Rituximab, which lead to a remarkable improvement of the visual acuity and gait ataxia.

Conclusion
This case adds a new facet to this relatively new disease of anti MOG antibody syndrome.
P83
Combined central and peripheral demyelination (CCPD): a case report

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Aims and Background
Acute and chronic demyelinating diseases (AIDP and CIDP) of the peripheral nervous system as well as acute and chronic demyelinating diseases of the central nervous system (ADEM and MS) are well described diseases with typical entity, diagnostic criteria and therapeutic recommendations. The presentation of both – a combined peripheral and central demyelination – was first described in 1992 and is characterized by a heterogeneous clinical presentation, variable disease course and challenges in therapeutic decision.

Case report
A 46 year old man was presented with a syncope and paraesthesia of both hands and feet since one week. On admission the patient had spastic distal paresis of the left leg (M4) and asymmetric glove-and-stocking type sensory disturbance and painful paraesthesia on both hands and feet. He also showed a sensory ataxic gait. Magnetic resonance imaging showed multiple high intensity cerebral lesions and two lesions in the spinal cord without contrast enhancement, not completely fulfilling the criteria for multiple sclerosis (McDonald Criteria 2017). CSF showed mild pleocytosis and elevated protein, no oligoclonal bands. Nerve conduction studies showed severe sensory and motor demyelinating polyneuropathy, fulfilling the criteria for AIDP. Nerve ultrasound showed typical signs of acquired demyelinating polyneuropathy with multiple focal swelling of different nerves. Serological tests for neurotropic infections, rheumatological disorders, antiganglioside-antibodies, neurofascin antibodies, aquaporin4-antibodies, MAG- and MOG antibodies were negative. The diagnosis of combined central and peripheral demyelination was made and treatment with intravenous immunoglobulin (IvIGs) was initiated. Five months later the symptoms did not improve clinically and nerve conductions were unchanged, so that the diagnostic criteria for CIPD were fulfilled. The magnetic resonance imaging was stable at 6 months follow-up.

Conclusion
Combined peripheral and central demyelination is rare but is supposed to be a new entity in the spectrum of demyelination diseases. Specific new antibodies like neurofascin or anti-MOG are described to be present in this disease. However, some cases like the one described here are sero-negative.
Model (PHREND®) for personalized prediction of treatment response in relapsing remitting multiple sclerosis (RRMS)

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Aims
In multiple sclerosis (MS), due to the high complexity and uncertainty of disease progression, it currently takes long time to find an appropriate therapy for an MS patient and currently the treatment decision depends on a significant portion of intuition. Our solution to support relapsing remitting multiple sclerosis (RRMS) patients and their doctors during this difficult journey is to distil the large amounts of available data into meaningful and relevant decision-making information as efficiently as possible.

Methods
This study employed clinical real-world data recorded in the NTD MS registry, a Germany-wide network of physicians in the fields of neurology and psychiatry founded in 2008. The registry includes about 25,000 patients with MS, which represents about 15% of all MS patients in Germany, with an average of observation period of 8.7 years. The PHREND App contains a data-driven mathematical regression model to predict MS disorder progression for individuals based on different therapies, taking into account two indicators of therapy effectiveness: number of relapses, and confirmed disability progression. We employed hierarchical generalized linear models (GLM) for both indicators of treatment response, with model parameters depending on patient’s profile and treatment. Additionally we implemented cross validation and quality of predictions assessment using the mean squared error (MSE), log-likelihood, and Harrell’s concordance statistic (C-Index).

Results
The results of the analysis revealed that predictive models provide robust and accurate predictions and generalize to new patients and clinical sites. The output of PHREND is an independent recommendation for the therapy that is statistically most likely to succeed for each individual patient, presented in a transparent and easy-to-understand way.

Conclusion
Applying personalized predictive models in RRMS patients is still new territory that is rapidly evolving and has many challenges. The proposed framework addresses the following challenges: robustness and accuracy of the predictions, generalizability to new patients and clinical sites, and comparability of the predicted effectiveness of different therapies. Nevertheless, we present the PHREND App already implemented in German doctors’ offices and we plan to expand our model to several other neurological disorders.
P85
Orofacial pain in dental practice: prevalence of neuropathic and musculoskeletal pain

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Aims
In this study, the results of clinical diagnostics of the population with orofacial pain based on multidisciplinary diagnostics were evaluated.

Methods
This population study consisted of 470 consecutive patients (mean age±SD was 41.7±17.8 years, range of age 10-88 years, 86% were female, gender ratio female: male was 6.1:1) who were referred to the Department of Removable Prosthodontics between 2001 and 2017. For the purpose of obtaining a differential diagnosis, a number of the patients were referred from the Clinic for Neurology and the Sestre milosrdnice University Hospital Center as a clinical basis for neuropathic orofacial pain. For patients with neuropathic pain and already established diagnoses, such as trigeminal neuralgia, it was necessary to determine possible comorbidity with TMJ-disorder.

Results
Patients with TMJ-related diagnoses (n=340) have the largest share in patient population with orofacial pain in general. Of this, osteoarthritis diagnosis (which also includes the comorbidity disc displacement) is the most comprehensive diagnosis category (n=197; mean age 47.4±17.2). The patients with disc displacement followed (n=144; mean age 29.9±13.6). Only 35 patients had pains caused by trigeminal neuralgia (mean age 52.9±13.0). A statistically significant age difference was determined for all three subgroups, with females prevalent (chi-square test p < 0.001). There is also a comorbidity with trigeminal neuralgia (16 patients with osteoarthritis and one patient from the subgroup of disc displacement). Persistent idiopathic facial pain was found in subgroups with osteoarthritis (n=19) and disc displacement (n=1). The use of therapy depended on the type of diagnosis since one of the first choices for diagnosis of TMJ was a fabrication of the Michigan stabilization splint. In the subgroup of patients with trigeminal neuralgia, the treatment with anticonvulsant drugs was applied in 54.3% of patients, anticonvulsant drugs in combination with acupuncture in 25.7% of patients and the treatment by acupuncture alone in 17.1% of patients. Only one patient (2.95 %) was treated with opioid non-steroidal anti-inflammatory drugs.

Conclusion
It is difficult to determine the prevalence of trigeminal neuralgia because the disease is often not recognized as neuralgia; hence the symptomatology is in dental practice initially related to odontogenic pain of unclear etiology.
Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients with Relapsing and Primary Progressive Multiple Sclerosis

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Aim
Ongoing safety reporting is crucial to understanding the long-term benefit–risk profile of ocrelizumab in patients with multiple sclerosis (MS). The safety and efficacy of ocrelizumab have been characterized in one Phase II study in relapsing-remitting MS (NCT00676715), two identical Phase III trials in relapsing MS (RMS; OPERA I/II [NCT01247324]/[NCT01412333]) and the Phase III trial in primary progressive MS (PPMS; ORATORIO [NCT01194570]) and their extensions. Here, we report ongoing safety evaluations from ocrelizumab clinical trials and open-label extension (OLE) periods up to July 2018, and updated post-marketing data.

Methods
Safety outcomes were reported for all patients who received ocrelizumab during the controlled treatment and associated OLE periods of the Phase II and Phase III MS clinical trials, plus the Phase IIIb trials VELOCE, CHORDS/CASTING and OBOE (ocreliumab all-exposure population; updated data-cut to include ENSEMBLE). The number of post-marketing patients exposed to ocrelizumab is based on estimated total number of vials sold, as well as US claims data. To account for the different exposure lengths, the rate per 100 patient years (PY) is presented. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities.

Results
In clinical trials, 3,811 patients with MS received ocrelizumab, resulting in 10,919 PY of exposure, as of February 2018. Reported rates per 100 PY (95% confidence interval) were as follows: AEs, 242 (239-245); serious AEs, 7.23 (6.73-7.75); infections, 74.5 (72.9-76.1); serious infections, 2.00 (1.74-2.28); and malignancy 0.45 (0.33-0.60). Updated cross-trial information and post-marketing data using a July 2018 data-cut will be presented at the conference.

Conclusions
The reported rates of events per 100 PY in the ocrelizumab MS all-exposure population continue to be generally consistent with those seen during the controlled treatment period in the RMS and PPMS populations. Long-term safety data will continue to be reported on a regular basis.
The Medical Informatics Platform (MIP): an innovative tool for sharing patients’ BIG data in clinical neuroscience across Europe.

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Medical and research activities in clinical neuroscience produce a massive amount of patients’ data that could leverage our knowledge and understanding of brain diseases. Unfortunately, despite growing incentives for open data, most of it remains currently locked in hospitals or labs, either for regulatory or cultural reasons. The Human Brain Project (HBP) has developed the MIP, an innovative tool to investigate, compare and analyze large patients’ datasets distributed across centers without requiring the data to be sent out from their site of origin. To achieve this goal, a MIP instance is installed in each participating hospital/lab, enabling harmonization of local data via pre-processing, data integration and anonymization techniques by the MIP data factory so as to be imported into the platform. The MIP central engine then enables federated web-based queries which will execute the same algorithm in each site in a coordinated way, to eventually provide aggregated findings. To this purpose, 16 analytical tools are deployed in each MIP algorithm factory, from standard descriptive statistics to complex supervised and unsupervised machine learning tools. Beyond anonymization, data privacy is further ensured by only allowing end-users to query aggregated findings, while not being able to investigate the datasets at the individual level. Similarly, databases cannot be copied or uploaded. The MIP is currently installed in 17 hospitals, with a fast track development to reach 30 in the near future. Datasets from several thousand patients are available in the fields of dementia and traumatic brain injury, and soon in that of epilepsy and mental health. Public datasets are also available for comparisons (ADNI, PPMI, EDSD). Data types include clinical information and pre-processed MRI 3D-T1 images with regional brain volume for 120 pre-defined regions of interest. Human intracerebral EEG recording will be added soon. MIP will help neuroscientists and clinicians to investigate and compare harmonize scientific big-data from harmonized pre-processed neuroimaging, neurophysiological, -omics and medical records using a user-friendly interface to run data-driven statistical analysis and predictive models. The MIP will link brain-science research, clinical research and patient care into a unique and accessible space, providing the scientific and clinical community with the tools to improve knowledge, diagnosis, early prediction and innovative treatment of brain diseases.
Patient reported outcomes identify factors that influence quality of life in MS patients treated with natalizumab. A post hoc analysis.

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Aim
The prospective, multicenter, single-arm, observational PROTYS study included 35 Patients who underwent one year of natalizumab treatment. Patient reported outcomes (PROs) including the Multiple Sclerosis International Quality of Life (MusiQoL) index, the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19), the Fatigue Scale of Motor and Cognitive Function (FSMC), the Work Productivity and Activity Impairment (WPAI), the Symbol Digit Modalities Test (SDMT), the EuroQoL-5D (EQ-5D) and the Beck Depression Inventory-Fast Screen (BDI-FS) were collected at baseline and after 1 year to identify factors which are central for the improvement in quality of life (QoL).

Methods
Changes in the above listed PROs over the course of treatment were investigated for the total population using the Wilcoxon Mann–Whitney test. Spearman’s correlation coefficients were used to investigate relationships between the change over 1 year in the MusiQoL global index, MusiQoL subscores, and other PROs. Analyses were run separately in the overall study population (n=35) and in the subgroup of patients with improvement in MusiQoL global index (n=21).

Results
In the total natalizumab population, improvements in the WPAI presenteeism WPAI score (r=-0.5439, p=0.0294) and in the MusiQoL subscores psychological well-being (r=0.4609, p=0.0053), symptoms (r=0.4279, p=0.0103) and sentimental and sexual life (r=0.4361, p=0.0248) were correlated with the improvement of the MusiQoL global index. This was consistent with the findings in the MusiQoL improved patients showing that improvement in MusiQoL global index correlated with the score of the MSISQ-19 for primary causes of sexual dysfunction (r=-0.5157, p=0.0167), the FSMC total score (r=-0.6300, p=0.0022) and in the presenteeism WPAI score (r=-0.5862, p=0.0452).

Conclusion
Improvements in overall quality of life over 1 year for patients initiating natalizumab in the PROTYS study are consistent with prior reports of natalizumab treatment effects on quality of life. Associations observed in PROTYS between overall quality life scores, MusiQoL subscores, and other PROs suggest improvements in patient psychological wellbeing, resolution of MS symptoms including fatigue and sexual dysfunction, and increases in workability may all be important factors contributing to the increases in overall quality of life.
P89
Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis

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Aims
To evaluate the effects of siponimod on cognitive processing speed (CPS) in SPMS using the Symbol Digit Modalities Test (SDMT).

Background
Cognitive impairment affects 50 – 70% of MS patients and is more severe in progressive than relapsing course. CPS is the most frequently affected cognitive domain; SDMT is the recommended gold standard measure of CPS. We previously reported a benefit of siponimod on CPS; here, we explore whether this benefit was affected by the CPS status at baseline.

Methods
SPMS patients receiving siponimod (N = 1099) or placebo (N = 546) in the EXPAND study underwent SDMT at baseline and at 6-monthly intervals. A mixed-model repeated measures determined statistically significant group effects and a Cox proportional hazards model determined if these effects were clinically meaningful. “Sustained” change was defined as change from baseline by ≥ 4 points sustained on all subsequent assessments. Subgroup analyses were performed for patients with or without cognitive impairment at baseline (impaired SDMT < 43; Drake et al 2018), and with a baseline SDMT ≥ median or < median.

Results
The proportion of patients with sustained improvement in SDMT was greater for siponimod versus placebo for patients with or without cognitive impairment at baseline, reaching significance for those without impairment (HR 1.49 [1.09,2.04]; p = 0.0126), and for those with baseline SDMT ≥ median and < median, reaching significance for those with baseline SDMT ≥ median (HR 1.46 [1.10,1.95]; p = 0.0094). Also, the proportion of patients with sustained deterioration was less with siponimod versus placebo for those with
or without cognitive impairment, reaching significance for both groups: HR 0.72 ([0.53, 0.96]; p = 0.0269) and HR 0.76 ([0.58, 1.00]; p = 0.0477), respectively, and among those with baseline SDMT < median and ≥ median, reaching significance for those with baseline SDMT < median (HR 0.65 [0.47, 0.89]; p = 0.0071).

Conclusion
Siponimod demonstrated significant functional benefits on CPS in SPMS patients, both for sustained improvement and against sustained deterioration in SDMT.
P90
New-onset gaze-evoked nystagmus as an early clinical sign of thiamine deficiency – a case report

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Background
The differential diagnosis of acute-onset, persistent vertigo is broad and dangerous, potentially life-threatening central causes must be searched for urgently. Here we discuss a treatable cause of acute vestibular syndrome that the clinician must not miss.

Case presentation
A 73-year-old male presented to the emergency room with a one-week history of worsening dizziness, gait imbalance and blurred vision on lateral gaze. He also had lost interest in daily activities recently. He had received daily intravenous antibiotics for 2.5 months due to infected liver cysts. Due to persistent nausea his food intake was very limited, resulting in a weight loss of 22kg. On clinical examination he showed marked symmetric horizontal gaze-evoked nystagmus (GEN) and mild horizontal spontaneous nystagmus to the right. The horizontal head-impulse test (hHIT) was abnormal to both sides. He showed sway on Romberg and his gait was mildly broad-based and ataxic. Based on his clinical presentation including subtle signs of encephalopathy and a history of nutritional deprivation, he was diagnosed with suspected thiamine deficiency and high-dose parenteral thiamine treatment was started. An MRI of the brain obtained the same day showed contrast-enhancement of the mamillarian bodies. Within 12 hours after thiamine replacement his symptoms had improved, on clinical examination his GEN had clearly decreased. Thiamine deficiency was confirmed later. On follow-up (2 weeks later) he showed further improvement, although both mild asymmetric (left>right) GEN and bilaterally impaired hHIT persisted.

Conclusions
With thiamine storage being sufficient only for up to 18 days, this case of prolonged very low food intake due to drug-related nausea/vomiting emphasizes the need to assess the risk for thiamine depletion and to establish appropriate supplementation to avoid clinically manifest deficiencies. While ocular motor abnormalities such as bilateral symmetric vestibular loss and nystagmus are frequent and characteristic early signs of thiamine deficiency, the classic triad is seen in only 16% of patients. Thus, in the context of nutritional deprivation, ocular motor abnormalities should prompt further diagnostic workup and immediate empirical parenteral thiamine supplementation to avoid more advanced and potentially irreversible signs of Wernicke’s disease including ophthalmoplegia and encephalopathy.
Estimating and accounting for the effect of MRI scanner changes on longitudinal whole-brain volume change measurements

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Introduction
Various technical factors can affect MRI based brain volume (BV) measurement. SIENA (Structural Image Evaluation Using Normalization of Atrophy) corrects for differences in imaging geometry using the outer skull surface for both time points and has been proposed to minimize this bias. Yet, SIENA cannot intrinsically overcome other technical factors influencing BV measurements in longitudinal studies.

Objective
To use MRI data from healthy control subjects (HCs) to adjust brain volume changes (BVCs) in multiple sclerosis (MS) patients for a major scanner upgrade.

Methods
In 2016, 20 MS patients from the Swiss MS cohort study (15 female; mean age 55±15 years; disease duration 25.3±14.5 years; 40% progressive MS) were scanned 6-14 times before and 2-3 times after and 26 HCs (12 female, mean age 31±8 years;) once 1 month before and 3 months after a major scanner upgrade (1.5T Siemens Healthineers Magnetom Avanto to 3T Skyra Fit). All scans were bias-field corrected. SIENA was used to measure whole brain volume changes on T1 weighted Magnetization Prepared Rapid Gradient Echo sequences. Mean change in the HCs was used to adjust for brain atrophy during the scanner change. In addition, a gender- and age-dependent factor was estimated based on a linear model. Both factors were internally validated in HCs using leave-one-out jackknife validation.

Results:
Estimated BV decreased in HCs and MS patients on average by -3.4±0.6% and -4.1±0.8% during the scanner change, respectively. There was no association between T2 lesion volume and BVCs during the scanner upgrade (Spearman's rank correlation=0.007; p = 0.98) in MS. The variance in BVCs before and after the scanner change was similar in MS patients (F-test, p = 0.78). The observed BVCs were adjusted by adding a fixed corrective term of 3.4% (95%CI: ± 0.27) based on the observed average changes in HCs. Age and gender in HCs had no significant additive value on this corrective term. Internal validation provided a variance of 0.35% for the jackknife estimator. A linear mixed effect model in MS confirmed this result as the adjusted brain volume changes during the scanner upgrade was not associated with the scanner type anymore (p = 0.29).

Conclusions
A scanner drift can cancel out BVCs in longitudinal cohorts. The inclusion of corrective fixed-effect terms for a major scanner upgrade based on changes observed in HCs may help to adjust for the known and unknown factors associated with a scanner upgrade.
P92
Transcallosal inhibition and mirror movements in amyotrophic lateral sclerosis

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Background
Pathologies of the corpus callosum (CC) have been described in ALS using imaging techniques (e.g., Agosta et al., 2010). Yet, little is known about functional involvement of this structure. Wittstock et al. (2007) describe altered transcallosal inhibition (TI) in a small group of ALS patients, as well as pathological mirror movements (Wittstock et al., 2011). Here, we studied ALS patients to characterize the functional involvement of the CC. We used two different transcranial magnetic stimulation (TMS) protocols to study TI. On the clinical level, we studied mirror movements (MM) during unilateral voluntary hand movements, as TI is responsible for the suppression of MM in healthy adults (Hübers et al., 2008).

Methods
1) We used a double-pulse TMS protocol (Ferbert et al., 1999) at different stimulus intensities to study short interhemispheric inhibition (S-IHI). A conditioning stimulus (CS) over one hemisphere preceded a test stimulus (TS) over the other. The amount of suppression of the TS-motor evoked potential (MEP) by the CS reflects the strength of S-IHI. Relevant pathology of the cortico-spinal tract was excluded by studying the central motor conduction time. 2) We studied ipsilateral silent period (iSP). Patients were asked to voluntarily activate one hand while a TMS stimulus was delivered over the ipsilateral hemisphere. The suppression of EMG activity in the ipsilateral hand reflects the iSP and serves as a marker of motor callosal interhemispheric inhibition (Meyer et al., 1995, 1998). In addition we studied MM clinically.

Results
Protocol 1: ALS patients showed significantly reduced S-IHI compared to healthy controls (p = 0.016).
Protocol 2: Seventyseven percent of patients showed alterations of the iSP (prolongation or complete loss) at least in one hemisphere compared to healthy controls (p = 0.01). Seventyone percent of patients showed clinically overt MM (p = 0.01).

Discussion
Here, we use different TMS-protocols to study the function of the CC in ALS. Chen et al. (2003) suggested that the mechanisms underlying iSP differ from those of S-IHI. The iSP is considered as a measure that provides complementary but not identical information on TI compared to S-IHI (Perez & Cohen, 2009). We found that alteration of TI is present in ALS and can be reliably studied using both protocols. In addition, most patients with reduced TI also showed clinically overt MM. TI might be a suitable marker in different stages of the disease.
Rare variant of Guillain-Barré syndrome after chikungunya viral fever: A Case Report

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Chikungunya (CHIK) viral fever is a self-limiting illness that presents with severe debilitating arthralgia, myalgia, fever and rash. Neurological complications are rare. We present a case of a 36-year-old woman who presented with acute onset progressive difficulty swallowing and left arm weakness. She was diagnosed with CHIK viral fever 4 weeks prior to admission. After investigations, she was diagnosed with a pharyngeal–cervical–brachial variant of Guillain-Barré syndrome. In hospital, she required ventilator support. Her condition improved after five sessions of intravenous immunoglobulin with almost complete resolution within 6 months of symptom onset. With frequent CHIK outbreaks, the neurological complications are increasingly seen in the emergency department. The knowledge of these associations will result in early diagnosis and treatment.
Aims
In CLARITY, No Evidence of Disease Activity-3 (NEDA-3) was achieved in more patients with relapsing multiple sclerosis (RMS) receiving Cladribine Tablets 10 mg (3.5mg/kg cumulative dose over 2 years [CT3.5]) versus placebo. NEDA-3 was determined (post-hoc) in patients receiving CT3.5 in CLARITY followed by placebo (CP3.5) or CT3.5 (CC7) in CLARITY-Extension.

Methods
NEDA-3 (no relapse, 6-month EDSS progression, T1 gadolinium-enhancing or active T2 lesions) was analysed in CLARITY-Extension Yr1 for CP3.5 (N = 98) and CC7 (N = 186). NEDA-3 was evaluated over 12-months to the end of Yr4 or Yr5. Patients were grouped into Yr3-4 and Yr4-5 by bridging interval (BI) between studies (≤ / > 43 weeks). Between-group differences were analysed by logistic regression.

Results
12 months up to Yr4-end after starting CLARITY, annual NEDA-3 was achieved in 46% of CP3.5 patients and 48% in the CC7 group, and to Yr5-end in 35% and 48% of the respective groups. No significant difference existed between NEDA-3 in the CP3.5 (41.5% [95% CI: 32.4, 60.0%]) and CC7 (48.0% [95% CI: 40.2, 64.4%]) groups after adjusting for BI duration.

Conclusions
Following CT3.5 in Yr1 and Yr2, annual NEDA-3 was sustained in RMS patients receiving either CT3.5 or placebo in CLARITY-Extension, and not significantly different between Yr3-4 and Yr4-5 groups. The CLARITY study: NCT00213135; The CLARITY Extension study: NCT00641537
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Updated safety of cladribine tablets in the treatment of patients with multiple sclerosis: Integrated safety analysis and post-approval data

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Aims
Pooling of long-term safety data for integrated analysis from the clinical trial program allows comprehensive characterization of the Cladribine Tablets (CT) 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as CT3.5) safety profile in patients with relapsing multiple sclerosis (RMS). Here, we use the latest integrated safety data for CT, from clinical studies including final data from the PREMIERE registry, to provide an update to the previously reported treatment emergent adverse event (TEAE) profile. Additionally, we report post-approval safety data from Europe.

Methods
The monotherapy oral cohort (CT3.5, N = 923, patient-years [PY] = 3936.69; placebo [PBO], N = 641, PY = 2421.47) was derived from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry. Incidences per 100PY were calculated for adverse events, cumulative to the end of PREMIERE. Adverse drug reactions (ADRs) including serious ADRs (SADRs; implied causality) from post-approval sources are also summarised.

Results
Demographics reported at first dosing date were found to be balanced among treatment groups, including mean age (37.8 years, CT3.5; 37.2 years, PBO), proportion of females (66.3%, CT3.5; 66.1%, PBO) and proportion of patients with prior disease modifying drug experience (19.9%, CT3.5; 20.4%, PBO). Incidences per 100PY for experiencing ≥ 1 serious TEAE were 3.80 (CT3.5) and 3.05 (PBO). Incidences per 100PY for serious lymphopenia (preferred term [PT]) were 0.10 for CT3.5 and 0 for PBO. For serious infections and infestations (system organ class), incidences per 100PY were 0.60 (CT3.5) and 0.42 (PBO); for serious herpes zoster (PT): 0.05 (CT3.5) and 0 (PBO). Incidences per 100PY for malignant tumours were 0.26 (CT3.5) and 0.12 (PBO). Separately, 922 ADRs from post-approval sources were reported in the Periodic Benefit-Risk Evaluation Report, of which 136 were SADRs; none of which are new safety findings for CT3.5.
Conclusion
This integrated analysis of trial data, exclusively focused on the frequency of serious TEAEs with CT3.5 in RMS patients, further establishes the safety profile of this dose. This profile is consistent with the previously published integrated safety analysis profile. No new major safety findings were identified in this latest dataset which includes final data from the PREMIERE registry. The pattern of post-approval ADRs was consistent with the clinical safety profile for CT3.5.
A series of cases with PERM in association with GAD, NMDA, LGI1 and other antibodies

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Aims
Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe syndrome that presents with autonomic features, hyperekplexia, painful spasms and breathing problems. It is part of the spectrum of the stiff-person syndrome (SPS) with anti-glutamic acid decarboxylase (GAD) antibodies in up to 80% of patients.

Methods
We present a series of 3 cases in The Republic of North Macedonia that were diagnosed as Progressive Encephalomyelitis with rigidity and myoclonus.

Results
A series of 3 cases have been processed, which are diagnosed as Progressive encephalomyelitis with rigidity and myoclonus (PERM). The initial symptoms of the patients were bilateral ataxia, dysarthria, the change of sensations in the area of the feet, moments of forgetting things, unstable posture followed by the involuntary movement of the lower limbs, shaking of the upper limbs. The goal is to show the association of the presence of certain antibodies to the progressive clinical manifestations of the disease itself. Furthermore, all patients were GAD, Hu D and Ri positive. Two were positive for the NMDA antibodies. Only one patient was positive for Anti-CMV, EBV Viral Capsid Antigen-Antibody (VCA) IgG, Anti Herpesvirus VZV IgG, anti-LGI1 antibodies. It is common that all three patients have been given/given series of plasmapheresis and IVIG cycles, but without any significant progress. Unfortunately, one ended up lethal, and the other two are not in an enviable state.

Conclusion
These three cases do not only show the clinical spectrum of PERM, but also the association of this disease with Hu, Ri, GAD, NMDA and LGI1, and other antibodies. This combination of antibodies may be responsible for the progressive character of this disease.
Validation of the Scoring Algorithm for a Novel Integrative Secondary Progressive Multiple Sclerosis (SPMS) Screening Tool

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Aims
To determine the sensitivity and specificity of a SPMS screening tool to support the diagnosis of patients with SPMS in clinical practice.

Background
Timely diagnosis of SPMS represents a challenge for clinicians in daily practice. The SPMS screening tool was developed to support early identification of patients who have progressed, or are at risk of progressing, from relapsing–remitting multiple sclerosis (RRMS) to SPMS. A mixed methods approach involving qualitative research with patients and clinicians and regression on data from a large real-world observational study (n = 2,791) was used to determine tool content and create the scoring algorithm.

Methods
MS neurologists in the USA, Canada, and Germany completed the digital tool for up to 10 patients each, for patients with a diagnosis of RRMS, SPMS and those where the clinician suspected transition to SPMS. ROC curves were used to determine the sensitivity and specificity of the tool and define the score thresholds that optimally discriminate between RRMS and SPMS diagnoses.

Results
20 neurologists completed the tool for 198 patients. Mean scores for patients with SPMS, suspected to be progressing SPMS, RRMS were (69.6 vs 55.2 vs 38.1, p < 0.001) respectively. A threshold of ≥58.85 identified patients with SPMS with sensitivity 0.82, specificity 0.84, area under the ROC curve [AUC] = 0.904 [95% CI 0.86–0.95]. A threshold of ≤ 51.80 identified patients with RRMS with sensitivity 0.83, specificity 0.82, while a threshold of ≤ 53.85 had sensitivity 0.89, specificity 0.76 using the sum of squares and Youden’s J index, respectively (AUC = 0.908 [0.87–0.95]).

Conclusion
These results demonstrate that the SPMS screening tool was able to differentiate between RRMS and SPMS patients with high sensitivity and specificity and thus also identify patients in transition. These findings support the validity and potential clinical utility of the tool to help recognize early signs suggestive of progressive disease.
Ultra-early and periinterventional angiographic cerebral vasospasm after aneurysmal subarachnoid hemorrhage predicts early onset of delayed cerebral vasospasm, delayed cerebral ischemia, and poor outcome.

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Background
There is limited but growing body of evidence that ultra-early angiographic vasospasm (UEAV), defined as cerebral arterial narrowing within the first two days after aneurysmal subarachnoid hemorrhage (SAH), is associated with delayed cerebral vasospasm (DCVS), delayed cerebral ischemia (DCI) and poor outcome. So far, detection of UEAV was based on radiologic imaging before IA treatment. In this study the phenomenon is studied in patients in whom UEAV was visualized during IA treatment.

Methods
This single-center study comprise a retrospective analysis of prospectively collected data of 173 consecutive patients that underwent either endovascular therapy or microsurgical treatment in a hybrid operating room within the first 48 hours after SAH. The association of onset and time to DCVS, DCI, and functional poor outcome with initial and periinterventional UEAV were analyzed by means of Cox proportional-hazards models. These predefined endpoints were further explored by accounting for known and suspected risk factors.

Results
Periinterventional angiographic vasospasm increased incidence and shortens time to onset of DCVS. Both, initial and periinterventional UEAV significantly increased the risk for DCVS (odds ratio [OR] 1.6, 95% confidence interval [CI] 1–2.1, p = 0.041), DCI (OR 5.9, CI 1.7–25.1, p = 0.001) and unfavourable outcome (OR 4.7, CI 1.7–13.4, p = 0.004). Further, clipping, female sex and increasing BNI Wilson score increased both the hazard for delayed vasospasm and DCI. A poor functional outcome was, in addition to UEAV, associated with increasing age at SAH, poor initial WFNS, and intraparenchymal hemorrhage.

Conclusions
Not only patients with initial but also those with periinterventional UEAV are at high risk of DCVS, DCI, and poor outcome after SAH. Therefore, periinterventional UEAV should be considered as an important warning sign and early monitoring as well as early aggressive therapy is warranted.
Outcome and Course of Sequelae of acromegaly after treatment of human growth hormone excess (AcroSequelae) - a SwissPit study

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Aim
Acromegaly, caused by a growth hormone (hGH) secreting pituitary adenoma, is a debilitating disorder, leading e.g. to obesity (OB), arterial hypertension (aHT), diabetes mellitus (DM), obstructive sleep apnea syndrome (OSAS), carpal tunnel syndrome (CTS), polyposis coli (PC). If remission (i.e. normal levels of IGF-1 and random hGH) is not achieved by surgery, irradiation and medical therapy (e.g. with somatostatin analogues) is indicated. The goal of this retrospective study is to assess the impact of therapy for acromegaly on these sequelae.

Methods
Data of acromegalic patients who were treated at the authors’ institutions from 2006 to 2018 and who were eligible for the Swiss Pituitary Registry (SwissPit) were retrospectively assessed for the following parameters: prevalence and course of OB, aHT, DM, OSAS, CTS, PC; therapies used and respective remission rates; prognostic factors for reaching remission.

Results
Sixty-three patients (mean age 52 years, 52% female) were included. Twenty-one (33%) suffered from OB, 35 (56%) from aHT, 16 (25%) from DM, 18 (29%) from OSAS, 18 (29%) from CTS and 3 (5%) from polyposis coli. Forty-five (71%) patients harbored micro- and 6 (10%) giant adenomas; 30% of the tumors invaded the cavernous sinus (i.e. Knosp grades 3 and 4). Sixty-one (97%) patients had surgery; 30 (49%) of these showed remission during a mean follow-up of 3 years. Postoperative drug therapies were used in all and radiotherapy additionally in 3 (5%) of the non-remission cases. In 16 (64%) of these patients remission criteria were fulfilled at time of study closure after a mean follow-up of 5 years. In the surgical cases relief of sequelae was detected as follows: OB, 10%; aHT, 18%; DM, 44%. In case of postoperative octreotide therapy, aHT disappeared in 20%, while DM, OSAS and obesity persisted. In case of combination therapies (e.g. cabergoline/octreotide) and after irradiation no change of the prevalence of sequelae was noted.

Conclusion
Even in a country with highly distinguished medical services as Switzerland, the prevalence of sequelae of acromegaly is noteworthy at the time of diagnosis. Surgical cure promises relief of sequelae in a considerable number of patients, while postoperative non-remission with need of further drug treatment and radiotherapy is associated with their persistence.
P100
An endovascular assisted non-occlusive cerebral high flow bypass – a technical feasibility study in a rabbit model.

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Objective
Temporary parent vessel occlusion to establish a high flow interpositional bypass carries the risk of infarcts. We investigated the feasibility of a novel technique to establish a high-flow bypass without temporary parent vessel occlusion in order to lower the risk of ischemic complications.

Methods
In ten New Zealand white rabbits, a carotid artery side to end anastomosis was performed under parent artery patency with a novel endovascular balloon device. Intraoperative angiography, postoperative neurologic assessments and postoperative MRI/MRA were performed to evaluate the feasibility and safety of the novel technique.

Results
A patent anastomosis was established in 10 of 10 animals; three procedure-related complications occurred. No postoperative focal neurologic deficits were observed. MRI/MRA findings include no infarcts, bypass patency in 50% of animals.
P101
Postoperative course and outcome of optic chiasm syndrome after pituitary surgery - A SwissPit Study

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Aim
Restoration of visual acuity (VA) and visual fields (VF) impaired by a sellar mass compressing the optic pathway is one of the main indications for pituitary surgery. Nevertheless, in spite of this being a major concern, reports focusing on the postoperative outcome and the evidence for predictive factors influencing this outcome are markedly underrepresented in the literature. The goal of this retrospective single-center study is to identify potential predictive factors for postoperative relieve of visual acuity impairment and visual field deficits of patients with sellar lesions and to describe the ophthalmological outcome.

Methods
Based on data of the Swiss Pituitary registry patients have to fulfill the following criteria for inclusion: pituitary surgery at the authors´ institution between 2002 and 2017; preoperative VA impairment and/or VF deficiency caused by a sellar lesion; complete pre- and postoperative ophthalmological and radiological follow-up of at least 3 months.

Results
162 patients (mean age 57 years, 54% female) were included. Pituitary adenomas were diagnosed in 146 (91%) of the patients, craniopharyngioma in 8 (5%) and non-neoplastic cysts in 5 (3%). The mean cranio-caudal diameter was 30mm. The mean tumor volume was 12cm³. The VF was deficient in 148 (91%) and the VA in 122 (75%) patients. Transsphenoidal approaches were used in 154 (95%) patients. Improvements of VF and VA were seen in 127 (86%) and 92 (75%) patients, respectively. 96 (65%) and 65 (53%) patients even showed full recoveries of VF and VA deficiencies, respectively. The mean duration of VF deficiencies was 7, 9 and 17 months in patients with full, partial and no recovery, respectively. In case of intraluesional hemorrhage VF (78% vs. 89%; p=NS) recoveries seemed to be less frequent. Postoperative worsening of VF was noted in a total of 2 (1%) patients. The risk for VF and VA worsening was higher in the patients operated with a transcranial (12%, 37%) than in those who had a transsphenoidal approach (0.6%, 4%).

Conclusion
Decompression of the optic pathway restores VF and VA in the majority of patients. There is a tendency for worse VF recovery rates with longer duration and in case of intraluesional hemorrhage. Worsening of VF and VA deficiencies is more common in transcranial approaches than in transsphenoidal surgery.
Anatomical Features of Primary Brain Tumors affect Seizure Risk and Semiology

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Aims
An epileptic seizure is the most common clinical manifestation of a primary brain tumor. Due to modern neuroimaging, detailed anatomical information on a brain tumor is available early in the diagnostic process and therefore carries considerable potential in clinical decision making. The goal of this study was to gain a better understanding of the relevance of anatomical tumor characteristics on seizure prevalence and semiology.

Methods
We reviewed prospectively collected clinical and imaging data of all patients operated on a supratentorial intraparenchymal primary brain tumor at our department between January 2009 and December 2016. The effect of tumor histology, anatomical location and white matter infiltration on seizure prevalence and semiology were assessed using uni- and multivariate analyses.

Results
Of 678 included patients, 311 (45.9%) presented with epileptic seizures. Tumor location within the central lobe was associated with higher seizure prevalence (OR 4.67, 95% CI: 1.90-13.3, p = 0.002), especially within the precentral gyrus or paracentral lobule (100%). Bilateral extension, location within subcortical structures and invasion of deeper white matter sectors were associated with a lower risk (OR 0.45, 95% CI: 0.25-0.78; OR 0.10, 95% CI: 0.04-0.21 and OR 0.39, 95% CI: 0.14-0.96, respectively). Multivariate analysis revealed the impact of a location within the central lobe on seizure risk to be highly significant and more relevant than histopathology (OR: 4.79, 95% CI: 1.82-14.52, p = 0.003). Seizures due to tumors within the central lobe differed from those of other locations by lower risk of secondary generalization (p < 0.001).

Conclusion
Topographical lobar and gyral location, as well as extent of white matter infiltration impact seizure risk and semiology. This finding may have a high therapeutic potential, for example regarding the use of prophylactic antiepileptic therapy.
Multidimensional Personalized Response Assessment to Microglia Modulators in Glioblastoma Bioreactors

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Background
Recently, strategies harnessing the non-neoplastic, immune tumor microenvironment (iTME) consisting of myeloid-derived macrophages and yolk sac derived microglia (termed TAMs) as well as adaptive immune components have been employed to treat glioblastoma (GBM). To evaluate the effect of TAM-modulating therapies in combination with T-cell checkpoint inhibitor approaches, we generated 3D GBM bioreactor cultures from patient-derived samples. Here, we report patient-tailored, tumor region specific response assessment to microglia modulators and T-cell checkpoint inhibitors using multidimensional fluorescent microscopy techniques.

Methods
GBM tissue fragments from the tumor center and periphery were placed into perfusion bioreactors shortly after resection and cultured for up to 3 weeks. Control conditions included non-perfused cultures of the same tissue. Cultures were treated with combinations of TAM and T-cell modulating, FDA approved drugs including anti-PD1, anti-CTLA4 and anti-CD47 antibodies. Tissue was harvested for histology, RNA extraction, and supernatants were processed for multiplexed cytokine analysis. Multidimensional CODEX technology analysis using a customized TAM/microglia-centric 50 marker panel was implemented, and a map of individualized response criteria to specific immunotherapies developed. Results We were able to cultivate viable GBM tissue with intact iTME. Tumor cell proliferation and invasion capacity were preserved for up to 3 weeks. Conventional immunohistochemistry confirmed the presence of TAMs and T cells. Treatment with immunomodulators resulted in a profound polarization shift of TAMs. Furthermore, cytokine analysis confirmed proinflammatory immune responses in most assessed samples. We present preliminary data of the CODEX analysis of our combinatorial immunotherapies in a series of 8 patient-specific explant samples.

Conclusion
GBM tissue could be incubated in the perfused 3D bioreactor model and kept viable for up to 21 days. The proposed model allows patient-tailored testing of immunomodulatory drugs by taking into account the patients individual iTME response.
Patterns of Care: Burr-Hole Cover Application for Chronic Subdural Hematoma Trepanation

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Background
Skin depressions may appear as undesired effects after burr-hole trepanation for the evacuation of chronic subdural hematomas (cSDH). Placement of burr-hole covers to reconstruct skull defects can prevent skin depressions, with the potential to improve the aesthetic result and patient satisfaction. The perception on its relevance appears to vary substantially among neurosurgeons. We aimed to identify current practice variations with regards to the application of burr-hole covers after trepanation for cSDH.

Methods
An electronic survey containing 12 questions was sent to resident and faculty neurosurgeons practicing in different parts of the world, as identified by an Internet search. All completed responses between 09/2018 and 12/2018 were considered. Descriptive statistics and logistic regression were used to analyze the data.

Results
A total of 604 responses were obtained, of which 576 (95.4%) provided complete data. Respondents had a mean age of 42.4 years (SD 10.5), 86.5% were male. The sample consisted of residents, fellows, junior/senior consultants, and department chairs from 79 countries (77.4% Europe, 11.8% Asia, 5.4% America, 3.5% Africa, 1.9% Australasia). Skin depressions were considered a relevant issue by 31.6% and 76.0% indicated that patients complain about skin depressions more or less frequently. Burr-hole covers are placed by 28.1% in the context of cSDH evacuation more or less frequently. The most frequent reasons for not placing a burr-hole cover were the lack of proven benefit (34.8%), followed by additional costs (21.9%), technical difficulty (19.9%), and fear of increased complications (4.9%). Most (77.5%) stated that they would consider placing burr-hole covers in the future, if there was evidence for its superiority. The use of burr-hole covers varied substantially across countries, but a countries’ gross domestic product per capita was not associated with its placement.

Conclusions
Only a minority of neurosurgeons' places burr-hole covers after trepanation for cSDH on a regular basis, even though the majority of participants reported complaints from patients regarding postoperative skin depressions. There are significant differences in the patterns of care among countries. Class-I evidence with regards to patient satisfaction and safety of burr-hole cover placement is likely to have an impact on future cSDH management.
Aim
Ventricular dilation due to cerebro-spinal fluid pathways obstruction is one of the most frequent complications of patients harbouring a posterior fossa lesion. Methods and timing to treat pre-operative ventricular dilation or post-operative hydrocephalus (HCP) are not homogeneous among different centers.

Methods
We retrospectively analyzed data of patients undergoing surgery for posterior fossa lesions from January 2007 to June 2018 at two neurosurgical centers. Demographics, lesion size and location (A = Extra-Axial Cerebello-Pontine Angle, B = Intrinsic Cerebellar Lesion, C = Extra-Axial Cranio-Cervical Junction, D = Intra-Axial Brainstem, E = Pineal Region), pre-operative and post-operative shunt procedures (permanent or temporary ventricular and spinal shunts, ventriculostomy and reservoir), presence and grade of pre-operative and post-operative HCP, and patient outcome were reviewed.

Results
One-thousand patients were selected for analysis. Patient groups were separately analyzed, based on the presence or absence of pre-operative ventricular dilation. 215 patients (21.5%) presented post-operative HCP. Tumor size showed a linear correlation with post-operative HCP occurrence (7.2% for lesions > 3.5 cm; p < 0.0001). As for the location, Group B had a significant augmented risk to present post-operative HCP (6.2%) or to maintain pre-operative HCP after surgery (22.8%), compared respectively to Group A (4.1% and 12.8%; p < 0.001) and Group C (3.7% and 7.4%; p < 0.005). Post-operative complications directly related to surgery were significantly related to ex-novo post-operative HCP and pre-operative HCP persistence (52.9% and 39%; p < 0.0001). Out of the 296 patients with pre-operative ventricular dilation, 132 patients presented regression of pre-operative HCP and only 21.2% of them had a pre-operative shunt procedure.

Conclusion
If not symptomatic, pre-operative ventricular dilation resolved after surgery without additional pre-operative shunt procedures in half the patients undergoing posterior fossa surgery. Intrinsic cerebellar lesions and tumor size seem to be independent risk factors for post-operative HCP occurrence and persistency of pre-operative HCP. In this cohort post-operative HCP occurrence is strongly related to post-operative complications.
Direct stimulation of the Söring ultrasonic aspirator handpiece for subcortical motor mapping: feasibility and safety of a new technique

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Aims
The goal of the study was to evaluate the feasibility and safety of a new technique for subcortical motor mapping using direct stimulation of the Söring ultrasonic aspirator handpiece (Söring GmbH, Germany).

Methods
We prospectively studied 14 patients who underwent microsurgical resections under general anesthesia for brain lesions located in the proximity of the corticospinal tract (CST) with subcortical monopolar motor mapping (train-of-five stimuli, biphasic pulses, pulse duration 0.4 ms, interpulse interval 1.5 ms) using direct stimulation of the Söring ultrasonic aspirator handpiece. Motor mapping was performed by applying a conductive and isolated stimulation clip (Inomed GmbH, Germany) on the dorsal part of the ultrasonic aspirator handpiece that thus became a concomitant stimulation device during tissue resection. The initial stimulation intensity was set to 8 mA. Once MEP responses were observed, the amplitude of stimulation was decreased in 1 mA steps, targeting identification of the motor thresholds. Minimal distance between the resection border and the CST was evaluated on postoperative diffusion tensor imaging and fiber tractography. Motor function was assessed 1 day after surgery, at discharge, and at 3 months.

Results
Procedures were technically successful and no complication was recorded. The so called “1 mA-1 mm” rule between motor-thresholds and distance from the resection border to the CST was observed again from the regression curve. The use of this rule is discussed in regard to the amplitude of the responses, to 95% confidence band of the regression and to the 95% prediction band. No permanent motor deficits were recorded.

Conclusion
Direct stimulation of the ultrasonic handprobe proved to be a safe and feasible technique for identification and preservation of the CST when using a combined tissue resection-stimulation technique. The use of this stimulation-ultrasonic resection device, beyond simplifying the intraoperative ergonomics by decreasing tool manipulations, allows for an integrated, accurate and continuous motor mapping during the resection process.
Does Minimally Invasive Transforaminal Lumbar Interbody Fusion (MIS TLIF) results in lower fusion rates? A retrospective study with 2 years follow-up

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Background
In recent years minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) has gained popularity. However, concerns remains regarding rate of fusion compared to standard open procedures. The main goal of our study was to analyse the occurrence of postoperative fusion rates, accuracy, complications and possible confounders in patients undergoing navigated MIS-TLIF.

Methods
Retrospective analysis of patients undergoing MIS-TLIF for degenerative spine disease in our department over a consecutive period of two years (January 2015 - December 2017). The modified Bridwell fusion criteria were used to assess fusion rates on CT-Scans. The primary endpoint was postoperative radiological fusion rate at 2 years. Secondary outcome measures were hardware and patients related intra and postoperative complications and accuracy of screw positioning with navigation.

Results
Out of 256 patients undergoing lumbar spine fusion 77 (30%) were treated with MIS-TLIF. Level operated per patients were 1.1 (± 0.26). Mean duration of surgery was 225 minutes. Expandable interbody cages were used in fifty-two cases (67%) Three screws out of 322 (0.9%), verified with iCT, were intraoperatively repositioned because of a lateral trajectory. Accuracy rate of screw position was 98.2%. At one month follow up 34 patients (44.1%) presented lower back pain. The overall rate of fusion was 66% (Bridwell 1-2). The overall complications rate was 17 (22%) out of which 4 (5.1%) were hardware related and 13 (16.8%) patient related. Revision surgery was performed in 4 (5.1%) cases, in 1 case because of an epidural haematoma in the immediate postoperative period, and in 3 cases because of hardware (2 cages and 1 screw) malpositioning. Overall, rate of cage mobilisation after surgery was 3.8% (3 patients). No patient required revision surgery when expandable cages were used. No patient underwent revision surgery for pseudoarthrosis.

Conclusion
Navigated MIS-TLIF is accurate and allows performing spinal fusion without surgeon exposure to radiations. Moreover, is safe and carries low amount of hardware complications. The rate of patient related complications is however not negligible, due to higher comorbidities in this specific population. Concerns remains regarding radiological fusion rates in such patients, which seems to be lower than previously reported. Use of autologous bone graft in adjunct to other bone substitutes (DBM) is strongly recommended.
Nicotine substitution in the acute phase of subarachnoid haemorrhage: What are the European practices?

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Aims
One-third of patients hospitalized with acute aneurysmal subarachnoid haemorrhage (aSAH) are active smokers. Continued smoking after aSAH carries a 6% higher mortality rate at 6 months compared to smoking cessation. Smokers with aSAH have usually no possibilities to smoke during their hospital stay and nicotine replacement therapy (NRT) is effective in this setting. However, NRT administered at the time of an aSAH is controversial owing to potential side effects. In the absence of randomized controlled trials, current guidelines of NRT use in aSAH are based on expert opinions and varies across countries. This study aims to assess the management of cigarette smoking among patients with aSAH with respect to NRT among European Neurosurgical centers.

Methods
A survey with 15 questions was distributed among practicing Neurosurgeons within the European Association of Neurosurgical Societies community. An invitation link by E-Mail was sent to 1,297 members of the EANS community worldwide. To avoid misclassification, only neurosurgeons practicing at high-volume neurovascular centres (≥ 30 treated aSAH cases per year) within 28 European countries were included. We stratified our results according to the use of NRT by neurosurgeons. χ² (Fisher’s exact test, two-tailed) was employed to compare responders. The p-value used for statistical significance was 0.05.

Results
A total of n = 158 participants (response rate 12 %) of which n = 101 met high volume European center criteria participated. Of these, n = 79 (78 %) practiced at University hospitals. About half of neurosurgeons offered NRT to smokers with aSAH routinely or on occasion (n = 60, 59 %), while n = 41 (41 %) never administered NRT, despite nearly all neurosurgeons (95, 94 %) assumed a neutral or beneficial short-term clinical outcome after aSAH when using NRT as compared to nicotine deprivation during hospitalization. N = 16 (27 %) of the 60 neurosurgeons who would offer NRT were aware of a specialized care team for smoking cessation in their clinic compared to only n = 7 (17 %) of 41 who never offer NRT (χ² distribution: 0.0001).

Conclusion
Approximately half of European neurosurgeons do not offer NRT to support smoking cessation during a hospitalization for aSAH, although a majority thought that use of NRT had similar or better health consequences than nicotine deprivation. A specialized care team for smoking cessation may help to improve use of NRT among smokers hospitalized for aSAH.
Microsurgical Creation of Complex Bifurcation Aneurysms with Different Wall Conditions in New Zealand White Rabbits – Introducing the Surgical Technique in a New Animal Model

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Aim
To further develop and improve endovascular treatment techniques for intracranial aneurysms, there is a need for animal models that respect rheological properties, aneurysm wall integrity, and hemodynamic conditions. Therefore, the aim of the present study was to design a novel reproducible and standardized surgical technique to create autologous arterial bifurcation aneurysms with different wall conditions in a one-stage surgery in rabbits.

Methods
Bifurcation aneurysms were created by arterial grafts, taken from the proximal right carotid artery in New Zealand White rabbits undergoing general anesthesia. Aneurysm grafts were either vital (n=5) or deteriorated (n=4). For vessel wall degeneration, arterial pouches were incubated with 100 units elastase for 20 minutes. For each group, the pouches were microsurgically sutured into an artificially created bifurcation of both common carotid arteries. Aneurysm and patency of parent artery was controlled by fluorescence angiography immediately after creation. At follow-up (28 days), all rabbits underwent contrast enhanced magnetic resonance angiography and fluorescence angiography before aneurysm harvesting.

Results
After a pilot series (n=4) a total of 9 rabbits were operated according to our established standard operative procedures. Mean surgery and anastomosis time for the vital group were 167 ± 12 minutes and 52 ± 4 minutes, respectively, and for the elastase group 199 ± 20 and 59 ± 8 minutes, respectively. Aneurysm patency rates of both vital and elastase treated aneurysms were 100% up to follow-up. Both groups revealed an increase in aneurysm size over time (vital: 5.26 ± 1.64 mm³ at the time of creation vs 20.79 ± 7.76 mm³ at follow-up, p = 0.04; elastase 9.89 ± 1.27 mm³ at the time of creation vs 23.13 ± 8.26 mm³ at follow-up, p = 0.14).

Conclusion
Our preliminary findings demonstrate the adequacy of a new rabbit model to create bifurcation aneurysms with different wall conditions in a one-stage microsurgical approach. Given the excellent long-term patency and property of aneurysm growth over time, this model may serve as an important tool for preclinical evaluation of novel endovascular therapies.
Microglia modulation in combination with tumor-targeting CAR T cell therapy for the treatment of glioblastoma

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Glioblastoma multiforme (GBM) is a fatal brain tumor resistant to all treatments. The tumor microenvironment (TME) of GBM consists of a large, dynamic compartment of immune system-related cells. The main players of the immune TME (iTME) are tumor-infiltrating, brain-resident microglia, macrophages (Mφ), and T cells. GBM is capable of re-educating and ultimately subverting the iTME to facilitate its growth and invasion of adjacent normal tissue. Previously, we showed that blockade of the “don’t eat me” signal – CD47 – on GBM cells with anti-CD47 antibodies prompted both in vivo Mφ- and microglia-induced phagocytosis through disruption of the CD47-SIRPα axis. We hypothesize that immunotherapeutic interventions such as this are insufficient in GBM if delivered as systemic monotherapies, because of tumor heterogeneity, the immunosuppressive iTME, and the obstacle of the blood brain barrier. For a more efficient targeting of GBM, we propose the combination of local microglia modulation with tumor cell targeting by local administration of genetically engineered chimeric antigen receptor (CAR) T cells to achieve therapeutic synergy. We further hypothesize that local reprogramming of microglia within the GBM-iTME facilitates the action of tumor-targeting immunotherapeutic strategies such as CAR T cell therapy. Among others, the epidermal growth factor receptor variant III (EGFRvIII) is a promising tumor-specific antigen currently used as a target in GBM clinical trials. Here, we characterize the EGFRvIII status of GBM cell lines and primary patient neurosphere-producing lines using fluorescent-activated cell sorting (FACS) and real time quantitative polymerase chain reaction (RT-qPCR). We show here the optimization process for lentiviral transduction of primary T cells and in vitro testing of second generation CAR T cells targeting EGFRvIII. Furthermore, we assess the effector efficiency of CD4- and CD8-positive CAR T cell subsets in double or triple co-culture settings with tumor cells and in combination with macrophages and anti-CD47 treatment.
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Association of persistent pain and implant malposition in sacroiliac joint fusion surgery

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Objective
About one quarter of patients with low back pain suffer from tenderness in the sacroiliac joint (SIJ). Minimally invasive surgical fusion of the SIJ using triangular titanium implants has been recently established as a means of controlling sacroiliac pain. Our aim was to assess the postoperative success and complication rates of the procedure after 3 months.

Methods
We retrospectively evaluated charts from patients undergoing sacroiliac joint fusion surgery. Subjective outcomes were categorized as worsening, no improvement and improvement. Postoperative computed tomography was used to control implant position. Malposition was defined as an aggregate of four features: penetration of a sacral foramen (S), peri-implant halo (I), incomplete penetration into the sacroiliac joint (J), fracture (F), (SIJF). We used chi²(Fisher’s exact test, two tailed) to assess potential associations between outcome and implant malposition.

Results
Twenty-one SIJ fusions were performed in 17 patients (9 female, 43%) with a mean age of 61 years (SD ±12 years) at our department, totaling 63 implants. Improvement of symptoms was reported in sixteen cases with SIJ fusions (76%) with a total of 16 malposition SIJF features observed on postoperative CT. Four cases (19%) reported unchanged complaints with 4 SIJF features and the remaining one (5%) complained of worsening pain in the absence of SIJF features. CT scans showed 20 SIJF-malposition features (S3, I4, J9, F4) in 10 patients. None of the misplaced implants 16/63 (25%) were considered relevant or requiring surgical revision. The misplacement features J and I were relatively more frequent in 5 cases with unchanged or worse pain (J in 2/15, I in 1/15) than in 16 cases with improved pain (J in 7/48, I in 2/48), (chi² distribution: 0.006 each). Other misplacement features (S, F) were less frequent among those with unchanged complaints or worsening pain.

Conclusion
Our experience showed that the use of triangular titanium implants to treat SIJ pain is a safe technique. The most frequent types of implant malposition were incomplete penetration into the sacroiliac joint (J) and peri-implant halo (I). Both were associated with worse patient-reported outcomes. Improvement was satisfactory in 76% of the cases what confirms external validity of pre-existing data for improvement of lumbar back pain. Internal validity showed no tangible association with the SIJF-features penetration of a sacral foramen (S) and fracture (F).
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Posterior Fossa Meningiomas: Perioperative Predictors of Extent of Resection, Overall Survival and Progression-Free Survival.

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Aims
Posterior fossa meningiomas (PFMs) often represent surgical challenges due to their proximity to neurovascular structures. Factors predicting the extent of resection (EOR), overall survival (OS), and progression-free survival (PFS) were identified and integrated in a prediction tool to offer evidence-based personalized therapeutic strategies.

Methods
All meningiomas managed surgically from 1990 to 2010 from a single-center were reviewed. A classification tree was created using the classification and regression tree recursive partitioning analysis that incorporated patient and tumor data available before surgery in order to predict the rates of gross total resection (GTR).

Results:
A total of 198 patients were identified (female-to-male ratio: 2.7, mean age 59.1 years) and compared to 1271 supratentorial meningiomas (STMs) operated in the same institution during the same time period. GTR was achieved less often (59.6% versus 81.9%; p < 0.01) in PFMs than STMs. Pre-operative neurological symptoms were predictive of higher Simpson grades (OR 2.19 [1.05; 4.58], p=0.04). Age was associated with reduced OS (OR 1.08 [1.04;1.12], p < 0.001). A KPS ≥ 70 was associated with higher survival rates (OR 2.70 [2.19;2.92], p=0.02). Higher WHO grades were associated with reduced OS (OR 3.56 [1.02;12.47], p=0.05). The GTR rate varies from 80% in patients without a preoperative deficit to 40% patients with a preoperative deficit, younger than 60 years old, and with adjacent bone invasion.

Conclusions
This study provides a classification-tree of the predictors of EOR in PFMs, based upon pre-operative demographic, clinical and radiological variables. An evidence-based management-protocol with estimated EORs may guide the decision-making process in PFMs.
Objective functional assessment using the "Timed-Up and Go" test in patients with lumbar spinal stenosis

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Object
Patient-reported outcome measures (PROMs) are standard of care for the assessment of functional impairment. Subjective outcome measures are increasingly complemented by objective ones, such as the “Timed-Up and Go” (TUG) test. We aimed to report pre- and postoperative TUG test assessments in patients with lumbar spinal stenosis (LSS).

Methods
A prospective 2-center database was reviewed to identify LSS patients, who underwent lumbar decompression with or without fusion. The subjective functional status was estimated using PROMs for pain (Visual analog scale; VAS), disability (Roland-Morris disability index; RMDI and Oswestry disability index; ODI) and health-related quality of life (hrQoL; Short-Form 12 physical component summary; SF-12 PCS and the Euro-Qol index; EQ-5D) preoperatively, as well as on postoperative day 3 (D3) and week 6 (W6). Objective functional impairment (OFI) was measured using age- and sex-standardized TUG test results.

Results
64 patients (n=32 (50%) male, mean age 66.8±11.7 years (SD)) were included. Preoperatively, they reported VAS back pain of 4.1±2.7, VAS leg pain of 5.4±2.7, RMDI of 10.4±5.3, ODI of 41.9±16.2, SF-12 PCS of 32.7±8.3, and an EQ-5D index of 0.517±0.226. The preoperative rates of severe, moderate and mild OFI were n=3 (4.7%), n=8 (12.5%) and n=5 (7.8%) and the mean OFI T-score was 116.3±23.7. At W6, 60 of 64 patients (93.8%) had a TUG test result within the normal population range (no OFI); three patients (4.7%) had mild and one patient (1.6%) severe OFI. The mean W6 OFI T-score was significantly decreased (103.1±13.6; p < 0.001). Correspondingly, the PROMs showed a decrease in subjective VAS back (1.6±1.7, p < 0.001) and leg pain (1.0±1.8, p < 0.001), disability (RMDI 5.3±4.7, p < 0.001; ODI 21.3±16.1, p < 0.001) and increase in hrQoL (SF-12 PCS 40.1±8.3, p < 0.001; EQ-5D 0.737±0.192, p < 0.001) at W6. The W6-responder status (=clinically meaningful improvement) ranged between 81.3% (VAS leg pain) and 29.7% (EQ-5D index) of patients.

Conclusions
The TUG test is a quick and easily applicable tool that reliably measures OFI in patients with LSS. Objective tests incorporating longer walking time should be considered if OFI is suspected but fails to be proven by the TUG test, taking into account that neurogenic claudication may not clinically manifest during the TUG test. Objective tests do not replace the subjective PROM-based assessment, but add valuable information to a comprehensive patient evaluation.
Objective measures of functional impairment for degenerative diseases of the lumbar spine: a systematic review of the literature

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Background
The accurate determination of a patient’s functional status is necessary for therapeutic decision-making and to critically appraise treatment efficacy. Current subjective patient-reported outcome measure (PROM)–based assessments have limitations and can be complimented by objective measures. We aimed to provide an overview on the available objective measures of function for patients with degenerative diseases of the lumbar spine.

Methods
We conducted a systematic review of the literature, following the PRISMA guidelines. Two reviewers independently searched PubMed, Web of Science, EMBASE and SCOPUS databases for permutations of the words “objective”, “assessment”, “function”, “lumbar” and “spine”, including articles on humans with degenerative diseases of the lumbar spine that reported objective measures of function, published until September 2018.

Results
Of 2389 identified articles, 82 were included in the final analysis. There was a significant increase of 0.12 per year in the number of publications dealing with objective measures of function since 1989 (95% CI 0.08–0.16, p < 0.001). Some publications studied multiple diagnoses and objective measures. The US was the leading nation in terms of scientific output for objective outcome measures (n=21; 25.6%), followed by Switzerland (n=17; 20.7%). Our search revealed 21 different types of objective measures, predominantly applied to patients with lumbar spinal stenosis (n=67 publications; 81.7%), chronic/unspecific low back pain (n=28; 34.2%) and lumbar disc herniation (n=22; 26.8%). The Timed-Up-and-Go (TUG) test was the most frequently applied measure (n=26 publications; 31.7%; cumulative number of reported subjects: 5181), followed by the Motorized Treadmill Test (MTT; n=25 publications; 30.5%, 1499 subjects) and with each n=9 publications (11.0%) the Five-Repetition Sit-To-Stand test (5R-STS; 955 subjects), among others. The reliability and validity of many of the less-applied objective measures was uncertain. There was profound heterogeneity in their application and interpretation of results.

Conclusions
Clinical studies on patients with lumbar degenerative diseases increasingly employ objective measures of function, which offer high potential for improving the quality of outcome measurement in patient-care and research. Our findings call for an agreement and standardization in terms of test selection, conduction and analysis to facilitate comparison of results across cohorts.
Conservative and surgical outcome of non-neoplastic cystic pathologies of the pituitary - A SwissPit Study

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Aim
As the use of cranial MRI to screen for causes of frequent non-specific symptoms such as headaches, vertigo etc. increases, the number of incidentally detected lesions rises. Pituitary incidentalomas, especially cystic lesions (e.g. Rathke's cleft cysts) have become common findings. Although mostly asymptomatic, they can cause hypopituitarism and optic chiasm syndrome. As surgery may lead to complications and spontaneous shrinkage has been described, the subject of the best management of these lesions remains controversial. The aim of this study is to compare conservatively observed cystic pituitary lesions to surgical cases, to assess indications for surgery and its outcome and to identify predictors for growth and adverse outcomes.

Methods
This retrospective single-centre database study is based on the Swiss Pituitary Registry, a GCP-conform and ethically approved online registry. Patients had to fulfill the following criteria for inclusion: diagnosis of cystic pituitary lesion on cranial MRI/CT between 2003 and 2017; comprehensive radiological, ophthalmological, endocrinological and surgical data collected at the author's institution; follow-up of >1 year.

Results
50 patients were included; 32 (64%; group A) were followed-up conservatively, 4 (13%, group B) of those had do undergo surgical resection due to symptomatic progress, and 18 (36%, group C) were operated initially. Surgery was transsphenoidal cyst fenestration in 95% of the patients. In group A 11% of the lesions did grow while 21% showed shrinkage during a mean follow-up of 27 (6-120) months. Lesions in group A were smaller than in groups B and C (0.35cc vs. 1.45cc vs. 1.71cc) and prevalence of hypopituitarism was lower (11% vs. 75% vs. 44%). None of the patients in group A showed visual symptoms, while 34% of the patients in group C complained of visual field deficits and 17% of visual acuity decline, respectively. All the cysts in group B had T1-hypo- and T2-hyperintense content, which differed from group A (p=.009). During a mean follow-up of 57 months (12-151) one patient in group C suffered from cyst recurrence. Hypopituitarism recovered in up to 67% of the surgical patients but in none of the patients of group A. Visual symptoms recovered in 83% postoperatively.

Conclusion
Observation is reasonable in asymptomatic patients with small cysts and shrinkage of the lesion is common. Surgery is indicated in large, symptomatic lesions and relief of symptoms may be expected frequently.
Thoracolumbar Corpectomy/spondylectomy for spinal metastasis: a pooled analysis comparing the outcome of seven different surgical approaches.

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Objective
Corpectomy or spondylectomy in the setting of spinal metastasis can be indicated to stabilize the spine, decompress the spinal canal and for cytoreduction. Several surgical approaches have been described. In this pooled analysis we compare surgical parameters and outcome measures between seven different approaches for thoracolumbar Corpectomy / spondylectomy. Summary of Background Data: It is not known which surgical approach is superior in term of operative and clinical outcomes.

Methods
A systematic review of literature has been performed including articles on corpectomy for thoracolumbar spinal metastasis. Data was extracted and sorted by surgical approach: en-bloc spondylectomy (group 1), transpedicular (group 2), costotransversectomy (group 3), mini open retropleural/retroperitoneal (group 4a), lateral extracavitary approach (group 4b), open transthoracic / transretroperitoneal (group 5), thoracoscopic (group 6). Comparison of demographics, blood loss, directly procedure related complications, operating time, pain relief rate and neurologic improvement rate were compared between approaches using 2 way ANOVA analyses.

Results
A total of 63 articles were included comprising data of 774 patients with various primary tumor entities. Mean age was 51.8 years, 54% of patients were female, on average 1.46 levels were treated per patient, mean follow up on average was 1.59 years. The following statistically significant findings were made: blood loss was lowest for mini open retropleural / retroperitoneal, thoracoscopic and transthoracic approach; directly procedure related complications were lowest for mini open retropleural / retroperitoneal and thoracoscopic approach; improvement of neurologic dysfunction was highest in mini open retropleural / retroperitoneal and en-bloc spondylectomy. Operating time was lowest in mini open retropleural / retroperitoneal approach.

Conclusion
Corpectomy generally was performed with low procedure associated complications and those patients with neurologic dysfunction had high rates of improvement. Minimally invasive techniques, mini-open retropleural / retroperitoneal and thoracoscopic, were superior to other approaches in many regards.
Cerebral aneurysms in young children: long-term clinical

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Background
Our aim was to report the long-term clinical and imaging outcomes of ≤ 15year-old (y.o) children treated for ruptured or symptomatic cerebral aneurysms and to identify prognostic factors for clinical outcome, recurrence and re-bleeding.

Methods
We retrospectively identified all pediatric cases of cerebral aneurysm from 2000 to 2015 and prospectively performed evaluation for long-term occlusion using brain MRI and clinical outcome measures: outcome favorable if King’s Outcome Scale for Childhood Head Injury (KOSCHI) was ≥5. We performed univariate and logistic binary regression to identify variables associated with clinical and imaging outcomes.

Results
Fifty-one children (aged 8.5 ± 1.1 years, mean ± SD with 37 ruptured and 14 symptomatic aneurysms) were included and endovascular treatments (84%) or microsurgical procedures (16%) were performed. Despite a 19.6% death rate, at mean follow-up of 8.3 years, 35 children (68.6%) had a favorable outcome. Annual bleeding and aneurysm-recurrence rates were 1.4±1.1% and 2.6±1.8%, respectively. Cerebral ischemia, whether initial or delayed within the first month, was predictive of poor clinical outcome in multivariate analysis (odds ratio (OR): 25; 95% confidence interval (CI): 0.43-143; p < 0.0001) whereas aneurysm size > 5mm was the only factor associated with recurrence (OR: 14.6; 95% CI: 2.4-86.1; p=0.003).

Conclusions
Two-thirds of studied ≤15y.o children, suffering ruptured or symptomatic cerebral aneurysms had long-term favorable outcome. Annual bleeding and aneurysm-recurrence rates are low after endovascular or surgical treatment. Long-term imaging follow-up helps to depict aneurysm recurrence or de novo aneurysm formation, and to prevent re-bleeding.
P118
Extent of resection (EOR) in inactive pituitary macroadenomas; microscopic versus endoscopic technique. A preliminary report on 62 consecutive microsurgical patients after volumetric independent assessment.

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Background
As we switched from the microscopic to the endoscopic technique in 2014, we decided to analyze our last microscopic cases using a volumetric tool by an independent investigator, in order to compare those results with a similar prospective cohort of patients operated with the endoscopic technique.

Methods
We analyzed 62 consecutive patients with inactive pituitary macroadenoma treated microsurgically by the same surgeon at our institution between 2008 and 2014. A single independent investigator performed the volumetric analysis based mainly on thin sliced MRI data (1mm slices, 0.5 x 0.5 pixel) before and after i.v. contrast agent. Tumor volume was assessed preoperatively and three months after surgery. For further analysis, we separated giant adenomas (n=14, >10 cm³), from mid-sized adenomas (n=16, 5-9.9 cm³), from small adenomas (n=32, up to 4.9 cm³). Potential predictors of EOR were tested for statistically significance.

Results
Overall, the mean preoperative tumor volume was 6.50 ± 4.79 cm³ (range: 1.02 – 19.84). The mean EOR was 95.6%, whereas complete tumor resection (EOR = 100%) could be achieved in 48 patients (77.4%). There was a highly significant correlation between the preoperative volume of the adenoma and the postoperative residual tumor volume was highly significant (p=0.000146). The EOR was 90.8% in giant adenomas, 95.5%, in mid-sized adenomas, and 97.8% in small adenomas. There was no significant correlation between preoperative Knosp-grade and postoperative residual tumor volume (p=0.735). Two patients required an operative revision due to CSF leakage (3.2%). There was no major morbidity and no mortality.

Discussion
EOR between in 90.8% and 97.8% can be achieved in patients with inactive pituitary macroadenoma selected for microsurgical tumor removal, mostly depending on preoperative tumor size. We will perform the same volumetric analysis on a consecutive cohort of patients operated using the endoscopic technique and report our results.
Posterior Fossa Meningiomas: Perioperative Predictors of Extent of Resection, Overall Survival and Progression-Free Survival.

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Background
Posterior fossa meningiomas (PFMs) often represent surgical challenges due to their proximity to neurovascular structures. Factors predicting the extent of resection (EOR), overall survival (OS), and progression-free survival (PFS) were identified and integrated in a prediction tool to offer evidence-based personalized therapeutic strategies.

Methods
All meningiomas managed surgically from 1990 to 2010 from a single-center were reviewed. A classification tree was created using the classification and regression tree recursive partitioning analysis that incorporated patient and tumor data available before surgery in order to predict the rates of gross total resection (GTR).

Results
A total of 198 patients were identified (female-to-male ratio: 2.7, mean age 59.1 years) and compared to 1271 supratentorial meningiomas (STMs) operated in the same institution during the same time period. GTR was achieved less often (59.6% versus 81.9%; "p < 0.01") in PFMs than STMs. Pre-operative neurological symptoms were predictive of higher Simpson grades (OR 2.19 [1.05; 4.58], p=0.04). Age was associated with reduced OS (OR 1.08 [1.04;1.12], "p < 0.001"). A "KPS ≥70" was associated with higher survival rates (OR 2.70 [2.19;2.92], p=0.02). Higher WHO grades were associated with reduced OS (OR 3.56 [1.02;12.47], p=0.05). The GTR rate varies from 80% in patients without a preoperative deficit to 40% patients with a preoperative deficit, younger than 60 years old, and with adjacent bone invasion.

Conclusions
This study provides a classification-tree of the predictors of EOR in PFMs, based upon pre-operative demographic, clinical and radiological variables. An evidence-based management-protocol with estimated EORs may guide the decision-making process in PFMs.
Objective
Sphenoid wing meningiomas are generally considered as skull base meningiomas (SBMs). However, given their surgical similarities with non-skull base meningiomas (NSBMs), we hypothesized that lateral sphenoid wing meningiomas (LSWMs) without bone invasion (BI) should be considered as NSBMs.

Methods
N=65 LSWMs without BI operated between 1990 to 2010 at a single-center were compared to N=352 NSBMs, represented by convexity meningiomas (CMs), and to N=23 SBMs, represented by spheno-orbital meningiomas (SOMs), with respect to baseline demographics, clinical presentations, Simpson grades, complications, adjuvant therapies, as well as overall survival (OS) and progression-free survival (PFS). Only WHO grade I meningiomas were included.

Results
No significant differences in baseline demographics, clinical presentation, or pre-operative KPS were found between the three groups. Simpson grade 1-3 was achieved in 90.1% of LSWMs, 97.1% in CMs (p=0.05), and 82.6% in SOMs (p=0.23). There were no significant differences in postoperative infection, hematoma, neurological worsening, 30-day mortality, or OS between the three groups. Lower re-treatment rates were observed in LSWMs and CMs compared to SOMs (p=0.06). With respect to PFS, there was no significant difference between LSWMs and CMs (89.1% and 88.5% at 5 years, respectively), whereas PFS was significantly higher in LSWMs than in SOMs (79% at 5 years) (p=0.05).

Conclusions
LSWMs without BI should be considered as an intermediate entity between NSBMs and SBMs. LSWMs are similar to SOMs with respect to extent of resection, but more similar to CMs with respect to re-treatment rates and PFS.
The Zurich Pituitary Score predicts utility of intraoperative high-field magnetic resonance imaging in transsphenoidal pituitary adenoma surgery

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Background
It is currently unclear if there are subsets of patients undergoing transsphenoidal surgery (TSS) in which intraoperative high-field magnetic resonance imaging (3T-iMRI) is particularly advantageous. We aimed to investigate whether a radiological grading scale predicts the utility of 3T-iMRI in pituitary adenoma (PA) TSS.

Methods
From a prospective registry, patients who underwent endoscopic TSS for PA using 3T-iMRI were identified. Adenomas were graded using the Zurich Pituitary Score (ZPS). We assessed improvement after 3T-iMRI in terms of gross total resection (GTR), residual volume (RV), and extent of resection (EOR).

Results
Among 95 patients, rates of conversion to GTR after 3T-iMRI decreased steadily from 33% for Grade I to 0% for Grade IV adenomas, with a statistically significant conversion rate only for Grade I (p = 0.008) and Grade II (p < 0.001). All Grade I adenomas were completely resected after 3T-iMRI. Median RV change was statistically significant for Grades I to III, but not for Grade IV (p = 0.625). EOR improvement ranged from a median change of 0.0% (IQR: 0.0% - 4.5%) for Grade I to 4.4% (IQR: 0.0% - 9.0%) for Grade IV, with a significant improvement only for Grades I to III (p < 0.05).

Conclusions
Interestingly, this study shows that clinical utility of 3T-iMRI is highest in the more “simple” adenomas (ZPS Grade I-II) than for the more “complex” ones (ZPS Grade III-IV). Grade I adenomas are amenable to GTR if 3T-iMRI is implemented. In Grade III adenomas, EOR and RV can be improved to clinically relevant levels. Conversely, in Grade IV adenomas, 3T-iMRI may be of limited use.
Early ventriculo peritoneal shunting in aneurysmal subarachnoid hemorrhage is associated with a lower rate of nosocomial meningitis

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Background
Early ventriculo-peritoneal (VP) shunting for hydrocephalus following aneurysmal subarachnoid hemorrhage (aSAH) might shorten the external ventricular drain (EVD) period and therefore reduce infectious complications. This potential advantage has never been investigated in terms of promoting a higher risk for delayed cerebral vasospasm (DCVS)-related morbidity. Objective of this study was to determine the association of early VP shunting with EVD-associated infections (EVDAI) and symptomatic DCVS as well as delayed cortical ischemia (DCI) and outcome at discharge.

Methods
A single-centre dataset of the Swiss Study of Subarachnoid Hemorrhage 2009-2018 was used to evaluate aSAH patients divided into an “early group” when a VP shunt procedure was performed ≤14 days and a “late group” if such a procedure occurred ≥15 days after ictus. Associations were assessed with the aid of descriptive, multivariate and logistic regression analysis.

Results
Among 274 consecutive aSAH patients, 39 (14.2%) were in need of a VP shunt. Patients in the late group (19 out of 39, 48.7%) had substantially lower levels of consciousness on admission. Late VP shunting was associated with more EVD-days in situ (OR 3.06, 95%CI 0.01-0.06) and a higher incidence of EVDAI (OR 2.09, 95 %CI 0.01-0.58). Accordingly, the catheter colonization to EVDAI ratio was lower (7/1 out of 20 vs. 7/7 out of 19). The occurrence of DCVS was similar between both groups (OR 0.42, 95 %CI -0.28-0.42). The detection of DCI (OR 1.74, 95 %CI -0.05-0.62) and the likelihood for a poor modified Rankin Scale at discharge (OR 0.04, 95%CI -0.34-0.35) remained non-significant.

Conclusion
Early VP shunting in good grade aSAH patients is associated with less EVD-days in situ and therefore lower rates of EVDAI. A higher risk for DCVS-related morbidity was not associated with the time-point of intervention. These findings need to be confirmed in larger cohorts.
Task-free evaluation of postoperative outcome in neurosurgery using day-to-day smartphone behavior

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Objective
The real-world behavioral implications of neurosurgical procedures remain poorly understood. Those may occur at the time-scale of hours – reflecting the immediate loss or gain of cognitive function – but certain outcomes may also evolve over months, driven by rehabilitation. The behavioral implications themselves may impact any of the various physiological processes: ranging from sensorimotor function to sleep.

Methods
In a prospective study (ClinicalTrials.gov Identifier: NCT03516162) we use continuous monitoring of behavior on the smartphone touchscreen interface before and after a neurosurgical procedure. We so far recruited 10 patients, scheduled to undergo either maximal safe intracranial tumor resection (focal pathology) or ventriculoperitoneal shunt insertion (diffuse pathology). We analyzed the patient’s smartphone behavior to infer processes related to sensorimotor functions, memory, behavioral control and sleep.

Results
All patients returned to their smartphones within 2 days of the surgery – with some returning to it within a few hours. There were substantial inter-individual differences in how the smartphone parameters were affected both in terms of temporal fluctuations and the behavioral features implicated. What was consistent across the sample was that the observed post-surgical recovery from baseline smartphone behavior was slower than the anticipated recovery based on the subject self-reports.

Conclusion
This preliminary analysis of the first 10 patients indicates that task-free assessments based on day-to-day digital behavior as measured continuously by analyzing a patient’s use of the smartphone touchscreen may offer a high-resolution and personalized account of the real-world behavioral patterns impacted in neurosurgery.
P124 Spinal drop metastases of glioblastoma multiforme before and after introduction of the “Stupp” scheme

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Objective
Glioblastoma multiforme (GBM) is the most common and most malignant primary brain tumor in adults. Metastatic lesions are rare. We investigated the occurrence of spinal drop metastases in patients with GBM before and after introduction of combined radio-/chemotherapy with temozolomide according to the EORTC (“Stupp”) scheme.

Methods
We performed a retrospective analysis including all patients who have been operated on GBM (WHO IV) in our department between 1990 and 2014.

Results
We encountered a total of 740 patients with histologically proven GBM who were treated within these 25 years in our department. Four patients were found to develop spinal drop metastases (0.54%). The median age of patients with spinal drop metastases was 57 years (range 20-64 years). The time interval between first surgery and the occurrence of spinal drop metastases was 5, 9, and 11 months, and 13 years months. All of these patients were initially diagnosed and treated before introduction of the “Stupp” schema. One patient, however, has received temozolomide for local GBM recurrence. In this case, the time interval between initial surgery for GBM and the occurrence of spinal drop metastases was as long as 13 years. In two patients, the spinal metastases were treated surgically with proven histological diagnosis. Spinal drop metastases were associated with a rapid deterioration of the clinical condition in all patients. Among the GBM patients who received radio-/chemotherapy according to “Stupp scheme”, no one developed spinal drop metastases.

Conclusions
Spinal GBM drop metastases are rare. In our series we discovered four of 740 patients (0.54%) suffering from spinal drop metastases. All of these patients were initially treated before combined chemo/radiotherapy with temozolomide was available. One patient, however, received temozolomide for local GBM recurrence. There were no spinal drop metastases detected in patients who were treated according to the “Stupp” scheme.
Reliability Measures of the 6-Minute Walking Test Smartphone Application (6WT app)

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Background
Objective functional measures are increasingly applied. The 6-minute walking test (6WT) has been used to determine disability in patients with degenerative disorders of the lumbar spine. However, the traditional 6WT is cumbersome to apply, as it requires specialized in-hospital infrastructure and personal. It was our objective to compare 6-minute walking distance (6WD) measurements with a newly developed smartphone app to the gold standard (distance wheel (DW)).

Methods
We developed a free iOS and Android-based smartphone app that allows patients to measure the 6WD in their home environment using global positioning system (GPS) coordinates. Measurements were obtained over a range of smartphone models, testing environments, walking patterns and speeds. The main outcome was relative measurement error (rME; in % of 6WD), with |rME| < 7.5% defined as reliable. We calculated the intraclass correlation coefficient (ICC) for agreement between app- or DW-based 6WD.

Results
Measurements (n=375) were reliable with all smartphone types, in neighborhood, nature, and city environments (without high buildings), as well as with unspecified, straight, continuous, and stop-and-go walking patterns (ICC=0.97; 95%CI 0.97–0.98; p < 0.001). Measurements were unreliable indoors, in city areas with high buildings, and for predominantly rectangular walking courses. Walking speed had an influence on the ME, with worse accuracy (2% higher rME) for every km/h slower walking pace (95%CI 1.4–2.6%, p < 0.001). Mathematical adjustment of app-based 6WD for velocity-dependent error mitigated the rME (p < 0.012), attenuated velocity-dependence (Coef 0.3, 95% CI -0.3 – 0.8, p = 0.336) and had a positive effect on accuracy (ICC=0.98; 95%CI 0.98–0.99; p < 0.001).

Conclusions
The new, free “6WT app” measures the 6WD conveniently using GPS coordinates, empowering patient to independently determine their functional status before and after (surgical) treatment. Measurements of 6WD obtained for the target population under the recommended circumstances are highly reliable.
P126
Comparison of intra- and postoperative three-dimensional digital subtraction angiography in evaluation of the surgical result after intracranial aneurysm treatment

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Background
Postoperative three-dimensional digital subtraction angiography (3D-DSA) is the gold standard in detecting and evaluating intracranial aneurysm remnants after clipping. Should intraoperative 3D-DSA (3D-iDSA) image quality be equally good as 3D-pDSA it could supplant 3D-pDSA as quality control and standard of care in follow-up of clipped IA. We directly evaluate and compare the quality of assessment of clipped IA in 3D-iDSA and 3D-pDSA.

Methods
From a prospective cohort of 221 consecutive patients who underwent craniotomy for intracranial aneurysm treatment in a hybrid operating room, we retrospectively studied those who had both intra- and postoperative 3D-DSA imaging of their clipped aneurysm. Variables included patient demographics and aneurysm characteristics. Comparison of intra- and postoperative 3D-DSA images (blinded for review) included parameters that affected image quality and differences between the two periods.

Results
The 26 patients with 32 clipped intracranial aneurysms underwent both intra- and postoperative 3D-DSA; mean interval of 11 ± 7 months between imaging examinations. Reconstruction with multiple clips was used in 14 (44%) cases. Of 15 remnants, 9 (60%) were small (< 2 mm). In comparing intra- and postoperative 3D-DSA, no discordance in assessment of the surgical result was noted for any clipped IA, and overall imaging quality was excellent for both modalities. Factors affecting minor differences in quality between intra- and postoperative images were not identified.

Conclusion
Compared with postoperative 3D-DSA, intraoperative images achieved equally high quality and effective, immediate interpretation of the surgical clipping result. With comparable imaging quality and no discordant findings, intraoperative 3D-DSA could replace postoperative DSA to become the standard of care in intracranial aneurysm surgery.
Preclinical extracranial aneurysm models for the study and treatment of intracranial aneurysms: A systematic review.

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Background
Animal models of saccular aneurysms are an important contribution to our basic understanding of the pathobiology of human intracranial aneurysm and needed to test novel treatment approaches and to train interventional neuroradiologists and neurosurgeons. Researchers are confronted with a broad diversity of models and techniques in various species. The purpose of this systematic review is to summarize and categorize all extracranial aneurysm models and their characteristics, discuss advantages and disadvantages, and suggest the best use of each model.

Methods
We searched the electronical Medline/Pubmed from 1950-2017 to identify basic models and their refinements and technical modifications for creation of extracranial saccular aneurysms in mice, rats, rabbits, dogs, and swine. Included studies were assessed on aneurysm specific characteristics (size, localization, and parent artery configuration), technical details of aneurysm creation (graft characteristics, time for creation, patency rate, and morbidity and mortality), and histological findings.

Results
More than 4’000 titles and abstracts were screened, and 476 studies underwent full-text analysis. From those 67 different techniques/models in 5 animals were identified and analyzed in detail. The techniques and modifications can be summarized into five main groups of experimental models: Sidewall, terminal, stump, bifurcation, and complex aneurysm models. The aneurysm pouches consist of either modified or untreated arterial or venous vessel segments.

Conclusions
Taking the potential confounding effects of the chosen species and techniques into consideration, basic biological concepts of novel intracranial aneurysm therapies can be tested in a great variety of models available today. This systematic review can serve as a compact guide for investigators to choose the most appropriate model from a wide range of different techniques that suits best experimental goals, practical considerations, and laboratory environment.
Comparison of Aneurysm Patency and Mural Inflammation in an Arterial Rabbit Sidewall and Bifurcation Aneurysm Model under Consideration of Different Wall Conditions

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Background
Biological processes that lead to aneurysm formation, growth and rupture are still insufficiently understood. Human histopathological studies and preclinical experiments in rats suggest increased cerebral vessel wall inflammation and cell degeneration to be driving factors for aneurysm initiation and growth. With this study, we aimed to investigate the natural course of vital and decellularized aneurysms in a rabbit sidewall and bifurcation aneurysm model with emphasis for aneurysm patency, growth and mural inflammation.

Methods
Arterial pouches were sutured end-to-side on the carotid artery of New Zealand White Rabbits. Vessel walls in these sidewall aneurysms were either vital (n=6) or decellularized (n=6). Likewise, vital (n=5) and decellularized (n=6) arterial pouches were sutured into an artificially created carotid artery bifurcation, forming standardized bifurcation aneurysms. For decellularization, a protocol using graft incubation in sodium dodecyl sulfate (SDS) 1% was established to decellularize the aneurysm wall. Patency upon creation was determined by fluorescence angiography. After follow-up of 4 weeks, all animals underwent magnetic resonance and fluorescence angiography. Aneurysms were then harvested and macroscopically and histologically evaluated.

Results
During the study period, no aneurysm ruptured. All sidewall aneurysms (vital and decellularized) thrombosed spontaneously during follow-up. Histologically, inferior thrombus organization was observed in decellularized aneurysms when compared to healing characteristics in vital aneurysms. In the arterial pouch bifurcation model, 3 out of 6 aneurysms with decellularized walls thrombosed spontaneously whereas all vital aneurysms (5/5) stayed patent, with relevant growth pattern in 2 cases.

Conclusion
The results of poor thrombus organization in decellularized rabbit arterial sidewall aneurysms confirm the important role of mural cells in aneurysm healing after intraluminal thrombus formation. The restriction of surrounding neck tissue as well as the low lumen to vessel ratio may have prevented aneurysm growth and rupture despite pronounced inflammation in decellularized aneurysms. In the bifurcation model, removal of mural cells did not increase the risk for aneurysm growth but resulted in a higher rate of spontaneous thrombosis, which may be explained by strong pro-thrombotic characteristic of the decellularized grafts.
**P129**

**Systematic Review and Meta-analysis of Methodological Quality in in-vivo Animal Studies of Subarachnoid Hemorrhage**

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**Introduction**

Due to increased awareness of wide-spread methodological bias and obvious translation roadblocks in subarachnoid haemorrhage (SAH) research, various checklists and guidelines have been developed over the past decades. In this study, we want to assess methodological quality standards among preclinical animal SAH studies.

**Methods**

We systematically reviewed 3415 preclinical animal SAH studies with regard to methodological quality, reporting of basic animal characteristics and technical considerations of SAH induction and correlated methodological quality with impact factor and number of citations of the corresponding articles.

**Results**

Despite the publication of ARRIVE guidelines in 2010, methodological shortcomings are still prevalent in preclinical SAH research. With regard to adequate SAH model description basic animal characteristics are usually well described, whereas technical parameters of SAH induction are frequently underreported. No relevant quality differences between species and standard models could be demonstrated. Better adherence to quality guidelines is not associated with a higher number of citations of a study neither with publication in a higher impact-factor journal.

**Conclusion**

Methodological shortcomings are prevalent in preclinical SAH research and have only moderately improved over the past 15 years. It seems that none of the species, model, or technique used in preclinical SAH research is superior in terms of methodological quality. High methodological quality does not seem to be a prerequisite for a high citation rate, neither for publication in a high-impact factor journal.
Predictive Analytics in Pituitary Surgery based on Machine Learning

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Background
Personalized medicine has moved to the forefront of medical research in the past decade, and can potentially impact clinical practice. For example, preoperative identification of patients at high risk for subtotal resectability or intraoperative cerebrospinal fluid (CSF) leaks may allow surgeons to better inform patients on the likelihood of outcomes and adverse events, adjust surgical targets, and create potential for prevention of complications. We develop robust predictive analytics that assist surgeons in preoperatively identifying the likelihood of a particular patient to experience gross-total resection (GTR), intraoperative CSF leaks, and endocrinological endpoints.

Methods
Using data from a prospective registry, machine learning-based prediction models were trained and internally validated. Class imbalance in the training set was handled by applying synthetic minority oversampling (SMOTE). A range of algorithms were applied, and we selected the best model based on area under the curve (AUC) on the validation set. The final models were then evaluated on the holdout set. Various countermeasures were taken to minimize overfitting.

Results
Data from 200 patients were available. Among all five models, we observed high performance measures at internal validation, indicating that the machine learning-based prediction models were robust, and outperformed conventional predictive analytics such as logistic regression. Specifically, AUC of up to 0.96, accuracy of up to 91%, sensitivity and specificity of up to 94%/89%, positive predictive value (PPV) and negative predictive value (NPV) of up to 89%/94%, and F1 score of up to 0.91.

Conclusion
Machine learning helps identify patients prone to certain outcomes, possibly enabling better, more personalized treatment. External validation and the development of a freely accessible web-based tool integrating multiple models will demonstrate the clinical practicality of such predictive analytics in patients undergoing surgery for pituitary adenoma.
Frameless navigated transcerebellar brainstem biopsy: Case report and review of the literature

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Background
Tumors located in the brainstem include a wide variety of differential diagnoses and require histological assessment to offer an optimal treatment strategy. Whereas the transfrontal trajectory has been widely described, there are a small number of cases reported documenting the feasibility of the transcerebellar route with, nevertheless, high morbidity and mortality rates. These reported techniques included frame-based stereotaxic approaches. We present a transcerebellar biopsy approach using the frameless navigated system.

Case presentation
We report of a 70-year-old woman presenting with vertigo, nausea, and cranial nerve palsies (NIII, NVI, NVII, NX, NXII). The admission MRI demonstrated in the T2/FLAIR sequence an enhancing lesion in the left pontine area expanding to the tegmentum and medulla oblongata. We performed a brainstem biopsy via transcerebellar route using the frameless VarioGuide® system (Brainlab, Munich, Germany). The postoperative clinical course was uneventful and the postoperative MRI confirmed the planned trajectory and target. An inflammatory, most likely a demyelinating disease, was diagnosed and the patient fully recovered during immunosuppressive therapy (steroids, plasmapheresis and methotrexate). At 21 days follow up, the MRI showed a partial remission of the lesion. Literature Review: We searched the PubMed database using the keywords ‘transcerebellar’, ‘suboccipital’, ‘brainstem’, ‘pontine’, ‘mesencephalon’, ‘biopsy’, ‘frameless’ and ‘VarioGuide’ in various combinations. Eight publications comprising 148 adult patients undergoing biopsy qualified for review. Diagnostic rates and surgical complications were analyzed. The majority of series were performed with a frame-based system, whereas two series with 11 patients in total with a transcerebellar approach using a frameless setting could be found. Overall, higher morbidity and mortality rates were registered in the transcerebellar groups. However, these results were not statistically significant.

Conclusions
There are various approaches available for brainstem stereotactic biopsy, including the suboccipital transcerebellar route. The frameless approach described in this report is technically feasible, fast, and might be associated with fewer complications compared to the traditional frame-based methods. The transcerebellar route is shorter and therefore probably more precise compared to the transfrontal approach.
P132
Outcome of Dermabond (TM) Prineo (TM) for Wound Closure after Intradural Spine Surgery in Children – preliminary results of eight consecutive patients

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Purpose
Tissue adhesive glue is well established for the closure of wound lacerations and short surgical incisions in children. In adults DermabondTM PrineoTM skin closure system (DPSCS), which consists of both tissue adhesive glue and a self-adhesive mesh, for closure of medium-length surgical incisions has been reported to enhance patient comfort and leads to good cosmetic outcomes. We aimed to investigate the outcome of DPSCS for spinal wound closure in children.

Methods
We prospectively collected data of all patients undergoing surgical repair of intradural spinal procedures, at our institution. Patients with revision surgeries or non-intradural procedures were excluded. Patients’ demographic and surgical data were collected. Wound healing during hospitalization, at two weeks and three months follow-up were evaluated.

Results
We included 8 consecutive patients in this study. One patient showed a minimal cutaneous dehiscence at the lower end of surgical incision, which was managed conservatively and healed with time. DPSCS was removed after an average of 13.9 days (IQR 13.25 - 14) by the surgeon (7/8 cases) or paediatrician (1/8 cases). In one case, an additional dressing was mistakenly placed on top of DPSCS, which led to an accidental removal of the DPSCS on the 10th postoperative day, however this did not affect wound healing. In another case, a cutaneous haemangioma adjacent to the surgical site was macerated due to the DPSCS requiring additional local care, while the surgical incision remained unaffected. All patients had satisfactory cosmetic outcome after three months. One patient did not reach the 3-month follow-up yet.

Conclusion
Our preliminary results show that DPSCS seems to be safe and leads to satisfactory cosmetic outcome for spinal wound closure in children. Its simple application facilitated professional and parental care. Nevertheless, in cases of skin malformations, traditional skin closure might be more suitable.
Preclinical intracranial aneurysm models for the study and treatment of intracranial aneurysms: A systematic review.

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Aims
Intracranial aneurysm (IA) are bulges of weak cerebral vessel walls that may lead to rupture and subarachnoid hemorrhage with often poor prognosis. The exact mechanisms behind their formation and progression remains unclear and there is currently no known drug therapy to stabilize and prevent IA rupture. This review aims to summarize the broad variety of available techniques and models in different species and analyze key features and best possible applications for the study of IA growth and rupture.

Methods
We conducted a systematic literature search using the PubMed database to identify preclinical studies using IA animal models. Suitable articles were selected based on predefined inclusion and exclusion criteria following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Included studies were reviewed and categorized based on the experimental animal used and the aneurysm model employed.

Results
Of 4,264 initially returned results, 3,930 articles were excluded based on the title and/or abstract and further articles after screening the full text (duplicates, article withdrawn, type of article letter/comment, language other than English), leaving 133 studies for detailed analysis. A total of 9 different models were found in rats (6), mice (5), canines (2), and rabbits (2). Rat models constituted the most frequently employed intracranial experimental aneurysm model (83 studies), followed by mice (37 studies), rabbits (11 studies), and 3 studies in canines. The most common techniques to induce cerebral aneurysms were surgical ligation of the common carotid artery and/or the renal artery with subsequent induction of hypertension, followed by elastase-induced creation of IAs in combination with corticosterone- or angiotensin-induced hypertension.

Conclusion
This review provides a comprehensive summary of the multitude of available models and techniques to study various aspects of aneurysm initiation, growth, and rupture. It will serve as a useful reference especially for scientists entering the field. Researchers need to be aware of advantages and disadvantages in order to choose the most appropriate model and technique to answer their scientific question.
P134
Accuracy of C1-C2-C3 screw fixation using intraoperative 3D fluoroscopy - navigation

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Aims
Spinal navigation is routinely used for more complex spinal procedures. In atlanto-axial instability, it represents a helpful instrument in order to reduce the risk of neurovascular injury, mainly of vertebral artery, during screws placement. Intraoperative 3D fluoroscopy, based on autoregistration of C1-C2-C3 segment or on surface matching of a preoperative CT, associates a safe screw positioning with a reasonable surgical time and a low level of radiation. We present a series of 12 consecutive cases of atlantoaxial instability in order to assess accuracy and safety of intraoperative 3D fluoroscopy – guided navigation in C1-C3 fixation.

Methods
Between December 2016 and September 2018, we retrospectively reviewed patients with C1-C2 instability who underwent posterior cervical fixation using spinal navigation with intraoperative 3D fluoroscopy. Cervical angio-CT scan was systematically performed in the preoperative setup. Cervical MRI was equally obtained in order to find a ligament involvement. All patients underwent clinical and radiological follow-up (cervical CT) after three months from the surgery.

Results
12 (8F, 4M) consecutive patients treated with posterior cervical fixation using the intraoperative 3D fluoroscopy – guided navigation were included. 7 patients underwent C1-C3 fixation, 5 patients at C1-C2 level. The following pathologies were treated: one C2 fracture Alonzo type I with C1-C2 luxation, three C2 fracture Alonzo type 2, one C2 fracture Alonzo type 3, one C2 fracture Effendi type I-II, two C2 miscellaneous fracture with C3 right superior articular facet involvement, one osteochondrosis of C1-C2 right joint, one arthrosis of C2-C3 joints, one C2 miscellaneous fracture, one cervical stenosis with C1-C2 myelopathy. 62 navigated screws were placed. Correct screw positioning was obtained in all cases (100%), without any intra or postoperative replacement. No vertebral artery injury was observed. Nine patients put on a collar for 6 postoperative weeks; three developed eschars due to the collar.

Conclusions
In our experience, spinal navigation with intraoperative 3D fluoroscopy has been reliable and safe in guiding C1-C3 screws placement.

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Introduction
The concept of Enhanced Recovery After Surgery (ERAS) entails recovery facilitation of patients who undergo surgery. As a result, ERAS might improve the overall functional outcome after surgery while maintaining high standards of care. As a part of ERAS in spine surgery, outpatient non-instrumented lumbar spine surgery (NILSS) has been reported as safe and effective. However, little is known on patients’ opinion regarding outpatient procedures.

Methods
Using a self-filled form, patients undergoing elective NILSS were asked their opinion regarding outpatient procedures. Their age, gender, working status, pre-operative Charlson Comorbidity Index (CCI) and Oswestry Disability Index (ODI) were recorded. Patients were asked if they would prefer outpatient management in their case. Moreover, their opinion on outpatient surgery in general was asked.

Results
A total of 10 patients were included (3 females, mean age 58.7±11.82 years; mean pre-op. CCI: 2±1.33, pre-op. ODI: 23±9.36, 5 patients working full-time). 7 and 3 patients were candidates for lumbar microdiscectomy and for lumbar decompression, respectively. Regarding their surgery, two patients were in favor of outpatient management and one patient was favorable only if a checkup was planned the day after the operation. 7 patients were not in favor of outpatient management. Regarding outpatient surgery in general, four patients considered it as a decrease in quality of the medical management, two patients considered it as a progress, one patient did not considered it as a major change and 3 patients had no opinion.

Conclusion
Despite previous data reporting the efficacy and safety of NILSS, early results show that a majority of patients are not ready to be treated as outpatients when it comes to elective NILSS.
P136
Inappropriate oxytocin secretion precedes SIADH-related hyponatremia after transsphenoidal pituitary surgery

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Inappropriate secretion of vasopressin or antidiuretic hormone (SIADH) occurs in at least 10% of transsphenoidal pituitary surgery cases and presents with risks. Its diagnosis is based on hyponatremia, with a peak of occurrence around day 7 after surgery and, to date, no early marker has been reported. Oxytocin (OXT) is secreted into the peripheral blood by axon terminals adjacent to those of ADH neurons in the posterior pituitary. OXT may therefore have the same postoperative course as ADH. Secretion of OXT within the days following pituitary surgery or remotely therefrom has however never been studied. Besides its role in childbirth and lactation, recent evidences suggested a role for OXT in sodium balance, either through a direct natriuretic effect on the kidney or by governing the envy of salt. Physiological contribution of this hormone in sodium balance remains, however, little known and, in particular, its contribution in the dysnatremias observed after pituitary surgery has not been investigated. In this study, we analysed the urinary output of OXT in patients subjected to transsphenoidal pituitary surgery. Interestingly, while no specific dynamics in OXT excretion were noted when all patients were grouped together, we observed that urinary secretion of OXT increases one day after surgery and is then normalized at 4 days post-surgery in patients who remained normonatremic. Furthermore, this normalization in the secretion of OXT was not present in the subgroup of patients that would later be diagnosed with SIADH. Taken together, these results show for the first time that urinary OXT output is influenced by transsphenoidal pituitary surgery, with its secretion increasing one day after surgery and coming back to pre-operative levels four days later. Interestingly, this excretion remains abnormally high in SIADH patients and this abnormal excretion preceded clinical hyponatremia, suggesting that abnormal dynamics of OXT secretion might act and serve as an early marker for transsphenoidal surgery-related SIADH.
P137

SEM analysis of experimentally induced aneurysms in rats at different time points during aneurysm formation

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Introduction
Ruptured intracranial aneurysms are the major cause of subarachnoid hemorrhage. Arterial hypertension is one of the important factors inducing haemodynamic stress which leads to aneurysm formation. Experimental animal models are useful to study the development of cerebral aneurysms. In our study we were looking at the time course of aneurysm formation by analyzing the number, location and size of cerebral aneurysms in a well-established experimental rat model.

Methods
Aneurysms were induced in Sprague-Dawley rats with the Hashimoto aneurysm model causing haemodynamic stress by ligation of the right common carotid artery and posterior branches of the bilateral renal arteries. In addition food was loaded with betaaminoproprionitrile and water containing 1% NaCl. Vascular corrosion casts were produced at time points 1, 3 and 4 months after aneurysm induction. Arterial changes in vascular corrosion casts were detected by scanning electron microscopy (SEM). Neck and dome size of aneurysms were measured with Image J.

Results
A total number of 32 treated animals were analyzed. In 4 out of 5 treated animals (80%) at one month after surgery aneurysmatic lesions could be detected, at 3 months in 10 animals out of 13 (76.9%) and at 4 months after surgery all 14 animals demonstrated aneurysmatic cerebral artery outpouches (100%). The number of aneurysms per animal increased over time (1.3, 2.2 and 2.8 at 1, 3 and 4 months). Most aneurysms were observed at the right ACA/OA branching site, fewer were found at the A1 and MCA bifurcation and only 2 aneurysms in the posterior circulation at 4 months FU. The dome size of aneurysms after aneurysm induction was 27.94 µm (±10.39) at 1 month FU, 31.45 µm (±17.78) at 3 months and significantly increased (53.26±47.77 µm; p < 0.02) at 4 months. The neck size of aneurysms at 1 month was 58.55 µm (±9.99), and did not change between 3 and 4 months FU (73.63 µm ±30.88 vs. 72.73 µm±50.36; p=0.93). The dome/neck ratio of aneurysms was 0.46 (±12) at 1 month, and differed significantly between 3 (0.45±0.25) and 4 months (0.85±0.48; p < 0.0001) at 4 months.

Conclusion
Our study demonstrates that the Hashimoto animal model is reliable and produces aneurysms in 80 to 100% of animals over time. We found significant morphological changes between 3 and 4 months FU time. This data is valuable information to determine adequate FU-time points for research questions that specifically focus on aneurysm initiation or aneurysm growth.
P138
The Swiss Pituitary Registry 2019 - An update on the first national registry for pituitary tumors: SwissPit

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Aim
The Swiss Pituitary registry (SwissPit) is a national database dedicated to serve clinical scientists in Switzerland as a source for (multicentric) studies on pituitary tumors. Founded in 2016 its feasibility and resourcefulness has meanwhile been shown in numerous projects and the number of partaking centers has grown. The registry is financially self-sustaining and members enjoy widespread possibilities to manage and assess their own individual data. The aim of this presentation is to give an update on the content, the projects and the goals of SwissPit.

Methods
Members have been asked to give information on their actual procedures, the number of patients entered in the SwissPit and the current studies based on SwissPit data.

Results
Neurosurgeons and endocrinologists from 5 Swiss tertiary referral centers are permanent SwissPit members. On May 1st 2019 detailed data of 780 pituitary patients was available in the registry (KSA, n=512; USB, n=200; KSSG, n=42; LUKS, n=16; USZ, n=10). 650 (83%) of the patients suffer from pituitary adenoma. Among those, nonfunctioning pituitary adenoma constitute the majority (n=438, 67%), followed by prolactinomas (n=107, 16%), and growth hormone secreting adenomas (n=71, 11%). Over 10 clinical trials are currently ongoing based on the data provided by SwissPit.

Conclusion
Thanks to the combined effort and the resources provided by its members the SwissPit has developed into a feasible, resourceful database for clinical trials on pituitary tumors in Switzerland. For more information on please refer to www.swisspit.ch.
P139
The prophylactic use of low molecular weight heparin in patients with external ventricular drains

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Aims
The routine use of low molecular weight heparin (LMWH) as venous-thromboembolism (VTE) prophylaxis in neurosurgical patients is controversial due to an increased risk of haemorrhage in this patient-group. One such neurosurgical intervention with an increased haemorrhage risk is the insertion and removal of external ventricular drains (EVDs) (1). This audit aimed to determine adherence to local VTE guidelines in this population, and determine the incidence of intraventricular haemorrhage and VTE in patients with EVDs. A comparison was made between those who received LMWH and to those who did not.

Methods
Data was collected through retrospective review of electronic patient records. All patients who received an EVD from 31st August 2018 - 1st January 2019 at a single institution were identified. Cranial imaging was reviewed by a single neurosurgical registrar, to assess for presence of intraventricular haemorrhage. Evidence of PE or DVT was sought from clinical notes. Patients were excluded if there was no cranial CT or MRI imaging following EVD insertion.

Results
36 patients were identified (adult n = 30; paediatric n = 6). The most common indication for EVD insertion was subarachnoid haemorrhage (n = 11). In patients who received LMWH whilst an EVD was in-situ (n = 6), intraventricular haemorrhage occurred in a third. In patients who did not receive LMWH whilst an EVD was in-situ, intraventricular haemorrhage did not occur. VTE occurred in two patients, both of whom received LMWH. Known pro-thrombotic risk factors (infection and immobilisation) were present in both patients where VTE occurred.

Conclusion
Intraventricular haemorrhage only occurred in patients who had LMWH administered whilst an EVD was in-situ, representing a marked increase in comparison to those who did not receive LMWH. VTE events only occurred in those with pro-thrombotic risk factors, despite administration of LMWH. The prophylactic use of LMWH should therefore be avoided in neurosurgical patients with EVDs, unless marked pro-thrombotic risk factors are present.
Proteomic map of glioma biopsies reveals functional defects in endocytosis

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Background
Decades of molecular genetic analyses have shown that gliomas accumulate genetic alterations leading to enhanced activity of growth factor receptor tyrosine kinases (RTKs) and mediators of downstream pathways. These alterations result in gain-of-function of EGFR, PDGFR, PIK3CA or BRAF, and loss-of-function of PTEN or NF1, to exacerbate proliferative responses.

Methods
We performed deep proteomic analysis of human gliomas of distinct genetic backgrounds, i.e. IDH, TERT statuses in combination with EGFR or PDGFRA amplification.

Results
Mass spectrometric analysis confirmed the R132H mutation in an IDH-mutant biopsy. By comparison with white matter control biopsies, proteomic quantification revealed dramatically high EGFR protein levels in biopsies carrying an EGFR amplification. However, we also noticed a general, somewhat moderate, overexpression of EGFR in glioma biopsies devoid of EGFR amplification. Furthermore, high EGFR was paralleled with decreased levels of core components of clathrin-mediated endocytosis (CME), i.e. subunits of the endocytic adaptor AP-2, clathrin (CLTC) and dynamin (DNM) proteins in a concerted manner. Western blotting confirmed these observations. Functional binding assays showed higher surface binding of transferrin and higher cell surface EGFR levels when endocytic machinery proteins were reduced. Ongoing CpG methylation analyses of endocytosis gene promoters revealed that part of them are subject to epigenetic silencing, thereby providing clues on an orchestrated down-regulation of the corresponding genes.

Conclusion
From these observations, we hypothesize that depletion of CME components increases the availability of RTKs at the plasma membrane to prolong exposure to growth factors. Subsequent enhanced and sustained growth factor response may result in selective advantage in tumorigenesis and progression. Current and future experiments focus on assessing and modulating growth factor signaling in glioma cells the context of impaired endocytosis.
P142
Glioblastoma Diagnosis: Communicating with Patients and Relatives

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The satisfaction during the therapy of glioblastomas is crucial in the care of patients and their relatives. To increase their satisfaction, it is necessary to know their needs, questions, and concerns in detail. It is as yet largely unknown how to communicate best with patients and their relatives during this therapy. This applies to the best way of conveying the diagnosis and other factors to be considered by physicians, nursing staff, and other involved parties. The present pilot study is based on 40 qualitative interviews with patients and their relatives at the cantonal hospital in Aarau (Switzerland), covering their needs, expectations, anxieties, concerns, and questions during the five phases of the therapy (pre-OP; post-OP; rehabilitation; chemotherapy and radiation therapy; survival). The findings identify 7 categorical factors that influence satisfaction with care: doctor-patient communication; anxieties and concerns; needs and expectations; trust; nursing behavior; criticism; additional support. These factors are described for each therapy phase by presenting examples from the interviews. From the shortcomings identified and expectations unmet, guidelines for health care communication in each therapy phase are established. It is hoped that these guidelines, if health care providers are made familiar with them, will increase patients’ and their relatives’ satisfaction. The guidelines identify patients’ and their relatives’ needs, expectations, concerns, and questions. They also provide a basis for selecting what content is to be disclosed at diagnosis and subsequent consultations. Concepts such as a case manager or an informational brochure are further presented as auxiliary means to be implemented.
P143
Assessment of a novel stereotactic frame-based setting for magnetic resonance imaging-guided laser-induced thermal therapy

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Aims
Magnetic resonance imaging-guided laser-induced thermal therapy (MRgLITT) was shown to be a viable tool in epilepsy and neurooncological surgery. Apart from its variety of therapeutic options, different potential operative and technical nuances also exist. In this technical report, the use and ability of a Riechert-Mundinger (RM) stereotactic system combined with a new drill guide kit for MRgLITT are firstly described.

Methods
A stereotactic frame-based setting was invented by combination of a conventional RM frame with a recently developed drill guide and centering screwing aid for bone anchors for application together with the Visualase neuro accessory kit and cooled laser applicator system. The apparatus was initially used for MRgLITT in a human head phantom and for stereotactic biopsy and consecutive MRgLITT in a brain tumor case thereafter.

Results
The application and potential of a RM stereotactic frame and an additional drill guide kit for MRgLITT was assessed. Both MRgLITT in a skull model and a stereotactic biopsy with subsequent MRgLITT in a neurooncological patient could be easily and safely performed by the system. Duration of surgery was not prolonged when compared to alternative methods and no technical problems or perioperative clinical complications could be observed.

Conclusion
By implementation of a novel apparatus, MRgLITT both in a phantom and in an exemplarily brain tumor case was successfully performed. In our preliminary experience, the combination of a traditional RM stereotactic system and an additional new drill guide tool provides neurosurgeons with the opportunity to reliable confirm the diagnosis by a frame-based biopsy and allows for highly accurate real-time MRgLITT.
Flat panel computer tomography in Hybrid operating room for neurological intervention: A phantom and retrospective study

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Introduction
Recently an increasing number of three-dimensional (3D) rotational angiography (RA) and flat panel computer tomography (FPCT) studies are being performed in hybrid operating room (OR). We conducted a phantom study to evaluate different intraoperative settings, FPCT protocols, and compare the radiation dose to a cohort of patients.

Material and Methods
An anthropomorphic x-ray head phantom, with or without neurophysiological monitoring electrodes and BIS-monitoring cable, was used. The phantom was held in the following frames; A. Metal Mayfield head holder, B. Carbon Mayfield plus steel pins, C. Carbon Mayfield plus half titanium pins, D. Carbon Mayfield plus titanium pins, E. Carbon Mayfield plus rubber head holder, or F. Carbon angiography table. The following 3D protocols (Artis Pheno, Siemens) were tested; 1. 4sec 3D RA; 2. 4sec 3D RA Head Care; 3. 5sec 3D RA-FPCT; 4. 4sec FPCT Head Care; 5. 6sec FPCT 70KV; and 6. 6sec FPCT 109KV. Subjective analysis of image quality was performed by 2 experienced readers, where they assigned a grade (1; poor to 3; excellent) in regard to metal artefact and noise. Clinical 3D RA and FPCT performed in our hybrid-OR from January to December 2018 were analyzed for protocol and radiation dose as a control.

Results
The presence of neurophysiological monitoring electrodes and BIS-monitoring cable did not have an effect on the radiation dose (mean 0.21 mSv with cables vs. 0.20 mSv without, p=0.9) in 3D RA acquisitions. The radiation dose was similar for the metal Mayfield head holder compared to carbon Mayfield in 3D RA acquisitions (mean 0.46 mSv vs. 0.48 mSv, p=0.9). Radiation dose of acquisitions in carbon Mayfield, with either steel, half titanium or titanium pins, were comparable within each protocol (ranging from 0.50 mSv in 4sec 3D RA to 2.5 mSv in 6sec FPCT 109KV acquisitions). Subjective analysis ranked image quality of the different head holders as follows; A. Steel Mayfield: 1.3; B. Carbon Mayfield plus titanium pins: 2.0; C. Carbon Mayfield plus half titanium pins: 2.0; D. Carbon Mayfield plus steel pins: 1.9, E. Carbon Mayfield plus rubber head holder: 2.1; and F. Carbon angiography table 2.6. Overall interrater agreement was kappa 0.66 (p < 0.001).

Conclusion
We believe our result present the first reference to assist in achieving an acceptable 3D acquisition image quality during hybrid-OR procedures, while maintaining the radiation dose as low as reasonable.
P145
Influence of inferior petrosal sinus drainage symmetry on detection of adenomas in Cushing’s syndrome

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Background
Asymmetric inferior petrosal sinuses (IPS) are not infrequently encountered during bilateral IPS sampling. There is little data on whether IPS symmetry influences success in predicting the adenoma side in patients with ACTH-dependent Cushing’s syndrome (CS).

Objective
To assess the influence of IPS drainage patterns on detection of an adenoma in CS. Methods Retrospective single-center cohort analysis reviewing records of patients with CS and negative MRI findings who subsequently underwent BIPSS. We evaluated demographic, laboratory, interventional, and histopathologic findings and clinical outcome for patients treated in our institution from June 1997 to January 2016.

Results
BIPSS was performed in 38 patients with a mean age of 45 ± 15 years. The overall technical success rate was 97% for bilateral cannulation. Asymmetric IPS were observed in 11 (39%) patients with Cushing’s disease (CD). A side-to-side ACTH ratio was not significantly different between patients with symmetric outflow and those with asymmetric outflow at baseline (8.6 ± 2.7 versus 16.4 ± 6.0; P = 0.45), but ratios were significantly different after ovine corticotropin-releasing hormone (oCRH) stimulation (6.0 ± 2.5 versus 35.7 ± 22.5; P = 0.03). BIPSS correctly predicted the side of the adenoma in 25 (96%) patients with CD. Prediction was better when the venous outflow was symmetric (100%) rather than asymmetric (93%), although the difference was not significant (P = 0.42). Remission from CS was achieved in 32 patients (87%), independent of the symmetry of IPS.

Conclusions
Bearing in mind the sample size of this audit, asymmetric IPS at least do not seem to diminish the accuracy of diagnosis of ACTH-dependent CS, nor do they influence the clinical outcome.
Aims
Recently, imaging techniques providing metabolic representations of the tissue, such as 1H MRS spectroscopy, are used to characterize discs degeneration. Several studies highlight that metabolites levels can be used as reliable indices of disc pain in the lumbar spine. However, only few studies focus on cervical intervertebral disc (IVD) degeneration. The purpose of this study is to identify promising biomarkers, detectable non-invasively by 1H MRS in the patient, to provide novel in vivo imaging opportunities of discogenic pain in the human cervical spine.

Methods
Fifteen biopsy of degenerated cervical IVD (ranging-age: 20-74 years) were dissected into annulus fibrosus (AF) and nucleus pulposus (NP) and water-soluble metabolites were extracted with the dual-phase method using methanol: chloroform: water (1:1:1). By 1H NMR spectroscopy the complete water-soluble metabolome was analyzed on a HR 700 MHz spectrometer. Differences in metabolic composition of AP and NP were calculated and related to the degree of disc degeneration (I-V Miyazaki grading system, MGS).

Results
We could detect changes in several well studied metabolites including lactate (Lac), choline (Cho), creatine (Cre), chondroitin (Chond), and glutamine (Gln). We observed a decrease in Cre-, Gln-, and Cho-concentrations and a significantly increase of Chond in NP, compared to AF. Strikingly, the difference in relative Chond between NP and AF was highest in low grade discs (grade 3) and significantly decreased with increasing degeneration grade (4 and 5). Moreover, we calculated several metabolic ratios and compared NP and AF tissues of grade 3,4 and 5 discs. Interestingly, between NP and AF tissue of low-grade discs we observed highest differences in Lac/Cre, Gln/Cre, and Cho/Cre ratios that decreases linearly with the increase of degeneration grade.

Conclusion
1H MRS spectroscopy-derived biomarkers, especially metabolic ratios such as Chon/Cre, Gln/Cre, or Cho/Cre in NP and AF and their comparison, are able to identify early stages of ID degeneration and they represent a good prognostic surgical outcomes for chronic cervical back pain.
Multidisciplinary management of benign aggressive vertebral hemangiomas in a hybrid room facility: a case-series

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Purpose
Vertebral hemangiomas (VH) account for 2-3% of all spinal tumors. The majority is asymptomatic and incidentally found on radiographic studies: 1% present with pain and/or neurologic deficits. We report our experience with the multidisciplinary management of aggressive thoracic VH by concomitant intraoperative sclerotization with sodium tetradecyl sulfate (STS), vertebroplasty, posterior decompression (with or without fusion) and surgical resection in a hybrid operating room (HR).

Methods
Patients consecutively admitted with aggressive spinal VH between 2007 and 2018 were included. Data regarding baseline demographics, presenting symptoms, location of the lesion, pre-operative embolization, length of the surgery, estimated blood loss (EBL) as well as follow-up (FU) were retrieved.

Results
Five patients were included (three females, mean age 65 years; range 59-75). Three patients presented with a progressive myelopathy. Two patients had isolated mechanical thoracic pain. All patients underwent a single-stage percutaneous sclerotization and vertebroplasty followed by a surgical open decompression associated with epidural intra-lesional injection of STS and subtotal resection of the epidural lesion. Two patients had pre-operative embolization. Mean procedural duration was 338 min (range: 210 – 480 min). All patients had EBL inferior to 500 mL. Patients had no evidence of lesion recurrence or progression at the end of the follow-up.

Conclusions
The single-stage multimodal management of aggressive VH is safe and effective. It allows for a direct intra-operative sclerotherapy combined with maximal tumor resection, resulting in reduced blood loss. The use of STS as a direct intra-operative sclerotizing agent is safe and reliable.
Aims
A pial arteriovenous fistula (PAVF) is a rare neurovascular pathology consisting of a direct connection between one or more arterial feeders and a single venous channel. Previously, a PAVF was considered a subtype of an arteriovenous malformation (AVM). In the current literature these are distinguished as two independent entities with different clinical, physiopathological and structural characteristics. We report a case of a surgically treated 37-year-old woman with an extremely rare combination of an unruptured PAVF and AVM.

Case Description
The AVM was mainly supplied by feeders of the middle cerebral artery and drained into the sigmoid sinus via an abnormally dilated and tortuous vein. Following its resection, intraoperative digital subtraction angiography (DSA) in the hybrid operating room revealed the presence of a PAVF, which had not been noted during the preoperative planning. Hence, the PAVF was completely disconnected, which was confirmed by DSA again.

Conclusion
This is the second reported case of an AVM-associated PAVF. Without the intraoperative DSA in the hybrid operating room, this unusual complex cerebrovascular entity would likely have been missed.
Anterior compressive cervicothoracic pseudomeningocele as a rare manifestation of idiopathic intrathecal hypotension: a case report and literature review

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Background
Spontaneous intracranial or intrathecal hypotension (SIH) is an underdiagnosed phenomenon predominantly presenting with low cerebrospinal fluid (CSF) pressure and postural headache in setting of CSF leak. Extrathecal CSF collections causing compression of the spinal cord or nerve roots present an even more rare subset of this disease with less than 20 cases described.

Case Description
We present a case of an anterior compressive pseudomeningocele between C2 and D7 in a 52-year old patient complaining about neck and bilateral radiculopathy. He was also known for multiple head and cervical traumas in the past being an ancient professional skier. Further investigations through a myelography and myelo-CT were able to postulate a CSF leak through a diskogenic osteophytic microspur at the level C5-C6. Our patient improved after a cervical blood patch and didn’t present any cranial positional symptoms.

Discussion and conclusion
Spinal manifestations are uncommon in cases of idiopathic or spontaneous CSF leak, occurring in about 6% of patients, but myelopathy and radiculopathy involving all spinal segments do occur. Contrarily to the cranial complains, the spinal manifestations usually are not positional and are caused by mass effect from an extradural CSF collection. The utility of multiple imaging modalities such as dynamic myelography and the use of epidural blood patches and fibrin glue polymers should be explored and surgery appears to be feasible if the symptoms persist despite other measures.
Multidisciplinary management of benign aggressive vertebral hemangiomas in a hybrid room facility: a case-series.

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Purpose:
Vertebral hemangiomas (VH) account for 2-3\% of all spinal tumors. The majority is asymptomatic and incidentally found on radiographic studies: 1\% present with pain and/or neurologic deficits. We report our experience with the multidisciplinary management of aggressive thoracic VH by concomitant intraoperative sclerotization with sodium tetradecyl sulfate (STS), vertebroplasty, posterior decompression (with or without fusion) and surgical resection in a hybrid operating room (HR).

Methods:
Patients consecutively admitted with aggressive spinal VH between 2007 and 2018 were included. Data regarding baseline demographics, presenting symptoms, location of the lesion, pre-operative embolization, length of the surgery, estimated blood loss (EBL) as well as follow-up (FU) were retrieved.

Results:
Five patients were included (three females, mean age 65 years; range 59-75). Three patients presented with a progressive myelopathy. Two patients had isolated mechanical thoracic pain. All patients underwent a single-stage percutaneous sclerotization and vertebroplasty followed by a surgical open decompression associated with epidural intra-lesional injection of STS and subtotal resection of the epidural lesion. Two patients had pre-operative embolization. Mean procedural duration was 338 min (range: 210 – 480 min). All patients had EBL inferior to 500 mL. Patients had no evidence of lesion recurrence or progression at the end of the follow-up.

Conclusions:
The single-stage multimodal management of aggressive VH is safe and effective. It allows for a direct intra-operative sclerotherapy combined with maximal tumor resection, resulting in reduced blood loss. The use of STS as a direct intra-operative sclerotizing agent is safe and reliable.
P151
Improving intraoperative evoked potentials at short latency by a novel neuro-stimulation technology.

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Aims:
Intraoperative monitoring of cranial nerve function records evoked responses at latencies of a few milliseconds. Unfortunately, these responses may be masked by the electrical artifact of the stimulation pulse.

Methods:
In electrical stimulation the return discharge of the pulse significantly contributes to the width of the electrical artifact. We have generated stimulation pulses with an ISIS Neurostimulator (inomed Medizintechnik GmbH) providing a novel stimulation artifact reduction technique. It delays the return discharge of the stimulating pulse beyond the latency of the expected physiological response. This delayed return discharge is controlled such that no unintended physiological response is evoked.

Results:
The stimulation method generated stimulation pulse artifacts with a tail of < 1 ms in both motor evoked potentials of the facial nerve (FNMEP) and somatosensory evoked potentials of the trigeminal nerve (trigSEP). Compared to conventional stimulation with immediate return discharge, the signal-to-noise ratio of the physiological response was significantly improved with the new stimulation methods. In some cases, only because of the new stimulation method the response signals were clearly identifiable.

Conclusion:
The reduced width of the stimulation artifact extends the toolbox of intraoperative monitoring methods by rendering the interpretation of cranial nerve evoked potentials more reliable. The new technique enhances the number of patients for whom intraoperative monitoring may aid in cranial neurosurgery. It may also be beneficial for nerve conduction recordings at short latency.
Aim:
Neurosurgical training has always been based on an apprenticeship model that requires considerable time and exposure to surgeries, and unfortunately at present time these requirements are hampered by several limitations (e.g. decreased caseload, worktime restrictions). Furthermore, teaching methods vary among residency programs due to cultural differences, monetary restrictions and infrastructure conditions. Therefore, surgical standards might differ among European countries, with the possible consequence of jeopardising residents’ training.

Methods:
The EANS Basic Brain Course has grown from a collaboration between Besta NeuroSim Center in Milano and Swiss Foundation for Innovation and Training in Surgery in Geneva and was held for 5 neurosurgical residents (PGY1-3) who participated to this first pilot experience in January 2019. The main goal was to cover all the basics aspects of cranial surgery, including both technical and non-technical skills. The course was developed in modules starting from the diagnostic path and communication with patients (played by professional actors), then moving to practical simulation sessions, rapid theoretical lessons, and discussions based on real cases and critical ethical aspects; at last, the candidates joined cadaver-lab sessions in which they practiced basic emergency procedures and craniotomies. The interaction between the participants and the faculties was created and maintained using role plays, that smoothly improved the cooperation during debriefs and discussions, thus making the sessions exceedingly involving.

Results:
At the end of the course, every trainee was able to complete the course curriculum and all the participants expressed their appreciation for this innovative format, with a particular emphasis on the time spent to learn non-technical skills, confirming that they feel this is a fundamental aspect of a comprehensive training in neurosurgery.

Conclusion:
It is possible that this combined concept of training on technical and non-technical skills, using emerging technologies along with pedagogic techniques, as well as cadavers-dissection courses, may become the state-of-the-art for European Neurosurgical training programs in the next future.
P153
Studying Brain Energy Metabolism on a Single Cell Level in vivo Using Optogenetics and Two-Photon Imaging

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Aims
Already short disruptions of energy supply to the brain lead to severe failure and major neurologic deficits, showing the significance of a properly functioning energy metabolism. However, processes involved in normal brain energy metabolism are still poorly understood and thorough examination in vivo is mandatory. Beside others, the role of lactate for cerebral energy supply is challenged. In this study, we aim to establish a method that allows simultaneous cellular imaging and optic stimulation in the mouse model.

Methods
For most experiments C57BL/6 mice were used. Mice underwent surgery that included the implantation of a head post, intracortical injections of viral vectors encoding for fluorescent proteins (the optogenetic actuator Channelrhodopsin-2 (ChR2), red fluorescent calcium sensor (RCaMP), green fluorescent calcium sensor (GCaMP) and lactate sensor Laconic) and the implantation of a chronic window for optical access. Fluorescent sensors were expressed in a cell-specific manner using respective promoters. A subset of experiments was performed in transgenic animals already expressing ChR2 in neurons. Animals were investigated using two-photon laser scanning microscopy. For ChR2 activation a 450nm blue laser light source was used.

Results
In C57BL/6 mice, only about 1/3 of the animals showed coexpression of Laconic, RCaMP or GCaMP with ChR2. In transgenic animals, coexpression was successful in about 2/3 of the cases. In cases of successful coexpression, a rise in the calcium signal could be seen upon optical stimulation. In a set of animals, also a rise in the neuronal and astrocytic Laconic signals was observed upon activation. Nevertheless, the fluctuations in the lactate signal were not always reproducible.

Conclusions
Taken together, this work shows the principle feasibility of cellular imaging and concomitant light stimulation in vivo. However, coexpression of several genetically encoded fluorescent metabolite sensors with ChR2 is challenging. The use of transgenic animals constitutively expressing ChR2 seems to improve the outcome. The combination of optogenetics and multisensor two-photon imaging has to be further refined in order to reproducibly and concisely study biological questions such as the role of lactate as an energy source of neurons.
Osteoblastoma in third cervical vertebra: Case report

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Introduction:
Osteoblastoma is a benign tumor, representing 1 to 5% of the primary bone tumors. The incidence of osteoblastoma involving the spine reaches 36%, from which even 40% affect the cervical segment, more commonly the posterior elements. Young male people are the most affected. The diagnosis is frequently late, as it usually courses with chronic cervical pain as the only symptom. However, when there is mass effect on nerve roots or the spinal cord, neurological manifestations such as radiculopathy or myelopathy do occur as well. The most sensitive radiographic examination used in osteoblastoma's evaluation is the bone scan. The treatment goal is complete surgical resection, which allows the complete regression of complaints and decrease the likelihood of recurrences.

Methods:
Here we report a case of a 16 years old Brazilian patient who presented since 2 months with left cervical pain as single symptom, without irradiation and non-responsive to medications such as non-steroidal anti-inflammatory drugs. In further investigation, a spine computed tomography revealed destruction of the posterior C3 arch and tissue invasion. The patient underwent a decompressive surgery with a tricortical iliac crest graft between C2 and C4 and arthrodesis with anterior cervical plaque from C2 to C4. Seven days later, a side mass screw was placed at the right side of C2, C3 and C4 through posterior access.

Results:
The histopathological examination was suggestive of osteoblastoma. After surgical excision, the patient had total resolution of the symptoms and no sequels. At the three-year follow-up, the patient was asymptomatic, had no restrictions on daily activities, and to date there has been no evidence of recurrence.

Conclusion:
During investigation of chronic spine pain cases in young patients, it is essential to consider osteoblastoma as differential diagnosis, aiming an early and complete surgical resection to avoid progression of bone destruction and neurological deficits as well as resolve the symptoms and prevent recurrences.
P155
Three-dimensional visualization of aneurysm wall calcification by cerebral angiography: Technical case report

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Background
We describe on a 57-year-old man with an incidental middle cerebral artery (MCA) aneurysm in whom a preoperative standard three-dimensional rotational angiogram (3D-RA) was used to depict luminal morphology along with 3D density rendering to precisely locate aneurysm wall calcification.

Methods
To detect aneurysm calcification, a native 3D-RA was acquired by acquisition of images with optimized parameters for calcium density visualization, followed by an intraarterial contrast-enhanced 3D-RA. Both data sets were then fused and postprocessed obtaining a 3D calcium volume rendering.

Results
Depiction of both the MCA luminal aneurysm morphology as well as calcium-rich components in the aneurysm wall was valuable to determine operative strategy.

Conclusion
Simultaneous imaging of luminal morphology and calcification within the same angiographic procedure allows for a plain and simple estimation of the degree and distribution of aneurysm wall calcification with limited amount of additional radiation dosage.
P156
Biochemical in-vivo imaging of Intervertebral Disc Degeneration with HR 1H NMR Spectroscopy in Cervical Spine

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Aims
The incidence of degenerative cervical change increases with age, but only a small proportion of patients report painful symptoms. Clinical MRI is the most used imaging technique to investigate cervical pain and radicular complaints, but the lack of a specific relationship between clinical data and MRI-data has led the need to find a new imaging method, capable to differentiate symptomatic and not symptomatic degenerative changes of the cervical spine. A potential future diagnostic alternative as HR 1H NMR spectroscopy is currently under investigation to quantify the biochemical changes of disc degeneration, as measured by alteration in collagen structure, as well as water and proteoglycan loss parameters associated with the disc degeneration cascade. The object of this study is to investigate MRS-derived biomarkers especially in cervical spine to permit a more accurate diagnosis and a better therapeutic indication.

Methods
Non-systematic literature review.

Results
“Chemically sensitized” and “mechanically sensitized” are the two mechanism at the genesis of the discogenic pain. The chemical mechanism at the basis of disc degeneration appears to be an insufficient diffusional nutrition of the disc linked to the aging of tissues, which result in an anaerobic metabolism. This leads to alteration of lactate and proteoglycan levels. HR 1H NMR spectroscopy can easily assessed those changes. Former studies have demonstrated that degenerating disc can undergo an inflammatory process that involves cytokines, like Interleukin-1β (IL-1β), and TNF as well as specific nociceptive mediators, such as prostaglandins (PG) and NO, which can be detected by the spectroscopy. The consequence of these processes is a matrix degradation of the disc, which results in a decrease of Collagen and Proteoglycans (N-Acetyl and myo-inositol) and therefore an increase in their degradation products, like aminoglycans (Creatine, GLY,ALA, LEU, VAL, ILE, HYP), - and -glucose. Current studies indicate a correlation between measured metabolite ratio changes and the severity of disc degeneration, especially for N-Acetyl, Choline, Carbohydrate’s regions and the ratios of proteoglycan to lactate and collagen.

Conclusion
Non-invasive HR 1H NMR spectroscopy is a promising investigative approach to detect and define the early stages of intervertebral disc degeneration facilitating more accurate diagnosis and a better therapeutic indication.
Novel soft subdural electrodes versus standard clinical arrays: a comparative pilot cadaver study

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Aims:
Subdural arrays remain an important neurosurgical technique as part of a phase II workup for pharmaco-resistant epilepsy. However, determining exact post-operative localization of subdural arrays can be problematic due to artifact caused by the implanted material. Furthermore, certain regions of the brain remain inaccessible to current semi-rigid grids due to anatomical constraints, notably in the sylvian fissure. In this study, we compared soft EcoG implants and current standard subdural grids for the first time in the human cadaver, in terms of artifact production, electrochemical properties, and surgical applicability.

Methods:
Standard clinical array: Ad-Tech 32 electrode (⌀ 2.3 mm) subdural grid. Soft experimental grid:32 electrode grid of same external and electrode dimensions. Implantation was done on a fresh-frozen and formalin-embalmed human cadaver head using both large craniotomy and letterbox craniotomy technique. Electrochemical characterization was performed before and after implantation on each electrode type. Post-implantation imaging was performed with X-ray, CT, and MRI.

Results:
Electrochemical characterization:The 1 kHz impedance of the soft electrodes was 0.52 ± 0.15
Assessment of velocity reduction after flow diverter stent implantations using 4D PCMRI

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Aim and context
Dense mesh flow diverter stents (FDSs) are broadly used for the endo-vascular treatment of wide neck intra-cranial aneurysms (IAs). As it name suggests, FDS induces flow reduction in the IA cavity and the subsequent progressive thrombosis that ultimately exclude the aneurysm from the circulation. Hemodynamic investigations were mainly performed using computed simulations and virtual deployments of stents but very few in-vivo measurements are reported. In the present study, we aimed to measure and visualize on patients, the impact of FDS on the IA velocity changes using 4D phase-contrast MRI (4D PCMRI).

Methods
We included patients treated with FDS and prospectively acquired 4D PCMRI data before and after stent implantation. A dedicated post-processing pipeline was developed to obtain accurate hemodynamic patterns and quantitative velocity changes in the vicinity of the aneurysm bulge. A metric was defined: the proportional velocity reduction ratio (PVRR) reflecting the percentage of systolic velocity reduction normalized with parent vessel flow rates to take into account physiological differences between pre-and post MRI examinations. Statistical differences of PVRRs were assessed for 3 groups defined by their occlusion times, namely 6, 12 months and no thrombosis at 12 months. Velocity patterns were described as modified by the FDS in direction and/or magnitude.

Results
We were able to assess quantitatively and qualitatively the flow modifications on a consecutive series of 23 patients. In particular, a trend was identified (p= 0.08) between PVRRs and occlusion outcomes as it could be expected (PVRRs gradually decrease from 6 months to 12 month's occlusion groups and no thrombosis group). However, qualitatively, no specific flow patterns changes were identified to be associated with fast nor delayed occlusion.

Conclusion
4D PCMRI is the only method to measure in-vivo velocity fields in 3D that allows us to characterize qualitatively and quantitatively the IA flow changes after flow diversion implantation. Our results showed a trend between the promising PVRR indicator and occlusion times but the small differences between the 3 groups put in perspective the role of hemodynamics among other parameters like neck-endothelialization, biological factor and anti-aggregation therapy that should be further investigated.
Angioplasty using Drug-coated balloon in Symptomatic Intracranial High-grade Stenosis: A Mono-Center Cohort Study of 26 Patients

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Symptomatic intracranial atherosclerotic disease (sICAD) is responsible for up to 10% of all ischemic stroke worldwide. Despite best medical treatment sICAD remains a challenging disease with high-recurrence rate. There is an ongoing debate on the use of endovascular technique in sICAD patients. Percutaneous, trans-luminal angioplasty using drug-coated balloon (DCB-PTA) represents a novel endovascular treatment option for sICAD. Recent small studies have shown feasibility and safety of this endovascular technique (1,2). We aimed to assess safety and feasibility of DCB-PTA in a larger cohort of sICAD patients and to evaluate mid-term data.

Methods:
Monocenter, cohort study of sICAD patients with DCB-PTA treatment at a comprehensive stroke center.

Results:
26 sICAD patients treated either with Neuro Elutax SV (Aachen Resonance, Germany) (n=7) or Sequent Please Neo (B.Braun, Germany) (n=19) with a mean follow-up of 16.3 months. Median NIHSS on admission was 1; median modified Ranking Scale (mRS) was 1 at follow-up. Peri-interventional complication rate was 8%; the recurrent stenosis rate was 15%.

Conclusion:
DEB-PTA is feasible and safe in patients with sICAD with low recurrence rate.
“Armed Kyphoplasty”: An Indirect Central Canal Decompression Technique in Burst-Fractures

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Background and Purpose
Burst-fractures are characterized by middle column disruption and may present posterior wall retropulsion (PWR). Their treatment indications remain controversial. Recently introduced vertebral augmentation techniques, using intra-vertebral distraction devices, such as vertebral-body-stents (VBS) and Spinejack (SJ), could be effective in fracture-reduction and fixation, and might obtain central canal clearance through ligamentotaxis. In this study we assess the results of “armed kyphoplasty” (AKP) using VBS or SJ in traumatic, osteoporotic and neoplastic burst-fractures with regard to vertebral body height (VBH) restoration and correction of PWR.

Materials and Methods
Retrospective assessment of 53 burst-fracture with PWR and no neurological deficit, in 51 consecutive patients, treated with AKP. PWR and VBH were measured on pre- and post-procedure CT. Clinical and radiological follow-up charts were reviewed.

Results
AKP was performed as a stand-alone treatment in 43 patients, combined to posterior instrumentation in 8, with laminectomy in 4. Pre-AKP and post-AKP mean PWR was 5,76 mm and 4,5 mm respectively (p < 0,001), and mean VBH was 10,82 mm and 16,66 mm respectively (p < 0,001). No significant clinical complications occurred. Clinical and radiological follow-up (1-36 months, mean 8 months) was available in 39 patients. Three treated levels showed a new fracture during follow-up, without neurological deterioration, and no re-treatment was necessary.

Conclusions
In the treatment of burst-fractures with PWR and no neurological deficit AKP obtains fracture-reduction, internal fixation, and indirect central canal decompression, and in selected cases might represent a suitable minimally-invasive treatment option, stand alone or in combination with posterior stabilization.
A1-A2 flow diverters placement for ACom aneurysms treatment is associated with a high risk of perforating branch infarction

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Aims
Flow diverter (FD) stents are endovascular devices developed to treat wide neck intracranial aneurysms. These stents disrupt the flow in the aneurysm resulting in progressive aneurysm thrombosis. The utility of these stents at and beyond the circle of Willis is still controversial for the risk of ischemic events in the perforating arteries covered by the increased mesh density in the stent concavity. We aim to report our experience in the treatment of anterior communicating artery (ACom) aneurysms with A1-A2 flow diverter placement, with emphasis on ischemic complications of the Heubner artery.

Method
We retrospectively analyzed all consecutive patients presenting ACom aneurysms treated with FD stents in our institution between October 2014 and December 2018. We included patients with Acom aneurysms treated with FD stents and assessed by a post-treatment cerebral MRI. Patients harboring large or giant Acom aneurysms with mass effect on brain parenchyma were excluded. Clinical outcomes were assessed according to medical record.

Results
Eleven patients harboring 11 Acom aneurysms were included in the analysis. Mean age was 49,2 ± 18,2 (years ± sd). Clinical presentations were the following: incidental discovery in 27,3% (3/11), angiographic recurrences of previously treated aneurysms in 72,7% (8/11). All procedures were successful. Cerebral MRI at day one revealed 63,6% (7/11) of focal ischemic events: bright spots in the ipsilateral caudate nucleus and fronto-parietal lobes in three patients, in the ipsilateral occipital lobe in two patients. Moreover, we report two cases of complete Heubner’s territory ischemia and we deplore two cases of post-procedural clinical complications, with symptoms resolved before hospital discharge.

Conclusion
The treatment with FD stents of ACom aneurysms is feasible, however our study suggests that incomplete or complete acute ischemic events of the Heubner artery are often detected with post-procedural MRI. Although patients’ symptoms resolved before discharge, the neuropsychological impact is not well known and larger series are needed.
Posterior communicating artery retrograde approach for intra-arterial super-selective treatment of Retinoblastoma

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Aim
Intra-arterial chemotherapy for retinoblastoma is a recent procedure that aim to reduce systemic complications and increase efficacy compared to intravenous chemotherapy. However, the superselective catheterization of the ophthalmic artery can be challenging. We report the experience of our tertiary referral center using this approach.

Methods
We retrospectively analyzed all consecutive patients treated at least once with retrograde approach via the posterior communicating artery (PCom) to access the ophthalmic artery, from February 2017 to February 2019. We analyzed clinical, angiographic and ophthalmic data. Endpoints included feasibility of the access to the ophthalmic artery, peri-procedural ophthalmic and neurological complications and tumor response.

Results
23 patients were included in the study. Mean age (years old, ±SD) at the procedure was 2.4±1.3. The total number of procedures (all routes confounded, including the PCom approach) was 73 and the mean number of procedures per patient was 3.6±1.9. Forty procedures were executed using the PCom approach, that was feasible in all procedures. We reported no neurological complication due to the procedure. One patient presented a thrombo-embolic occlusion of the left postero-inferior cerebellar artery (PICA) during the procedure, successfully managed with thromboaspiration. Seven patients had intra-arterial chemotherapy as a first line treatment, without intravenous chemotherapy. These patients had a mean number of 2.8±0.4 treatments. In this group of patients, we reported five complete responses on the last ophthalmologic control and two enucleations. Sixteen patients had interventions after a previous combined IV and/or local treatment. We categorized these patients in different groups, salvage treatment after intravenous chemotherapy (IVC), salvage treatment after intra-arterial chemotherapy (IAC), treatment after IVC and IAC, treatment after bridging IVC. In these subgroups of patients, 10 patients had inactive tumor at the last follow-up, two had an active tumor and two had enucleation.

Conclusion
Our study suggests that the retrograde approach is feasible and effective for the treatment of RB. Even though neurological complications seem similar to the carotid approach, more data are required to assess the safety of this approach, in particular for ophtalmic complications.
Intra-Arterial Chemotherapy for Retinoblastoma: 10 years experience of a single center

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INTRODUCTION
Several invasive treatment options have been developed for retinoblastoma. Focal therapies, such as laser therapy, cryotherapy and thermotherapy, are often used alone or in conjunction with other treatment modalities. Initial experiences of selective ophthalmic artery infusion were performed by placing a balloon distal to the ostium of the ophthalmic artery to divert Melphalan infusion directly into the ophthalmic artery. The technique was then modified to allow for super-selective catheterization of the ophthalmic artery, infusing chemotherapy directly through the micro catheter. Via a transfemoral approach, a microcatheter is visualized and directed under digital subtraction angiographic guidance to super-selectively catheterize the origin of the ophthalmic artery. Our aim is to show our experience with this procedure, that we perform since 2008.

METHODS
IAC was performed as primary or secondary treatment for patients with intraocular retinoblastoma using Melphalan with or without additional Topotecan. Chemotherapy was injected through the ophthalmic artery after catheterization of the internal carotid artery in most of cases, but sometimes for anatomical reasons, alternative arterial routes were used, such as selective catheterisation of branches of external carotid artery to delivery chemotherapy via anastomoses with ophthalmic artery. Also, navigation through the posterior communicating artery to catheterize more directly and easily the ophthalmic artery.

RESULTS
Of 209 eyes of 193 patients with retinoblastoma, 72 (35 %) had IAC as primary treatment and 137 (65 %) had IAC as secondary treatment. The eyes were classified by International Classification of Retinoblastoma (ICRB) as group A (n=1, 0,5%), group B (n=24, 11,5 %), group C (n=14, 6,7%), group D (n=125, 60%), group D-E (n=5, 2,3%) and group E (n = 23, 11%). For 17 eyes (8%) the grading of tumor is unknown. The median number of IAC sessions was 3. We performed 544 injections of chemotherapy, 437 injections of Melphalan alone and 107 of Melphalan with additional Topotecan. Complications of IAC included occlusive choroidopathy, palpebral oedema or palpebral erythema, ptosis.

CONCLUSION
Our experience suggests that IAC is a safe and effective treatment for patients with retinoblastoma. Careful patient selection and experienced surgeons are critical for achieving the best treatment outcome.
Achievable Aspiration Flow Rates with Large Balloon Guide Catheters during Carotid Artery Stenting

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Aim
Emergency carotid stenting is a frequent endovascular procedure preceding intracranial thrombectomy. Balloon guide catheters positioned in the common carotid artery (CCA) are frequently used in these procedures. Our aim was to determine if mechanical aspiration through the working lumen of a balloon occlusion catheter during the steps of a carotid stenting procedure achieve flow rates that may lead to internal carotid artery (ICA) flow reversal.

Methods
Aspiration experiments were conducted using a commercially available aspiration pump. Aspiration flow rates/min utilizing a phantom containing blood-mimicking-fluid with 5 different types of carotid stents inserted into a balloon guide catheter were measured. Measurements were repeated three times with different pressures in the phantom (50, 75 and 100mmHg). To determine if the achieved aspiration flow rates were similar to physiologic values, flow rates in the ICA and external carotid artery (ECA) in 10 healthy volunteers were measured using 4D-flow MRI.

Results
Aspiration rates ranged from 25 to 78 mL blood mimicking fluid / min, dependent on the stent model. One stent model was available in two different sheath sizes dependent on the stent diameter. Mean blood flow volumes in volunteers were 210 mL/min in the ICA and 101 mL/min in the ECA.

Conclusion
Based on the results of this study, aspiration flow rates through the working lumen of a 9F balloon guide catheter with a carotid stent inserted reach up to 80% of antegrade ECA flow in the best case. Therefore, in case of strong collateral flow from ECA to ICA during CCA occlusion, flow reversal in the ICA is most likely achieved with the smallest diameter stent or the stent model with the shortest outer stent sheath.
Cerebrospinal fluid dynamics in the optic nerve subarachnoid space using diffusion weighted MRI in patients with idiopathic intracranial hypertension

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Introduction:
Idiopathic intracranial hypertension (IIH) is a neurological disorder characterized by elevated intracranial pressure (ICP). The ophthalmologic hallmark of IIH is papilledema (PE). Impaired contrast loaded cerebrospinal fluid (CSF) flow contrast within the optic nerve (ON) subarachnoid space (SAS) in 16 patients with IIH and PE by CT cisternography has been reported [Pircher et al. Frontiers Neurol 2018;9:506-507]. However, due to the invasive nature of CT cisternography, a non-invasive tool to examine CSF flow dynamics is desirable. By using MRI, the particles moving parallel to a magnetic field gradient undergo a phase shift, proportional to their velocity which can be used to determine the flow velocity range on diffusion weighted imaging (DWI). The aim of this study was to examine the CSF flow velocity in the ON SAS in patients with IIH and PE compared to healthy controls by applying DWI.

Methods:
Images of 10 patients with IIH (20 ONs, 50 ± 20 y.) and 11 healthy controls (22 ONs, 60 ± 13 y.) were acquired using a 3T whole body magnet with a 32-channel head coil using DWI with following parameters: b = 50 s / mm², TE / TR = 65 / 2000 ms, 6 slices, 1 mm slice thickness, each slice acquired 120 times. This allowed to estimate the flow velocities of coherent moving particles through phase contrast images as described in detail in Boye et al. 2018 [Boye et al. Clin Exp Ophth 2018;46:511-518]. Since the phase shift of the diffusion sequence is highly irregular, results are presented as Flow Range Ratio (FRR) which allows the comparison between different groups.

Results:
The mean FRR was 0.58 ± 0.1 in patients with IIH and 0.63 ± 0.05 in healthy controls. The difference between IIH patients and healthy controls was statistically significant (p < 0.05).

Conclusion:
CSF flow velocity was decreased in IIH patients with PE compared to healthy controls. This study reports reduced CSF flow conditions in ON SAS as a measure of FRR in IIH and PE patients. Impaired CSF flow is damaging for the ON and reduced CSF flow dynamics might be involved in the pathomechanism of PE in IIH. DWI can be a useful non-invasive tool to examine CSF flow dynamics within the ON SAS.
Feasibility and Safety of Angioplasty using Drug-coated Balloons in Ostial Vertebral Artery Stenosis: A Single-center Case-Series

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Objective:
Ostial vertebral artery stenosis (OVAS) is a relevant cause of acute ischemic posterior circulation stroke. Percutaneous trans-luminal angioplasty (PTA) might offer a promising treatment modality, but re-stenosis rate is high. So far, little is known about recanalization using drug-coated balloons (DCB) in OVAS. We aimed to show feasibility and safety of DCB-PTA in OVAS.

Methods:
Retrospective, mono-center case series of eight patients with ostial vertebral artery stenosis (≥ 50%) treated with PTA using a drug-coated balloon.

Results:
Median age was 72 years (IQR 61-80) with a 3:5 female: male proportion. Patients were treated with NeuroElutax SV and SeQuent Please NEO. Median pre-interventional stenosis degree was 73% (IQR 65-83) with a median lesion length of 6mm (IQR 4-10). Median post-interventional stenosis degree was 39% (IQR 24-50). All treated vessels remained patent. No major complications such as dissection, vessel perforation, hemorrhage or ischemic events occurred. Moreover, we did not detect any restenosis during a median follow-up period of 4.5 months.

Conclusions:
PTA using drug-coated balloons is feasible and safe in patients with ostial vertebral artery stenosis.
Computer processing of a large number of slices for pattern recognition in special areas of the brain

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Brain mapping is the next analytic step for presenting the results of structural and functional neuroimaging in the form of sets of maps that contain additional thematic analytical layers. Multilevel data integration in single map from different sources is a valuable method for the recognition and analysis of combined spatial-temporal characteristics of specific brain regions. Using this method primary experimental data received from sets of time series slices are integrated into a single space with single coordinate system. Every map’s level contains metadata regarding the data sources. Spatial data processing tools are effectively used for handling heterogeneous 2D slice images that are obtained using various brain scanning techniques.

Aims.
Here we present the possibilities regarding the use of GIS applications for the pattern recognition and comparative analysis of electronic medical records, with the ultimate goal of determining tumor area within the brain. The resulting data can be used to compare tumor size on the basis of aggregate data obtained over the course of several years using a variety of tomographic techniques.

Methods.
Analyzed electronic medical records contain images obtained using various CT and MRI equipment from the three year period and processed in accordance with the Digital Imaging and Communications in Medicine Standard (DICOM) (http://dicom.nema.org). Control primary image series were grouped by date and type of observation, total slices number was 2129. The data were processed using the open source software program QGIS (http://qgis.org), including additional analysis modules. The location of the tumor at different periods of time was contoured using isolines. Isoline calculation with a given tolerance is performed using Gdal_contour plugin (http://www.gdal.org)

Results.
Comparative analysis of tumor size was performed for each dataset using the precise coordinates for tumor borders. Maximum squares of the tumor, which were calculated by plane slices in 5 consecutive radiologic tests on different dates, are 208.16; 231.90; 250.60; 80.63 and 102.86 square millimeters.

Conclusion.
In our work we examined the feasibility of GIS technology for processing a large number of slices obtained from electronic medical records. Our results demonstrate that GIS applications can be useful for pattern recognition in neuroimaging.
What neuroradiologists should know about notochordal remnants: normal variants and pathology.

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Aim: the aim of this educational poster is to illustrate normal variants and pathology related to notochordal remnant. This should offer a better understanding of these entities and therefore facilitate their correct detection and diagnosis.

Methods:
we have conducted a search in our PACS over the last ten years by using the following search terms: Persistant craniopharyngeal canal, Thornwaldt cyst, ecchordosis physaliphora, benign notochoral cell tumor and chordoma. The cases were analyzed with CT and MRI and principal findings will be illustrated.

Results:
the most representative cases at level of the brain and spine of normal variants and pathology have been selected. Some lesions can appear as cystic abnormalities homogeneous / heterogeneous while others as a persistent canal and or mass. When one abnormality is detected, it is recommended to search for other concomitants abnormalities along the midline.

Conclusion:
a better understanding of normal variants and pathology related to notochordal remnants is useful for daily practice of every neuroradiologist and avoid incorrect and unnecessary investigations.
P169
Diagnostic value of susceptibility weighted imaging in clinical practice

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AIM
SWI is a high-spatial-resolution 3D gradient echo MRI technique, including magnitude, filtered phase, SWI (combined post processed magnitude and phase) and SWI minimum intensity projection. The aim of this educational poster is to illustrate the diagnostic value of susceptibility weighted imaging in clinical practice.

METHODS
We conducted a search in our PACS over the last three years to identify brain MRI at 1.5 and 3T with SWI, containing the following terms in the report: amyloid angiopathy, venous thrombosis, ischemic injury, arterial thrombus, developmental venous anomaly, cavernoma, capillary telangiectasia, diffuse axonal injury, hemorrhage, abscess, oligodendroglioma, multiple sclerosis, amyotrophic lateral sclerosis and Parkinson disease. We used magnitude and post processed SWI images on one hand, and phase images on the other to differentiate paramagnetic (deoxyhemoglobin, intracellular methemoglobin, hemosiderin and ferritin) and diamagnetic (calcium) substances: positive versus negative or no shift. Lesions were classified etiologically as vascular, neoplastic, infectious, neurodegenerative and traumatic diseases.

RESULTS
SWI allows identification of recent and chronic hemorrhage from different sources (trauma, neoplastic diseases with high-grade gliomas in particular, vascular malformations with cavernoma, capillary telangiectasia, as well as ischemia with hemorrhagic transformation) and calcifications (oligodendroglioma rather than astrocytoma for example). SWI detects iron deposits in key locations in some degenerative diseases, such as « motor band sign » along the precentral cortex in amyotrophic lateral sclerosis and the « absent swallow tail sign » suggestive of Parkinson's disease. SWI allows a good depiction of veins: engorged veins containing deoxyhemoglobin in venous thrombosis, dilated veins with increased oxygen excretion fraction delineating the mismatch area in arterial stroke; and the « central vein sign » in multiple sclerosis. Finally, SWI can differentiate abscess, with the « dual rim sign », from glioma.

CONCLUSION
The SWI imaging is a precious tool increasing the diagnostic sensitivity and specificity of MRI for a wide range of acute and chronic pathologies. Magnitude image is sensitive to the phenomenon of magnetic susceptibility and is currently part of the routine protocol for brain exploration particularly at 3T. In addition, phase mapping can identify variations in susceptibility between different tissues.
Micro-CT and dual-energy CT of the thrombus in acute ischemic stroke patients undergoing thrombectomy

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Introduction:
Thrombectomy has allowed to improve the outcome of patients with acute stroke. Selection of patients is based on brain tissue imaging. Little is known about the composition of the clot before intervention. The aim is to evaluate the capacity of dual-source CT to determine clot composition and compare it to micro-CT of the same clot after extraction.

Materials and Methods:
14 patients (10 male, 4 female, ages: 34-90) with acute stroke were included in this study. All patients underwent mechanical thrombectomy after dual-source CT (Siemens Force, Erlangen). A stroke CT protocol was performed with pre-contrast images as well as angio-CT, perfusion CT and post-contrast images. After extraction, the clot was imaged on a micro-CT. The images were loaded up to Osirix and regions of interest were defined on the clot and values were measured in Hounsfield Units. Clinical scores were assessed by the NIHSS scale. Recanalization was measured by the TICI score.

Results:
Recanalization was obtained in all patients of our series. clinical Hounsfield units were between 54 and 66, whereas the values measured in the clots were between 57 and 60. Time to recanalization was between 8 and 110 minutes.

Conclusions:
Clinical CT as measured by dual-energy CT reflects composition seen on micro-CT.
Imaging of arachnoid cysts and webs of the spinal canal

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AIMS
Imaging and differential diagnosis of cystic lesions of the spine can be challenging. The aim of this study is to describe the imaging characteristics of arachnoid cysts and spinal webs of the spinal canal based on a cohort of our institution, as well as to propose an optimal imaging protocol for these lesions.

METHODS
We retrospectively collected data from 40 patients (36 MRI studies and 4 CT studies in case when MRI was not performed) examined in our institution during the last 10 years and in whom an arachnoid cyst or arachnoid web was described in the report. Subsequently, a consensus second reading was performed for all images by two expert neuroradiologists. Subjects were 33 adults and 7 children (mean age: 47.8 years; range: 1-91 years), with a sex ratio 24F:16M, presenting for spinal MRI/CT between April 2009 and March 2019.

RESULTS
Arachnoid cysts’ diagnosis was far more frequent than webs’ (35 diagnoses of arachnoid cysts versus 1 diagnosis of spinal web and 4 cases with a differential diagnosis of both). Most arachnoid lesions were located in the dorsal segment of the spine (23/40 cases). Mass effect on the spinal cord or cauda equina/spinal roots was present in all cases. In 4 cases of CT imaging the suspicion of arachnoid cyst was based on the presence of bone scalloping of the spinal canal.

CONCLUSIONS
MRI is the study of choice for the diagnosis of cystic lesions of the spinal canal. Meticulous analysis of spinal MRI images with an adequate protocol including high resolution T2 images is necessary for the differential diagnosis between arachnoid cysts and spinal webs and the guidance of optimal therapeutic approach.
Dose-optimized computed tomography of the cervical spine in patients with shoulder pulldown: is image quality comparable with a standard dose protocol in an emergency setting?

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Aim:
Superimposing soft tissue and bony structures in computed tomography (CT) of the cervical spine (C-spine) is a limiting factor in optimizing radiation exposure maintaining an acceptable image quality. Therefore, we assessed image quality of dose-optimized (DO) C-spine CT in patients capable of shoulder pulldown in an emergency setting.

Methods:
DO-CT (105 mAs/120 kVp) of the C-spine in trauma settings was performed in patients with shoulder pulldown if C5 was not superimposed by soft tissue on the lateral topogram, otherwise standard-dose (SD)-CT (195 mAs/120 kVp) was performed. 34 DO (mean age, 68y ± 21; BMI, 24.2 kg/m² ± 3.2) and 34 SD (mean age 70 y ± 19; BMI 25.7 kg/m² ± 4.4) iterative reconstructed CTs were evaluated at C2/3 and C6/7 by two musculoskeletal radiologists. Qualitative image noise and morphological characteristics of bony structures (cortex, trabeculae) were assessed on a Likert-scale. Quantitative image noise was measured and effective dose (ED) was recorded. Parameters were compared using Mann-Whitney-U-test (p < 0.05).

Results:
At C2/3, DO-CT vs. SD-CT yielded comparable qualitative noise (mean, 1.3 vs. 1.0; p = 0.18) and morphological characteristics, but higher quantitative noise (27.2 ± 8.8HU vs. 19.6 ± 4.5HU; p < 0.001). At C6/7, DO-CT yielded lower subjective noise (1.9; SD-CT 2.2; p = 0.017) and better morphological characteristics with higher visibility scores for cortex (p = 0.001) and trabeculae (p = 0.03). Quantitative noise did not differ (p = 0.24). Radiation dose was 51 % lower using DO-CT (EDDO-CT 0.80 ± 0.1 mSv; EDSD-CT 1.63 ± 0.2 mSv; p < 0.001).

Conclusion:
C-spine CT with dose reduction of 51% showed no image quality impairment. Pulldown of both shoulders allowed better image quality at lower C-spine segments as compared to a standard protocol.
A neuromorphic system-on-a-chip detecting High-Frequency Oscillations in electrocorticography

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Aims:
High Frequency Oscillations (HFO) in electrocorticography are biomarkers for the Epileptogenic Zone (EZ). Automated HFO detectors ensure a prospective definition of a clinically relevant HFO but are currently not operating in real-time. Moreover, they demand high signal quality and aggressive filtering that entail large and power-hungry processors. Here we propose an end-to-end system for the neurosurgery room.

Methods:
We designed an analog signal acquisition frontend interfaced to an ultra-low-power Spiking Neural Network (SNN) in a System-on-a-Chip (SoC). This setup is capable of analog signal preconditioning and spatiotemporal pattern recognition in real-time. The analog frontend amplifier has a switchable gain (max 58dB) and two band-pass filters tuned to [80Hz-250Hz] and [250Hz-500Hz] to extract Ripples (R) and Fast Ripples (FR), respectively. An asynchronous delta modulator generates events projecting to a SNN of 7 neurons, the excitation and inhibition parameters are balanced, so the network achieves as many true positives as possible while avoiding false positives. The results are compared to a linear method performed directly on the input spikes. The detection is trained and tested on data taken from a published set of HFO that were validated against surgery outcome [2].

Results:
The analog frontend, simulated in standard 0.18μm CMOS technology, consumes 6.2 μW/Ch power and 0.15 mm²/Ch area on silicon. The classification spiking neural network provides 44.9% sensitivity and 80% specificity for detecting HFO over a test dataset, while the linear method provides 100% sensitivity and 4% specificity. The SNN is compatible to be implemented on a neuromorphic processor.

Conclusion:
Event-based techniques are capable of real-time bio-signal classification with extreme power-efficiency. Employing these schemes relaxes constraints on neural-recording amplifiers and filters, thereby enabling a battery-powered systems, which may aid the medical team during epilepsy surgery.
P174
Mu oscillations during emotional face processing in epilepsy patients and normal controls

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Aims:
Event-related desynchronization (ERD) of the sensorimotor mu-rhythm has been proposed as a signature of the activity of the human mirror neuron system and is sensitive to the perceptual processing of emotional faces (Moore et al., 2012). Patients with temporal lobe epilepsies (TLE) have been shown to display deficits in facial and prosodic emotion recognition (Meletti et al., 2003, 2009; Bonora et al., 2011; Broicher et al., 2012), but whether these deficits are associated with a reduction in mu ERD is not yet clear. The primary objective of this study is to differentiate between brain electrical responses of people with and without TLE to fearful and neutral facial expressions.

Methods:
13 patients diagnosed with TLE (9 female; age mean 40 ± 13SD; TLE side: 7 right, 4 left, 2 bifocal) and 26 healthy control subjects (HC, 17 female; age mean 40 ± 11SD) participated in the study. While viewing 128 brief films (each 3sec) of actor faces showing either neutral or fearful expressions, continuous EEG signals were recorded from Ag/AgCl scalp electrodes, referenced to the linked mastoids. The clips were shown on a computer screen in pseudo-randomized order with an interval of 2000 ± 250 ms of blank screen followed by a fixation cross (1000ms). To keep subjects engaged we mixed 16 control trials with pictures of faces marked with a red dot in between the clips and instructed subjects to push a button when control pictures appeared.

Results:
Both neutral and fearful faces lead to a significant ERD in mu band (8-13 Hz) at electrode position C4 in the TLE group (Wilcoxon test; neutral p = .009, fearful p = .005) and in the healthy control group (Wilcoxon test; neutral p = .001, fearful p = .001) beginning approximately 500ms after stimulus onset. Both groups showed approximately the same amount of significant ERD (HC 74%, TLE 77%). No statistical significant effect was found between the two conditions of emotion (fear vs neutral; TLE p = .331; HC p = .089) or the two subject groups (neutral p = .471; fearful p = .531).

Conclusion:
Mu component event-related desynchronization occurred to neutral and fearful faces in both groups. This desynchronization is believed to indicate a simulation of the action of producing an observed facial expression that is apparently independent from the valence of the facial expression.
Despite normal neurological bedside and electrodiagnostic, some patients with non-specific neck arm pain (NSNAP) have heightened nerve mechanosensitivity upon neurodynamic testing [1, 2]. It remains however unclear whether this is associated with a minor nerve injury. The aim of this study was to evaluate potential differences in somatosensory function among patients with unilateral NSNAP with and without positive neurodynamic tests and healthy controls. Quantitative sensory testing was performed in 40 patients with unilateral NSNAP; 23 with positive upper limb neurodynamic tests (ULNTPOS) and 17 with negative neurodynamic tests (ULNTNEG). The protocol comprised thermal and mechanical detection and pain thresholds as well as mechanical pain sensitivity, wind-up ratio and dynamic mechanical allodynia. All parameters were measured in the maximal pain area on the affected side as well as over the corresponding area on the unaffected side. Symptom severity, functional deficits, psychological parameters, quality of life and sleep disturbance were also recorded. Fifty-seven percent of patients with NSNAP had positive neurodynamic tests despite normal bedside neurological integrity tests and nerve conduction parameters. Clinical profiles did not differ between patient groups. Somatosensory profiling revealed a more pronounced loss of function phenotype in ULNTPOS patients compared to healthy controls. Hyperalgesia (cold, heat and pressure pain) was present bilaterally in both NSNAP group. The ULNTNEG subgroup represented an intermediate phenotype between ULNTPOS patients and healthy controls in both thermal and pressure pain thresholds as well as mechanical detection thresholds. In conclusion, heightened nerve mechanosensitivity was present in over half of patients with NSNAP. Our data suggest that NSNAP presents as a spectrum with some patients showing signs suggestive of a minor nerve dysfunction.
Muscle hypertrophy in a patient with multifocal motor neuropathy (MMN) – a case report

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Introduction:
Multifocal motor neuropathy (MMN) is a rare immune-mediated, purely motor neuropathy, characterized by asymmetric, progressive and predominantly distal muscle weakness without significant sensory involvement. Conduction block affecting the motor nerves is a characteristic finding of the disease. The clinical correlation is muscle weakness and an increased contraction response to muscle percussion. Muscle atrophy may occur late in the course of the disease. However, muscle hypertrophy in weakened muscles is rare and has been reported just in a small number of patients (1). Other positive motor symptoms as fasciculations, myokymia and cramps are reported more common.

Case report:
A 42 year old man presented with a 3 year history of gradually progressive, painless weakness of the right upper limb associated with marked muscle hypertrophy, fasciculations and cramps involving the forearm extensor muscles. Clinical examination showed moderate to severe flaccid paresis mainly of wrist, finger and thumb extension. Fasciculations, myokymia and cramps were noted in these hypertrophied and weakened muscles. Sensation was normal to all modalities. CSF analysis showed slightly raised protein. Antigangliosid GM1 antibodies were negative. Nerve conduction studies revealed right radial neuropathy with proximal conduction block. Needle EMG demonstrated fasciculation potentials as well as cramps in radial innervated muscles. Overall the clinical history and paraclinical results raised the diagnosis of an immune mediated motor neuropathy. Therefore the patient was commenced on IVIg infusion. The weakness improved rapidly in the first weeks after the infusions. In a clinical follow up 3 months later the muscle hypertrophy, fasciculations and cramps were resolved.

Conclusion:
Focal hypertrophy in demyelinating neuropathies with conduction block is not common, but has been described before (1). Spontaneous motor unit activity in affected muscles, e.g. fasciculations and myokymia arise from terminal branches of blocked axons distal to the chronic conduction block. It is suggested that this ectopic activity is caused by the hyperexcitability of the axons (2) and consecutively may cause muscle hypertrophy, when occurred over years. Experimental nerve excitability measurements with threshold tracking technique shows membrane hyperpolarisation distal to the site of conduction block in MMN (3).
P177 Low-intensity sinusoidal electrical stimulation in patients with peripheral neuropathic pain

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Background and aims:
Slowly depolarizing transcutaneous currents by low-intensity sinusoidal stimulation have been demonstrated to preferentially activate C-nociceptors in human skin. Thereby, ongoing stimulation revealed profound accommodation of C-fibers in healthy subjects, but increased pain in patients with neuropathy. We verified this observation in patients suffering from peripheral neuropathic pain and additionally investigated their responsiveness to depolarizing half-sinewave stimulation.

Methods:
19 patients (age 51.1 ± 14.8yrs) suffering chronic pain for 9.2 ± 7.9yrs were diagnosed as mononeuropathy (n = 4), polyneuropathy (n = 9), radiculopathy (n = 5) and plexopathy (n = 1). Sinusoidal stimuli of 4 Hz were delivered at intensities of 0.05 – 0.4 mA for 2.5 (10 pulses) and 60 sec to the patients affected and non-affected skin sites. Also, half-sine wave stimuli of 500 ms duration and 0.2 – 1 mA intensity were administered and patients requested to estimate pain intensity for each stimulus paradigm (sinusoidal / half sine-wave) on a numeric rating scale (NRS, endpoints 0 to 10).

Results:
Regardless the delivered current intensity, sinusoidal stimuli (10 pulses) were perceived less painful at the affected versus non-affected body sites (n.s., p > 0.1, ANOVA). Half-sinewave pulses were felt more painful at the affected versus non-painful skin site (p < 0.005, ANOVA), particularly at supra-threshold intensities (0.8 and 1 mA). Pain ratings upon continuous sinusoidal stimulation (60 sec, 0.2 mA) remained at almost same levels at the non-painful skin (NRS 2 - 3) during the whole 1 minutes stimulation. In contrast, at the neuropathic skin sites, stimuli were rated at onset with about NRS 1 - 2 and perceived increasingly painful over time (NRS ~ 3 at 60 sec). Correspondingly, the increase of pain between the initial 5 sec and the end of stimulation was three- to four-fold at the painful body site.

Conclusions:
Prolonged electrical stimulation of C-nociceptors caused a gradually increasing pain sensation in symptomatic skin, suggesting an enhanced axonal excitability in painful neuropathic skin. Significantly elevated pain upon half-sinewave stimuli at this body site indicate increased supra-threshold responses of particularly polymodal C-nociceptors. Our results suggest that the tetrodotoxin (TTX) sensitive sodium channel NaV1.7 might be underlying the observed axonal hyperexcitability in neuropathic pain patients.
P178
The relation between neuronal firing, local field potentials and hemodynamic activity in the human amygdala in response to an aversive dynamic visual stimuli

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Aims:
Aversive visual stimulation elicits neuronal responses in the human amygdala but a comprehensive understanding of the underlying electrophysiology is still lacking.

Methods:
We recorded intracranial electroencephalography (iEEG), hemodynamic responses and single neuron activity from the amygdala of patients with epilepsy who viewed dynamic visual sequences of fearful faces (aversive condition), interleaved with sequences of neutral landscapes (neutral condition).

Results:
Comparing aversive versus neutral stimuli, we observed enhanced high gamma power (HGP, >60 Hz) in the amygdalae outside the Seizure Onset Zone (9/14 nSOZ-amygdalae, p=0.019). Delta power (1-4 Hz) was decreased in 11/11 nSOZ-amygdalae and also in 2/3 amygdalae within the SOZ. Across participants, the HGP enhancement occurred predominantly during the first 2 s of aversive sequence viewing, while the delta reduction lasted for the whole sequence (i.e. 24 s). In 5 participants with implanted microwires, neuronal firing rates were enhanced following aversive stimuli, and exhibited positive correlation with HGP and BOLD signal.

Conclusion:
While aversive visual stimulation modulated power in the delta / high gamma frequency bands and in neuronal spiking within the amygdala, HGP responsiveness differentiated between healthy and epileptogenic amygdalae and may contribute to presurgical evaluations for epilepsy surgery. In summary, we provide a comprehensive investigation of amygdalar responses to aversive stimuli, ranging from single-neuron spikes to local field potentials and hemodynamic responses.
Evaluation of temporal integration of central auditory processing in patients with Tinnitus

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Since the work of Brocca, the Central Auditory Processing has been the target of multiple studies. The mechanisms that are performed in the central pathways and neuronal activity assigned to the CAP allow the individual to locate the sound, perform auditory discrimination, recognize auditory patterns, present resolution, integration and temporal ordering and interfere in hearing in acoustic competitive environments. There are few papers that associate alterations in the CAP and tinnitus. The objective is to evaluate the temporal integration of CAP in individuals with tinnitus, and with a hearing loss of less than 40 dB. The instrument used was a dichotic temporal integration test, the Pattern Duration Test. The sample consisted of 58 individuals, from the ENT Consultation of HFAR-Porto, with a mean age of 56.6 years (27-66; sd 9,09), 37 men, mean hearing of 26.1 dB (11, 9-40.0 dB, sd 7.16) and with an average complaint of 4.96 years (0.5-40.0; sd 7.37). The results obtained for the PDT are an average of 83.2% (44-100; dp 14,11). The t-test to compare with normality, which is 88.5%, shows a value of -2.777, which with a significance of 0.008, allows to state that the sample has significantly lower values than normality. These data may reveal some alteration in the auditory cortex associated with the recognition of the duration pattern, or effect of the presence of tinnitus, responsible for the recognition of the duration pattern. A comparison of means and gender showed slightly lower values for female, but without statistically significant differences was performed. An analysis was performed between the results obtained and age using the Pearson test, and no correlation between age and CAP was obtained. Conclusion: These results agree with what would be expected, from the literature, which allows us to assume that we are dealing with alterations that are located mainly in the peripheral area of the hearing. In certain situations, the tasks of recognizing the duration pattern may be compromised by involvement of the cortex and auditory pathways. For confirmation, a future study using different intensity values to confirm PDT results and another type of test to evaluate other components of the CAP associated with time processing is suggested.
Debilitating and Inoperable Common Peroneal Nerve Rupture Following Minor Knee Trauma: A case report

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Aims and Background:
Common peroneal nerve palsy is considered to be the most common[1,2] peripheral nerve injury in the lower extremities. It may be caused by non-traumatic[3] as well as by traumatic[4] injuries. In traumatic peroneal nerve injuries the risk of peroneal nerve injury tends to correlate with the energy and mechanism of the knee injury[4]. In sports it is influenced by the type of sport and its associated risk of trauma (e.g. high risk in American football or striking combat sports vs. low risk in running or cycling)[4] as well as by the number of people exposed (e.g. common for skiing vs. uncommon for combat sports, though exposures vary widely depending on the geographic region). The risk of traumatic peroneal nerve injury in sports is considered to be high in contact sports and in injuries of contusion/dislocation, particularly those involving the posterolateral soft tissue of the knee[4].

Case report:
We present a case of a young patient who suffered a devastating peroneal nerve rupture following a relatively mild-seeming overextension injury of the left knee with injuries to the posterolateral knee compartment including injuries to the lateral collateral ligament and the fibular insertion of the biceps tendon. Due to a total rupture of the peroneal nerve with full retraction of the entire nerve tissue far proximally inside the epineurium there was no surgical option to reconstruct the nerve, neither by suture nor by grafting, even though the peroneal and ischiadic nerve were explored to as far a proximal point as surgically feasible. These findings left a young patient with a poor prognosis, excluding all chances of recovering near-normal function of the left peroneal muscles. Results: We present the findings of the electrophysiological and nerve ultrasound studies and review the literature on the injury mechanisms and management options for irreparable peroneal nerve damage. We discuss the consequences and possible caveats in the future management of such cases.

Conclusion:
To our knowledge this is the first case of an irreparable peroneal nerve rupture following a relatively mild injury (no high-speed injury, no open trauma, no high-energy sport), including one ligament rupture and a partial tendon rupture.
P181
Patients’ Real-World Experience with Erenumab (Aimovig®) in the Prevention of Migraine in Switzerland

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Aims
In July 2018 erenumab was approved in Switzerland by Swissmedic. Erenumab is a monoclonal antibody targeting the CGRP receptor (calcitonin gene-related peptide receptor) for the prevention of migraine. Since introduction of Aimovig® to the public in Switzerland, it has not been analyzed how patients respond to the medication in daily clinical practice. Since August 2018 the Headache Center Hirslanden Zurich (HC) has been treating 132 patients with the new medication until February, 2 2019. With this high number of patients the HC plays a leading role in the treatment of migraine with erenumab. With a simple data collection we aim to obtain preliminary real-world data from patients in Switzerland. Post marketing erenumab data from other countries are not available until now.

Method
Patient data from HC were obtained by a very short and simple questionnaire. 35 patients reported from September to December 2018 on the efficacy and tolerability after starting the treatment with erenumab. We asked patients about changes in their headaches/migraine frequency (1) and intensity (2), changes in their quality of life (3) and about their tolerability of the product (4) after taking the first or consecutive doses of erenumab.

Results
Overall, 24 patients (68.5 %) stated that their headaches were better, of which 21 (60 %) observed reduced headache frequency and 17 (48.5 %) reported less severe headache intensity. 17 patients (48.5 %) observed improved quality of life (multiple answers were possible). 2 patients could reduce their migraine attacks to zero after starting the treatment. In contrast, only 10 patients (28.5 %) observed no improvement in their headache status. Good tolerability was reported by 24 (68.5 %) patients. No severe side effects were reported. The most common side effect was constipation in 6 patients (17 %).

Conclusion
With the simple data we aim to provide an initial impression of patients’ real-world experiences with erenumab until more reliable data will be collected and published. More than 2 / 3 showed immediate improvement in their migraine. Our preliminary Aimovig data correspond nicely to results from studies (Reuter et al., 2018, Tepper et al., 2017) as well as practical experiences in other countries (USA).
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The SQUARE study design: A multi-centric, non-interventional study to evaluate the impact of erenumab on quality of life in a real-world population with migraine.

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Aims:
Real-world evidence has become an important cornerstone for evaluating newly registered pharmaceuticals. Erenumab (Aimovig), an antagonist of the calcitonin gene-related peptide (CGRP) receptor, received Swiss marketing authorization as a migraine prophylaxis in July 2018 [1]. Here, we present the design of the non-interventional SQUARE study (Swiss QUality of life and healthcare impact Assessment in a Real-world Erenumab treated migraine population, CAMG334ACH01) evaluating erenumab in clinical practice.

Methods:
A total of 193 adult patients with migraine will be enrolled in approx. 20 sites across Switzerland. Patients are included upon informed consent if they are willing and able to complete questionnaires and diaries. Patients with prior use of CGRP (receptor)-based therapies or recent use of investigational drugs are excluded. Visits at 0, 3, 6, 12, 15, 18, and 24 months (± 1 month) were chosen to match those required for reimbursement in Switzerland [2], to monitor the treatment interruption mandatory for reimbursement after 12 months, and to capture long-term effects. Patients who discontinue or switch therapy are also followed. Headache Impact Test (HIT-6) after 6 months compared to baseline was chosen as primary endpoint. Other endpoints include modified (monthly) migraine disability assessment test (mMIDAS) and impact of migraine on partners and adolescent children (IMPAC). Integration of the “Migraine Buddy” mobile application allows collection of migraine days and acute migraine medication days at high resolution without imposing additional burden to study sites.

Results:
SQUARE was approved by the competent ethics committee on Feb 13th, 2019, and the first patient was recruited on Feb 18th, 2019. Primary results are expected in 2021.

Conclusions:
This study is among the first to describe the impact of erenumab in a real-world setting. Similar studies will be conducted in other countries, allowing pooling and cross-comparison. Results from this endeavor will corroborate the body of evidence available for erenumab in medical practice.
Assessment of the Efficacy of Erenumab During the Open-Label Treatment (13–24 Weeks) of Subjects with Episodic Migraine Who Failed 2–4 Prior Preventive Treatments: Results of the LIBERTY Study

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Objective:
To assess efficacy of erenumab in the first three months of the open-label extension phase (OLEP; 13–24 weeks) of the LIBERTY study.

Background:
Results of the LIBERTY study (NCT03096834) demonstrated efficacy of erenumab 140 mg in episodic migraine patients with prior preventive treatment failures.

Design/Methods:
In the double-blind treatment phase, 246 patients were randomized to placebo and erenumab 140 mg for 12 weeks, following which, patients completing that phase (N=240) were enrolled in OLEP, to receive monthly erenumab 140 mg. Outcomes measured monthly throughout to week 24 were achievement of at least 50%/75%/100% reduction in monthly migraine days (MMD), change from double-blind treatment phase baseline in MMD, monthly acute migraine-specific medication days (MSMD), Headache Impact Test (HIT-6TM) total score, everyday activities (EA) and physical impairment (PI) as measured by the Migraine Physical Function Impact Diary (MPFID); in the overall population, patients on continuous erenumab and in patients switching from placebo to erenumab.

Results:
Overall, 228/240 (95.0%) patients completed the 24 week visit of the OLEP. In the overall population at Week 24, 39.2%, 15.9% and 7.0% patients achieved ≥50%/≥75%/100% reduction in MMD. The mean (standard deviation [SD]) change from double-blind treatment phase baseline in MMD was −2.7 (4.4) and −1.4 (3.0) in MSMD; and −7.6 (8.0), −2.5 (9.2) and −4.0 (9.0) in HIT-6 TM, MPFID-PI and MPFID-EA scores respectively. Patients with continuous use of erenumab showed sustained efficacy in all outcomes assessed. Patients who switched from placebo to erenumab in the OLEP showed improvement from the first measurement at Week 16 on all outcomes assessed.

Conclusions:
Efficacy of erenumab was sustained throughout 24 weeks in a hard to treat patient population with multiple prior preventive treatment failures. Overall, efficacy data over 24 weeks (assessed over weeks 13–16, 17–20 and 21–24) was generally in line with prior erenumab trials.
Benefit-Risk Assessment of Galcanezumab versus Placebo for the Treatment of Episodic and Chronic Migraine: Results from EVOLVE-1, EVOLVE-2, and REGAIN Clinical Trials

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Aim:
To evaluate the benefit-risk profile of galcanezumab (GMB) versus placebo (PBO) for the treatment of episodic (EM) and chronic migraine (CM) in adults.

Methods:
Data from three pivotal phase 3 trials of GMB were used to estimate response rates (RR), a clinically meaningful outcome for decision makers, based on monthly migraine headache day (MHD) reductions in patients with EM (EVOLVE-1 and EVOLVE-2; 6-month treatment duration) and patients with CM (REGAIN; 3-month treatment duration). Corresponding numbers needed to treat (NNT) for one patient to benefit from drug and numbers needed to harm (NNH) for one patient to be harmed by drug based on discontinuation due to adverse events (DCAE) were estimated for each trial separately.

Results:
For EVOLVE-1, NNT were 5 and 6 with GMB 120 and 240 mg, respectively, at 30% RR, 5 for both doses of GMB at 50% RR, and 6 for both doses at 75% RR; EVOLVE-2: 5 for both doses of GMB at 30% and 50% RR, and 7 and 6 with GMB 120 and 240 mg, respectively, at 75% RR; REGAIN: 8 for both doses of GMB at 30% RR, 9 for both doses at 50% RR, and 40 and 24 with GMB 120 and 240 mg, respectively, at 75% RR. In all trials, the proportion of patients achieving these RRs was significantly higher in patients treated with GMB 120 mg and 240 mg versus those treated with PBO. Corresponding NNTs were similar across trials (5 to 9) with the exception of those obtained for ≥ 75% RR in REGAIN (24 to 40). Across all trials, NNH based on DCAE were 92 and 57 (EVOLVE-1), 213 and 46 (EVOLVE-2), and not relevant as higher risk with placebo (NR) and 295 (REGAIN) with GMB 120 mg and 240 mg, respectively.

Conclusion:
In all trials, GMB showed a favorable benefit-risk profile versus PBO based on low NNTs for RR and higher NNH for DCAE. Higher NNTs observed in patients with CM may be due to higher disease burden (higher baseline MHD and greater disability) of these patients and shorter treatment duration (3 vs. 6 months).
Patients' Experience with Medical Cannabis in the Treatment of Migraine

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Aims
Cannabis has an established history in the treatment of headache disorders (Lochte et al., 2017). It has been used for both symptomatic and prophylactic treatment of headache. Between 1839 and its ban in the United States in 1937, cannabis was highly esteemed as a headache remedy by prominent physicians (Lochte et al., 2017). However, no placebo-controlled clinical trials on the efficacy of cannabis in headache treatment have been published. In Switzerland, CBD (cannabidiol) preparations (with less than 1 % tetrahydrocannabinol) are approved by the Bundesamt für Gesundheit for migraine treatment. With a retrospective analysis, we aim to obtain first insights on the efficacy of medical cannabis in the prophylactic treatment of migraine in Switzerland.

Method
In December 2018 and January 2019, the Headache Center Hirslanden Zurich conducted a short survey on 41 patients who used at least one of the three medical cannabis products (Sativex®, Sativa-Öl®, Cannabisöl®) approved in Switzerland (n=41). The sample consists of 29 (71 %) females and 12 (29 %) males. The patients reported retrospectively on changes in their 1) migraine, 2) general condition, 3) sleep quality, 4) tone of neck muscles, and on 5) tolerability since the first intake of the medication (13 patients in 2018, 13 patients in 2017, 8 patients in 2016, and 7 patients in 2015).

Results
10 patients (24 %) reported a reduction in migraine, 13 (32 %) stated to feel generally better, 19 (46 %) observed improved sleep quality, and 7 (17 %) felt less tension in neck muscles. In contrast, 2 patients (5 %) stated their migraine worsened, 3 (7 %) said they generally felt worse, 2 (5 %) reported a reduction in sleep quality, and 10 (24 %) observed fatigue. Some patients reported on mood changes (4 negative, 4 positive), increased appetite (2), and nausea (3).

Conclusion
With our retrospective analysis we aimed to provide an initial impression of patients' experiences with medical cannabis in their migraine treatment. This survey shows that medical cannabis helped in almost one out of four to reduce their headaches. More importantly, cannabis helped patients to regulate their sleep quality (in almost half of patients) and improve their general well-being. This preliminary analysis corresponds to experiences in other medical fields: medical cannabis is able to help in some cases; however, patients' reactions vary widely.
FIREFISH Part 1: 1-year results on motor function in babies with Type 1 SMA

Aim:
Type 1 spinal muscular atrophy (SMA) is a debilitating neuromuscular disease, in which untreated babies fail to achieve major motor milestones and typically die before 2 years of age. SMA is caused by reduced levels of the survival of motor neuron (SMN) protein from deletions and/or mutations of the SMN1 gene. A second SMN gene, SMN2, produces low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing to increase SMN protein levels. Here, we aimed to determine the effect of risdiplam on motor function in babies with Type 1 SMA in the FIREFISH Part 1 dose-finding study.

Methods:
FIREFISH (NCT02913482) is an ongoing, multicenter, open-label, operationally seamless study of risdiplam in babies aged 1-7 months at enrollment with Type 1 SMA and two SMN2 gene copies. Exploratory Part 1 (n=21) assesses the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels. Confirmatory Part 2 (n=40) is assessing the safety and efficacy of risdiplam.

Results:
In a Part 1 interim analysis (September 2018), 93% (13/14) of babies had ≥4-point improvement in CHOP-INTEND total score from baseline at 8 months (Day 245; median change of 16 points). From baseline to Day 245 the number of babies meeting the following HINE-2 motor milestones increased: full head control (6/14, 43%), horizontal or upward kicking (7/14, 50%), rolling to side or from prone to supine (4/14, 29%) and sitting with or without support (6/14, 43%). To date, no drug-related safety findings have led to withdrawal of any baby from the study and no significant ophthalmological findings have been observed. One-year motor milestone data will be presented from FIREFISH Part 1.

Conclusions:
In the FIREFISH Part 1 dose-finding study, risdiplam improved motor function in babies with Type 1 SMA. FIREFISH Part 2 is ongoing worldwide.
Resting State Thalamocortical Networks during Early Lifespan and their Relation to Cognitive Performance

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Background
The thalamus has complex anatomical and functional connections with the rest of the brain and is involved in a diverse range of cognitive processes. However, developmental characteristics of thalamocortical connections and their relation to cognitive processes remain largely unknown. Therefore, the aim of the present study was to investigate developmental characteristics of thalamocortical connectivity patterns and their potential relation to cognitive performance.

Method
Resting state functional connectivity between the thalamus (subdivided into 679 voxels) and eight cortical functional networks (default mode, left/right executive, dorsal attention, salience, sensorimotor, visual and auditory) was analyzed in a large healthy human pediatric sample (N=101, aged 5 to 25, mean 14.4). To examine developmental effects in all networks, the sample was subdivided into different age groups (young children: 5-8; children: 9-11; adolescents: 12-15; young adults: 16-25). Cognitive performance, including nonverbal IQ, processing speed, inhibition and switching was assessed using neuropsychological tests.

Results
All eight resting state networks showed strong functional connections to the thalamus at rest, with no effect for sex (p > 0.05). However, group analyses revealed significant increases in thalamocortical connectivity strength in the salience and the left executive network throughout development. In contrast, thalamocortical connectivity of the attention network weakened throughout development. All remaining resting networks showed no age dependent change of functional connectivity. Brain-behavior analyses revealed significant positive correlations between processing speed and thalamocortical connectivity of the salience and left executive network. Moreover, individual inhibitory abilities were negatively correlated with thalamocortical connectivity of the dorsal attention network.

Conclusion
Thalamocortical networks with different functional roles are characterized by specific maturational trajectories. Networks involved in higher-level cognition co-evolve with the maturation and establishment of higher order cognitive functions throughout childhood and adolescence. Our findings are important to shed light on the maturational effects of thalamocortical interactions and underlying mechanism of neurological and neuropsychological diseases associated with the thalamus.
P188
Long-term follow-up of vein of Galen malformation: improvement in management is still needed

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Objective
To describe the long-term outcomes at the time of schooling of children with vein of Galen aneurysmal malformation.

Methods
Retrospective observational study on a consecutive cohort of patients with vein of Galen aneurysmal malformation. We included patients with at least one Francophone parent, born between January 1, 2006 and December 31, 2009 and aged between 6 and 11 years at the time of long-term evaluation. The neurological outcome was assessed with the KOSCHI score and eight neurological and behavioral items from the Rivermead post-concussion questionnaire.

Results
During this period, 127 patients were taken in charge. Of these, all 52 patients with at least one Francophone parent (5 fetuses and 47 children) were included. At the long-term evaluation time-point, 33 patients were alive and 19 patients had died. Risk of post-natal death was associated with severe neonatal cardiac failure (p=0.018) or iso- or supra-systemic pulmonary hypertension (p=0.009). Among the 33 survivors, 58% had a good outcome with normal schooling and 32% a poor outcome, nine of which had specialized schooling and six a severe psychomotor retardation. Moreover, among the good-outcome patients, a large proportion had neurodevelopmental alterations with potentially disabilities.

Conclusion
Long-term outcome of patients with vein of Galen aneurysmal malformation appears to be less favorable than outcome described at the short- and medium-term, even in the absence of encephalomalacia injury at birth. Even patients with good outcome often have minor neuropsychological disorders that may have repercussions on learning and requiring routine testing with appropriate rehabilitation or medical management.
Update from SUNFISH Part 1: Safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data in patients with Type 2 or 3 spinal muscular atrophy (SMA) treated with risdiplam (RG7916)

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Aim
SMA is caused by reduced levels of survival of motor neuron (SMN) protein from deletions and/or mutations of the SMN1 gene. While SMN1 produces full-length SMN protein, a second gene, SMN2, produces low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA to increase SMN protein levels. The objective of this study was to determine safety, tolerability and PK/PD in patients with Type 2 or 3 SMA who received risdiplam for the duration of the SUNFISH Part 1 dose-finding study, and exploratory efficacy data in patients treated for at least 1 year in Part 1.

Methods
SUNFISH (NCT02908685) is an ongoing multicenter, double-blind, placebo-controlled, operationally seamless study (randomized 2:1, risdiplam:placebo) in patients aged 2-25 years, with Type 2 or 3 SMA. Part 1 (n=51) assesses safety, tolerability and PK/PD of different risdiplam dose levels. Pivotal Part 2 (n=180) is assessing the safety and efficacy of the risdiplam dose level that was selected based on results from Part 1.

Results
SUNFISH Part 1 included patients of broad age ranges and clinical characteristics (functional level, scoliosis and contractures). To date, a sustained, >2-fold increase in median SMN protein versus baseline was seen after 1 year of risdiplam. Adverse events have been mostly mild, resolved despite ongoing treatment and reflect the underlying disease. No drug-related safety findings have led to withdrawal. Safety, tolerability and PK/PD will be presented from all patients in Part 1. Exploratory efficacy will be presented in patients treated for ≥1 year.

Conclusions
To date, risdiplam has been shown to be well tolerated and leads to sustained increases in SMN protein. Despite not being designed and powered to detect efficacy, patients on risdiplam experienced improvement over 12 months on the Motor Function Measure versus natural history.
Craniocervical artery dissection in childhood – a systematic review of the literature and results from the Swiss Neuropaediatric Stroke Registry

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Background
Craniocervical artery dissection (CCAD) in children has mainly been described in stroke studies. However, the incidence of CCAD has not been reported, and little is known about CCAD presenting with non-stroke symptoms. The goal of this study was to gain a comprehensive overview on CCAD in childhood including data from a population based ischemic stroke study, and summarizing the evidence of other presenting forms of pediatric CCAD.

Methods
Population based observational study, the Swiss Neuropaediatric Stroke Study (SNPSR) and a systematic review of the literature.

Results
Out of 203 publications, we extracted 382 pediatric CCAD cases, 12 patients with CCAD were registered in the SNPSR. Of the total of 394 patients, 120 were female. Thirty-four were neonates; the remainder had a median age of 9 (IQR 6-14) years. Trauma in the month prior to CCAD was described in 195 (33 severe, 125 mild, severity unknown in the remainder). Presenting signs and symptoms were mostly due to ischemia (320 cerebral, 1 spinal), followed by intracranial hemorrhage (36), and non-stroke local mass effect (12). CCAD was localized in the anterior circulation in 215, in the posterior circulation in 172 and in both in 7. The most commonly involved vessels were the internal carotid artery (161) and the vertebral artery (132). Localization was extracranial in 50%, intracranial in 45% and both intra- and extracranial in 5%. Forty-three children died. Survivors had a good outcome defined by independence in activities of daily living in 66%. CCAD-recurrence was described in 7 patients.

Conclusion
CCAD has been described throughout all pediatric age groups including neonates, with preceding trauma being the single most important risk factor. Presentation is largely due to cerebral ischemia or hemorrhage, exceptionally due to a local mass effect only. Unlike in adults, intracranial is almost as frequent as extracranial localization. The case fatality rate is high, but two-thirds of survivors have a good outcome, with CCAD recurrence being very rare.
P191
Functional and cognitive outcomes in patients with covert cognition during acute intensive rehabilitation

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Aims
To investigate the functional and cognitive evolution of acute patients presenting with cognitive motor dissociation (CMD) during intensive neurorehabilitation.

Methods
141 patients admitted to the Acute Neurorehabilitation Unit (Lausanne, Switzerland) were retrospectively included. We investigated their functional and cognitive status at admission and on discharge using several outcome and neuropsychological scales (Glasgow Outcome Scale, Early Rehabilitation Barthel Index, modified Rankin Scale, Disability Rating Scale, Rancho Los Amigos Levels of Cognitive Functioning, Functional Ambulation Classification Scale). Patients were separated into three groups according to their clinical diagnosis at admission using the Coma Recovery Scale-Revised [1] complemented by the Motor Behaviour Tool [2] which allows to identify patients with CMD [3]. Three groups were CMD vs true Disorders of Consciousness (DOC) vs non-DOC. We performed Uni- and multivariate analyses to compare the different functional and cognitive outcomes.

Results
Overall, the results indicated that patients with CMD were significantly associated with a better functional outcome and potential of improvement than patients suffering true DOC. Furthermore, outcomes of CMD patients did not significantly differ from those of non-DOC patients. Finally, at discharge approximately 30% of CMD patients were considered not having recovered consciousness if assessed only with the CRS-R.

Conclusion
Our findings support the fact that CMD patients constitute a separate category of patients with different potential of improvement and functional outcomes than patients suffering from DOC. This reinforces the need for them to be recognized as soon as possible, as it could have a direct impact on patient care and influence life and death decisions.
P192
Early electromyographic evaluation of the ICU-acquired Weakness in septic shock patients ventilated longer than 72 hours: preliminary results

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Background
Patients hospitalized in the Intensive Care Unit (ICU) are at risk for developing severe disabilities, ICU-acquired weakness in particular. Immobilization in bed and sepsis are known risk factors. ICU-acquired weakness has been associated with prolonged mechanical ventilation duration, increased in ICU and hospital length of stay, significant decrease in functional capacity, and higher mortality. An early screening using a specific diagnosis protocol could help improving the management of patients suffering from ICU-acquired weakness.

Aim
To demonstrate the feasibility and acceptability of a simplified nerve conduction protocol. This protocol is designed to significantly earlier detect ICU-acquired weakness in patients suffering from septic shock and ventilated for more than 72 hours.

Methods
A prospective study is currently conducted at the ICU (CHUV, Lausanne). All the participants undergo a physical examination of muscle strength and a simplified nerve conduction protocol, the peroneal nerve test (PENT). Each participant is tested once a week until pathologic responses are detected or discharge from the ICU.

Results
Fifteen patients have been included so far. Two patients withdrew consent. From the thirteen patients analyzed four were females (31%) and 9 (69%) were male participants. The protocol was successfully performed on each patient and indicated whether the results were pathologic or not. Three patients (23%) presented normal results, four patients (31%) showed signs of polyneuropathy and six patients (46%) of myopathy. Mean time elapsed between ICU admission and first intervention protocol was of 97,84 ± 27,26 hours.

Conclusion
Preliminary results endorse the initial hypothesis of the study. A prompt detection would enable an early interdisciplinary treatment and would prevent usual complications and severe disabling consequences.
Benefits and Harms of Levodopa in Stroke Rehabilitation.

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Background and Objective
Levodopa given in addition to rehabilitative therapies may be associated with a patient-relevant enhancement of functional motor recovery in stroke patients. However, benefits and harms of this treatment approach are not well known.

Methods
We performed a literature search in order to retrieve clinical data about the use of levodopa given with the idea to enhance motor performance. This includes studies in healthy subjects as well as in stroke patients. We focused on (i) the frequency of adverse events including mortality and on (ii) data about efficacy. For the latter we conducted a rapid systematic review and a preliminary meta-analysis searching Medline, the Cochrane Library, and clinicaltrials.gov using “stroke” AND “levodopa” combined with standard filters for randomized controlled trials (RCTs).

Results
In healthy subjects, levodopa compared to placebo was associated with faster and better learning and with a better motor performance. Safety concerns were absent. In stroke patients, clinical and observational studies published as full papers (n=6) showed that adverse events were infrequent and no death was reported. Including DARS, a UK-based ‘Dopamine-in-Rehabilitation-of-Stroke-trial (DARS), not yet published as full paper, we identified 6 RCTs comparing levodopa versus control in stroke patients, for which data on motor outcome stratified to the type of study treatment were publically available. We observed a small non-significant trend towards a more favorable motor outcome in levodopa-treated stroke patients as compared to control patients (Standard Mean Difference [95% Confidence Interval]) =0.15 (-0.25 to 0.55)). Importantly, the heterogeneity between trials was considerable (I²=67%). Qualitative or quantitative data about the neurorehabilitative therapy given in combination with levodopa or control were available in only 1 out of 6 RCTs. Two further RCTs are currently recruiting. The protocol of a Cochrane review is in preparation.

Conclusion
There is scope for benefit from applying levodopa in addition to rehabilitative therapy in stroke patients. More solid trial data is required to ensure that this approach is both safe and effective. Thus, participation in the ongoing trials is recommended, in particular as the importance of the co-administered rehabilitative therapy sessions is addressed.
Salivary cortisol as a biomarker for stress level in acute patients with severe brain injuries: A feasibility study

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Background
Salivary cortisol is a safe and non-invasive measure of hypothalamic-pituitary-adrenal axis functioning, and is a commonly measured biomarker of the human stress response. Natural environments are recognized to contribute to healing and mediate the negative effect of stress.

Aims
The primary aim of this pilot study is to determine feasibility and acceptability of a salivary cortisol collection protocol for acute severely brain-injured patients. A secondary aim is to evaluate the influence of exposure to natural settings compared to enclosed rooms on salivary cortisol concentration as an index for the level of stress.

Methods
We will conduct a prospective randomized design at the acute neurorehabilitation unit (CHUV, Lausanne). Patients will be exposed to two conditions: an enclosed room in the hospital and a therapeutic garden located in the enclosure of the hospital. In both indoor and outdoor conditions, they will be put at rest without stimulation. At baseline and at follow-up (10 minutes after the beginning of the condition), salivary cortisol will be measured.

Hypotheses
We expect to demonstrate the feasibility and acceptability of salivary cortisol collection in a sample of severely brain-injured patients. Furthermore we expect a decrease in salivary cortisol in the outdoor condition, hence indicating the positive effect of natural environments on the stress level of patients with severe brain injuries. Such effect would be very valuable to endorse the restorative benefits of nature as a significant resource for early neurorehabilitation.
Tendon vibration is able to evoke illusory sensation of movement due to closing a sensorimotor loop in the central nervous system elicited from afferent signals from muscle spindles1,2. As such, proprioceptive stimuli have been used in early neurorehabilitation after brain lesion to increase bodily awareness and arousal3. But it is not yet clear to which degree illusory movement sensation depends on cognition, and thus, might be also present in patients with disorders of consciousness (DOC). In this study we set out to determine electroencephalogram (EEG) correlates of elbow movement illusion in a healthy population as a preparation for a study with DOC patients. Thirteen healthy participants were recorded with EEG during one session of proprioceptive stimulation. Each participant received stimulation via two vibrators on the biceps and triceps tendon on the medial part of the elbow. In the active condition, vibration frequencies were chosen to induce a proprioceptive sensory illusion of elbow movement, while in the control condition the vibration did not have this effect. The EEG montage consisted of 16 channels covering the sensorimotor cortex. The signal was sampled at 500 Hz, bandpass filtered between 0.1 and 40 Hz and artifactual epochs semi-automatically excluded. Power spectral densities have been computed and the difference between the experimental conditions tested with cluster based permutation tests adapted for multiple comparisons across frequencies. We found that 12 out of 13 subjects have significant (p < .05) differences between the two conditions in the alpha (8-14 Hz) or beta (18-30 Hz) range in at least one EEG channel. Four subjects displayed elevated alpha power during the perceptive illusion while three showed decreased alpha power. In the beta band seven subjects showed a power depression during the illusion and one an elevation. Eight subjects displayed the same significant pattern across at least two recorded channels (max. 8). Our results hint that illusory perception of movement produces detectable EEG correlates in sensorimotor areas, and that this effect is present in the majority of a healthy population. Still, this result needs to be confirmed in additional studies. Further, we are interested to correlate the EEG patterns with the subjective strength of the illusion, plan to expand to a high-density EEG coverage and to incorporate functional magnetic resonance imaging to identify illusion-related loci in (sub)cortical regions.
Intravenous thrombolysis for acute ischemic stroke due to intracranial artery dissection: a single-center case series

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Background
Only case reports of intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) due to intracranial artery dissection (IAD) have been published so far.

Aims
We present our single-center experience of IAD-related AIS treated with IVT.

Methods
We selected all consecutive patients with IAD-related AIS treated with IVT from the Acute STroke Registry and Analysis of Lausanne between 2003 and 2017. We reviewed demographical, clinical and neuroimaging data and also recorded hemorrhagic complications, mortality within 7 days and modified Rankin Scale at three-months.

Results
Among 181 AISs related to cervicocephalic dissections, 10 (5.5%) were due to IAD. Five of those patients received IVT and were included in this study. Median age of treated patients was 62 years; hypertension and dyslipidemia were the most frequent vascular risk factors. IAD locations were distal internal carotid artery, middle cerebral artery (M1), anterior cerebral artery (A2), and, in two cases, the basilar artery. All anterior circulation IAD were occlusive or subocclusive, while the two basilar artery IAD caused arterial stenosis. After IVT, there were no subarachnoid or symptomatic intracranial hemorrhage. One patient had an asymptomatic hemorrhagic infarct type 1. Two patients died within seven days from ischemic mass effect. The other three patients had a favorable clinical outcome at three-months.

Conclusions
In this small, single-center case series of IAD-related AIS, thrombolysis seemed to be relatively safe. However, IVT efficacy and the likelihood of arterial recanalization remain uncertain. Further studies are needed to confirm the safety and assess the efficacy of IVT in these patients.
Thrombectomy and thrombolysis of isolated posterior cerebral artery occlusion: cognitive, visual and disability outcomes

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Objective
To investigate efficacy and safety of acute revascularization with IV thrombolysis (IVT) and/or endovascular treatment (EVT) in ischemic stroke from isolated posterior cerebral artery occlusion (IPCAO), by assessing recanalization, hemorrhagic complications, cognitive, visual and disability outcomes.

Methods
For this retrospective single-center cohort study, we selected all consecutive stroke patients with IPCAO from the ASTRAL registry between 1/2003 and 6/2018 and compared 1) IVT to conservative treatment (CTr) and 2) EVT to best medical therapy (BMT, i.e. CTr or IVT) in terms of cognitive domains impaired after stroke, 3-months visual field defect and disability. Unadjusted analysis, multivariable logistic regression and propensity score matched analyses were performed.

Results
Among 106 patients with IPCAO, 21 received EVT (13 bridging), 34, IVT alone and 51, CTr. Median age was 76 years, 47% were female and median NIHSS was 7. Complete recanalization at 24-hours was more frequent with IVT than CTr (51% vs. 9%, p=0.003) and with EVT compared to BMT (68% vs. 34%, p=0.021). Higher proportions of good cognitive, visual and disability outcomes were observed in IVT vs. CTr, adjORs (95%CI) = 2.94 (0.35–24.4), 2.01 (0.58–7.01), 1.65 (0.60–4.52) respectively, and in EVT vs. BMT, adjORs (95%CI) = 4.37 (0.72–26.53), 4.28 (1.00–18.29), 1.44 (0.51–4.10) respectively. Hemorrhagic complications and mortality did not increase with IVT or EVT.

Conclusion
Both EVT and IVT are associated with a higher rate of 24-hour recanalization, without increase in hemorrhagic complications. Cognitive, visual and disability outcomes seem better with IVT than CTr and best with EVT.
Lactate neuroprotection in permanent ischemia and in the presence of recombinant tissue plasminogen activator

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Background
The monocarboxylate lactate has been shown to have neuroprotective effects in some experimental models of stroke and in human acute traumatic brain injury patients.

Aims
To further investigate the use of lactate in experimental in vivo stroke models prior to its use in clinics, we tested its effects in permanent ischemia and its compatibility with the only currently available drug for the treatment of acute ischemic stroke, recombinant tissue plasminogen activator (rtPA).

Methods
We intravenously injected mice with 1 μmol/g sodium L-lactate 1 h or 3 h after permanent middle cerebral artery occlusion (MCAO) and looked at the lesion size and neurological outcome 24 h later. Further exploring the possible clinical application of lactate to patients undergoing recanalization therapy, we administered intracerebroventricularly 2 μl 100 mmol/L sodium L-lactate in combination with 0.9 mg/kg of intravenous rtPA to mice subjected to 35 minutes transient MCAO and compared the lesion size and neurological outcome of the combined treatment with that of single treatments, 24 h and 48 h post-reperfusion.

Results
We show a beneficial effect of lactate on permanent ischemia when administered 1 h after ischemia onset, reducing the lesion size and improving neurological outcome. Changes in the metabolic profiles related to tissue demise could underlie the decreased protection at 3 h. We also show that the protective effect of lactate combined with rtPA is not as strong as lactate administered alone, although it still has positive effects on the functional outcome and attenuates the deleterious effects of rtPA.

Conclusions
The present work gives a lead for patient selection in future clinical studies of treatment with inexpensive and commonly available lactate in acute ischemic stroke, namely patients not treated with rtPA but mechanical thrombectomy alone, or patients without recanalization therapy.
Sleep-wake Patterns after Stroke: A prospective study of 438 patients

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Background
Sleep and stroke are common and reciprocally related. Sleep/wake disorders (SWDs) are associated with an increased risk and a poorer outcome after stroke. Moreover, SWD may appear “de novo” after stroke. Finally, sleep may promote neuroplasticity and eventually outcome after stroke. However, data on sleep changes after stroke are very limited. The overarching aim of the study is to assess prospectively and systematically the frequency and characteristics of SWD in patients after stroke. In this report we specifically focus on 1) the changes in sleep duration, fragmentation and circadian rhythmicity over the first year following stroke, 2) whether the observed changes relate to stroke severity.

Patients and methods
We recruited 438 patients (85% with stroke, 15% with TIA, mean age 65 years (range 21-86), 64 % male), and interviewed them regarding medical history, risk profile and pre-stroke sleep-wake behavior. Interviews were conducted at hospitalization and 1, 3, 12 and 24 months after the event. Data collected included assessment of sleep-wake behavior, validated questionnaires on sleepiness, fatigue, sleep quality and depression, and functional outcome and recurrent events. In a randomly selected subgroup of 114 patients, actigraphy was performed at 1, 3 and 12 months after stroke.

Results
The mean NIH-S score of the cohort was 3.5 (SD 4.5, range 0-40) at admission and 1.2 (SD 2.1, range 0-18) at discharge. Subjective time-in-bed increases in the 12 months after stroke compared to pre-stroke levels (pre: 499 min. SD 78; 1 month: 537 min. SD 74; 3 months 520 min. SD 77; 12 months 517 min. SD 75). This increase was higher in patients with moderate stroke at hospital discharge (NIHSS > 4 vs NIHSS < 4) after 1 and 3 months (both p < 0.005), and normalized after 12 months. Actigraphy data similarly showed a stroke severity dependent increase in “time in bed” and “actual sleep time”, as well as a decreased relative amplitude of the circadian rhythm (p < 0.05).

Conclusion
Preliminary results of an ongoing study show an increase in time-in-bed after stroke, which depends on stroke severity and improves over time. Further analyses are needed to better understand 1) the potential relationship between increased sleep needs and stroke recovery and 2) the determinants of changes in sleep duration after stroke.
An usual stroke on CT-scan in an unusual patient

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Background
Performing a brain scan on a horse is challenging, requiring specific adaptations. Scanning has to be performed under general anesthesia. However, the information obtained by this examination may help to estimate the mechanism leading to the lesion as well as evaluation of the neurological consequences.

Objective
We report the case of a filly who suffered an ischemic cerebrovascular stroke, confirmed by a brain CT scan. Methods We conducted a retrospective veterinary chart and CT-scan review of a filly. The filly’s veterinary charts and its associated imaging features (CT-scan) were reviewed. A neurological clinical examination including visual field examination was performed to assess the neurological outcome two months after onset and especially any remaining visual field impairment.

Results
A review of the CT-scan by a radiologist specialized in cerebrovascular diseases detected a right occipital cortico-sub-cortical hypodense lesion (arrows). This was interpreted as a scar in right posterior cortical watershed zone related to hemodynamic infarction secondary to the known anaphylactic shock. Main limitations The visual pathways in the horse are crossed-over in part, aiding binocular vision when the horse looks ahead. On the other hand, when looking sideways or backwards, a horse’s eyes move and see independently. Visual clinical examination in the horse remains difficult to assess.

Conclusion
This case highlights that detection of brain lesions at CT could explain the etiology of the observed neurological deficits in animals during veterinary check-ups. Careful reading by a specialized radiologist for interpretation may be required to rule out limited lesions.
Preceding ischemic events improve early stroke severity but not outcome

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Objective
Acute ischemic stroke (AIS) severity and its dynamics are determined by a variety of pathophysiological factors. We aimed to analyze whether preconditioning by a preceding ischemic event (PIE) could influence AIS severity and outcome.

Methods
Using consecutive AIS from the Acute STroke Registry and Analysis of Lausanne (ASTRAL) we analyzed the associations between admission National Institute of Health Stroke Scale (NIHSS) and demographics, risk factors, past medical history, PIE and stroke features using multivariable linear regression models. We also investigated whether such associations could be found for the subsequent 3-month outcome in terms of the Modified Rankin Scale (mRS).

Results
Of 3530 consecutive AIS patients (43% female, median age 73 years), 1001 (28.4%) had one or several preceding PIEs (45.0% TIA, 55.0% ischemic stroke; 30.7% had multiple events). After adjusting for multiple pre-hospital, clinical, and laboratory confounders, admission NIHSS was significantly lower in patients with PIE than without (NIHSS reduction by 1.35 points, CI: 0.67 to 2.03). This association was mainly seen in short duration PIEs and was independent of the delay between PIE and AIS; single, short-duration PIEs in the same territory had the highest impact on the subsequent stroke (NIHSS reduction by 2.87 points, CI: 1.75 to 4.00). The adjusted 3-month mRS post stroke was, however unfavorably affected by the presence of a PIE (cumulative OR 0.83, CI:0.72 to 0.96).

Conclusion
The presence of PIE was independently associated with a significant reduction in AIS severity at admission, but not with improved clinical outcome. Single, short duration PIEs in the same territory seemed to be most beneficial.
Predictors for Returning to Paid Employment After Transient Ischemic Attack and Minor Ischemic Stroke

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Returning to paid work (RTW) is of utmost relevance for stroke survivors and is associated with enhanced quality of life [1], [2]. Additionally, post-stroke unemployment has dramatic socioeconomic consequences, especially in the youngest population during their most productive years [3], [4]. Inconsistent evidence highlight that post-stroke RTW varies from 4% to 91% [5]. Our goal was to determine which early factors within the first week after a first-ever Transient Ischemic Attack (TIA) or Minor Ischemic Stroke (MIS) (i.e. NIH Stroke Scale, NIHSS < 4) are associated with stroke’s survivors’ ability to RTW in a prospective cohort study (n = 60) conducted in a single-center stroke unit. RTW was defined as having the same or higher percentage of paid work 3-months after the index cerebrovascular event compared to pre-stroke employment state. We first conducted univariate analyses between patients that did (RTW) or did not RTW (noRTW) on i) physiological (hyperlipidemia (statin treatment before stroke or post-stroke LDL cholesterol > 2.6 mmol/l)¹, TSH1, arterial hypertension (HTA)¹, radiological (Lesion Site/infra- Vs. supratentorial)¹), ii) cognitive (decline (IQCODE)¹, impairment (MoCA)¹,²) and iii) psychological/demographic measures (NIHSS¹,², modified Ranking Scale (mRS)², Hospital Anxiety and Depression Scale (HAD)¹,², age¹, gender¹, type of work (blue Vs. white collars)¹), within 7 days after stroke onset(¹) and at 3-months follow-up(²). On the basis of the univariate results along with prior hypotheses we conducted multivariate logistic regression analyses assessing the impact of the predictors on the likelihood that the patients would RTW. Univariate comparison revealed that patients that RTW had lower NIHSS¹,² (resp., p < .05 and p < .01), mRS² (p < .001) and HAD² (p < .01) scores while they were 3 times less likely to have hyperlipidemia¹ (p < .05). The regression model including NIHSS¹,², mRS², HAD², hyperlipidemia¹ and age¹ as predictors revealed that the model was statistically significant (p < .001) and could distinguish between RTW and noRTW patients with 84.8% probability. Specifically, patients without hyperlipidemia¹ were 11 times more likely to RTW (p < .05). Against all odds, our results suggest that known or newly diagnosed hypercholesterolemia at stroke onset is the only major contributor to RTW after a first-ever TIA or MIS, even if RTW and noRTW patients differ on stroke severity, physical and cognitive impairment and mood.
Intravenous thrombolysis for acute ischemic myelopathy: Four new cases and literature review

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Background
Intravenous thrombolysis (IVT) is a well-established treatment of ischemic stroke within 4.5 hours. However, its effectiveness in acute ischemic myelopathy (AIM) is unknown.

Purpose
We describe a series of four AIM patients treated with IVT within 4.5 hours and review the current literature to explore this treatment feasibility, potential safety and efficacy.

Methods
We reviewed all routinely collected clinical, radiological and follow-up data of patients with a final AIM diagnosis who received acute IVT in our stroke network. We also reviewed thrombolysed AIM patients in the literature.

Results
Four patients (3 women) aged 57 to 83 years presented with acute uni- or bilateral extremity paresis. After excluding contraindications by brain and spinal imaging in most patients, IVT was administered at 135, 190, 240 and 245 min. We identified seven other thrombolysed AIM patients in the literature. In the entire cohort, no hemorrhagic complications were seen and short- and long-term outcomes were favorable in half of the patients.

Conclusions
After appropriate acute imaging, IV thrombolysis for AIM is feasible and potentially safe within 4.5 hours. Given the potential benefit of this treatment, it warrants further efficacy and safety studies.
Timing is brain: The impact of endovascular therapy start time on neurological outcome

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Aims
The increasing number of patients eligible for endovascular therapy (EVT) in extended working hours could be a potential source of fatigue for the stroke management team leading to poor outcome. We sought to investigate the association between EVT start time in acute ischemic stroke (AIS) and long-term neurological outcome.

Methods
This retrospective cohort study was performed using stroke registries from two tertiary stroke centres. All AIS cases treated with EVT from January 2012 to December 2018 were analysed. The primary outcome was the score on the modified Rankin Scale (mRS) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention at a given EVT start time would lead to lower scores on the modified Rankin scale than at other EVT start times (shift analysis). Secondary endpoints were EVT start-to-recanalisation time, modified treatment in cerebral ischemia (mTICI) score, number of EVT passes and rate of symptomatic intracranial haemorrhage (sICH).

Results
Available for analysis were 1,558 cases that were equally allotted into twelve EVT-start-time periods: 08:00-10:20, 10:20-11:34, 11:34-12:40, 12:40-13:37, 13:37-14:41, 14:41-15:55, 15:55-17:15, 17:15-18:55, 18:55-20:55, 20:55-22:57, 22:57-02:07 and 02:07-07:58. With the exception of a small, yet significant difference in age, no significant differences were observed in patient characteristics nor in stroke characteristics. The primary outcome favored EVT start times in the morning at 08:00-10:20 (OR, 0.53; 95% CI, 0.37 to 0.75; P < 0.001) and 10:20-11:34 (OR, 0.62; 95% CI, 0.44 to 0.87; P = 0.006), while it disfavored EVT start times at the end of the working day at 15:55-17:15 (OR, 1.47; 95% CI, 1.03 to 2.09; P = 0.033) and 18:55-20:55 (OR, 1.54; 95% CI, 1.07 to 2.22; P = 0.020). Symptom onset-to-EVT start time was significantly higher and use of IV t-PA significantly lower between 10:20-11:34 (P < 0.004 and P = 0.012, respectively). No statistical difference was observed in mTICI score, number of EVT passes, sICH, or EVT start-to-recanalization time between any time periods.

Conclusion
EVT for AIS in the morning leads to better long-term neurological outcome, despite having a statistically longer symptom onset-to-EVT start time, while EVT at the end of the work day leads to poorer long-term neurological outcome.
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Revascularization of carotid artery occlusion using stenting versus angioplasty in endovascular management of tandem occlusion stroke.

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Introduction  
The use of extracranial internal carotid artery (ICA) stents after mechanical thrombectomy (MT) may be a source of morbidity and mortality. Studies comparing patients who received stenting to patients who do not receive stenting have a higher number of patients with failed intracranial reperfusion in the non-stenting group. In this study, we analyzed the impact of extracranial ICA stenting in tandem occlusion stroke in patients with successfully intracranial reperfusion.

Methods  
This monocentric, retrospective cohort observational study reviewed all consecutive MT patients from January 2013 to May 2017. All patients with occlusions in the anterior circulation due to ICA atherosclerotic plaque embolus, TOAST 1, and were successfully reperfusion of at least 50% of the initially occluded target territory were included. Patients with a concomitant extracranial, or tandem, ICA occlusion which required MT and permanent stenting (stenting group) were compared to patients with extracranial atheromatous ICA plaques, which did not require permanent carotid stenting but were treated only by MT (non-stenting group). The three endpoints of this analysis were mortality rate at 90 days, good functional outcome defined as modified rankin scale (mRS) scores 0-2 at 90 days and symptomatic ICH (sICH). Outcomes were reported as odds ratios (ORs), indicating the odds that the intervention would lead to increased mortality rate, an improvement of at least one point on the mRS in a shift analysis and decreased rate of sICH.

Results  
One hundred and two patients were included of which 42 were treated by MT and ICA stenting (stenting group) and 60 were treated by MT without stenting (non-stenting group). No significant differences observed as it relates to demographic data, stroke characteristics, symptom onset to groin puncture or groin puncture to final reperfusion time intervals. Univariate logistic regression showed a higher probability of mortality at 90 days in the stenting group than that in the non-stenting group (OR 2.78, 95% CI 1.21-7.25, P=0.03). Stenting was not associated with a significant difference in functional independence at 90 days or rate of sICH compared to the non-stenting group.

Conclusion  
Stroke patients with successful intracranial reperfusion after MT had a higher probability of mortality within 90 days when concomitant stenting of the extracranial ICA was performed compared those patients who did not receive stenting.
Prediction of disorientation after brain damage: two versions of a task

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Orbitofrontal reality filtering (ORFi) describes a thought control mechanism which adapts the cortical format of upcoming memories depending on their relation with ongoing reality (1). Failure of this mechanism induces reality confusion as evident in confabulations that patients act upon and disorientation. The experimental correlate of this failure is a performance drop in the second of two runs of a continuous recognition task. However, two studies questioned the specificity of the task (2, 3). Up to now ORFi was only studied in amnesic patients. In the present study, we explore (i) the reliability of the task to predict disorientation in unselected brain damaged subjects (irrespective of lesion type, aetiology and memory deficit); (ii) whether reliability can be increased by providing feedback during task performance. 42 patients (age 64.3 ± 12.9 years) hospitalized for neurorehabilitation after first-ever brain injury were recruited. On two separate days, they responded to a 20 items questionnaire of orientation, and performed the two versions of a continuous recognition task consisting of two runs composed with the same pictures. In one version, the investigator explained the task at the beginning and once or twice during testing (no-Feedback, ‘nFb’); in the other version, a symbol provided feedback on correctness after each item (with-Feedback, ‘wFb’). Task performance was described by a measure of learning in the first run (Item recognition; IR) and a measure of the performance decrease in the second run (Temporal context confusion, TCC = relative increase of false positives in the second run). Orientation correlated both with IR and TCC. Correlation was stronger with TCC than with IR in the task wFb (TCC, $P < 0.0001$; $R = -0.71$; IR, $P < 0.0001$; $R = 0.61$) than in the task nFb (TCC, $P < 0.01$; $R = -0.44$; IR, $P < 0.01$; $R = 0.46$). A failure of ORFi is a strong predictor of disorientation in patients with brain injury in general. However, in this heterogeneous sample, learning capacity (IR) also contributed to the prediction of orientation. The reliability of the task with immediate feedback is better than the original version providing instruction but no feedback during the task. It also has the advantage of being less investigator dependent.
Introduction
In multiple sclerosis (MS), the frequency of immunoglobulin (Ig) deficiency has not been investigated thoroughly. Therefore, we aim to evaluate the frequency of Ig deficiency (IgG, IgM, IgA) and its association with immunotherapy and disease course in two independent MS cohorts.

Methods
In our retrospective cross-sectional study, MS patients from the following two centers were included: Bern University Hospital (Bern, Switzerland) and Eginition University Hospital (Athens, Greece). The definition of Ig deficiency followed international recommendations (IgG < 7.0g/L, IgM < 0.4g/L, IgA < 0.7g/L). The Mann-Whitney test, the ANOVA test, and the multiple linear regression analysis were employed.

Results
In total, 327 patients were identified retrospectively (Bern/Athens: n = 226/101). Ig deficiency was frequently observed in both cohorts (Bern/Athens: IgG: 15.5%/14.9%, IgM: 16.9%/7.0%, IgA: 3.9%/2.0%), even when considering only untreated MS patients (Bern/Athens: n = 140/58; IgG: 7.9%/8.6%, IgM: 12.5%/5.2%, IgA 0%/1.7%). Independently of age, secondary-progressive MS patients had lower serum IgG concentrations than relapsing-remitting and primary-progressive MS patients (both: p ≤ 0.01). Compared to patients without disease-modifying treatment, IgG concentrations were lower in patients treated with rituximab (p = 0.001; n = 42/327), intravenous corticosteroids administered ≤4 weeks before blood sampling (p < 0.001; n = 16/327), natalizumab (p < 0.001; n = 48/327), and fingolimod (p < 0.01; n = 6/327).

Conclusion
Our study demonstrated high prevalence rates of Ig deficiency in MS patients with and without disease-modifying treatments. Rituximab, intravenous corticosteroids, natalizumab, and fingolimod were associated with lower IgG concentrations. Our findings are clinically important because Ig deficiency may predispose to treatment complications such as infections and interfere with standard serological testing, e.g., antibodies against John-Cunningham or Varicella-Zoster virus.
Quantitative magnetic resonance angiography as a potential predictor for cerebral hyperperfusion syndrome: a preliminary study.

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Objective
Cerebral hyperperfusion syndrome (CHS) is a rare but devastating complication of carotid endarterectomy (CEA). This study sought to determine whether quantitative hemodynamic assessment using MR angiography can stratify CHS risk.

Methods
In this prospective trial, patients with internal carotid artery (ICA) stenosis were randomly selected for pre- and postoperative quantitative phase-contrast MR angiography (QMRA). Assessment was standardized according to a protocol and included Doppler/duplex sonography, MRI, and/or CT angiography and QMRA of the intra- and extracranial supplying arteries of the brain. Clinical and radiological data were analyzed to identify CHS risk factors.

Results
Twenty-five of 153 patients who underwent CEA for ICA stenosis were randomly selected for pre- and postoperative QMRA. QMRA data showed a 2.2-fold postoperative increase in blood flow in the operated ICA (p < 0.001) and a 1.3-fold increase in the ipsilateral middle cerebral artery (MCA) (p = 0.01). Four patients had clinically manifested CHS. The mean flow increases in the patients with CHS were significantly higher than in the patients without CHS, both in the ICA and MCA (p < 0.001). Female sex and a low preoperative diastolic blood pressure were the clearest clinical risk factors for CHS, whereas the flow differences and absolute postoperative flow values in the ipsilateral ICA and MCA were identified as potential radiological predictors for CHS.

Conclusions
Cerebral blood flow in the ipsilateral ICA and MCA as assessed by QMRA significantly increased after CEA. Higher mean flow differences in ICA and MCA were associated with the development of CHS. QMRA might have the potential to become a noninvasive, operator-independent screening tool for identifying patients at risk for CHS.
mTORc1 augments glucocorticosteroid efficacy in Multiple Sclerosis

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Aims
Glucocorticoids are frequently used for treatment of multiple sclerosis relapses. We investigate the potential of an mTORc1 inhibition to enhance steroid efficacy.

Methods
In vitro human and murine T cell apoptosis and in vivo MOG35-55 Experimental Autoimmune Encephalomyelitis (EAE) were used to investigate if mTORc1 inhibition increases glucocorticoids efficacy. Positive results of the screening experiments were than in vitro and in vivo confirmed taking advantage of conditional knockout mice with T cell specific deficiency for mTORc1 or the glucocorticoid receptor.

Results
mTORc1 inhibition using different drugs (e.g. everolimus, rapamycin, voxtalisib, and vitamin D) lead to an increase of human T cell apoptosis in vitro. The potential to inhibit mTORc1 was checked by analysing phosphorylation of a downstream target of the mTORc1 pathway. Combination therapy of everolimus and methylprednisolone ameliorates EAE disease course compared to respective monotherapies. Mechanistically, the increased effects of glucocorticoids were caused by an upregulation of the glucocorticoid receptor protein via the mTORc1 pathway. Relevance of the glucocorticoid receptor was validated in mice with T cell specific GR deficiency. Here methylprednisolone treatment had no therapeutic effect on EAE disease course. Finally, in addition to pharmacological inhibition the relevance of the mTORc1 pathway was also investigated using mice with T cell specific deficiency of mTORc1 activity. In these mice, the pharmacological inhibition of mTORc1 did not lead to an upregulation of the glucocorticoid receptor and combination therapy with methylprednisolone did not ameliorate clinical course of EAE disease or increases in vitro T cell apoptosis.

Conclusions
mTORc1 inhibition increases therapeutic efficacy of glucocorticoids via an upregulation of the glucocorticoid receptor. These data suggest that mTORc1 inhibition might be a potential target to overcome glucocorticoid resistance in patients with multiple sclerosis.
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BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis

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Objective
To study blood oxygen level–dependent cerebrovascular reactivity (BOLD-CVR) as a surrogate imaging marker for crossed cerebellar diaschisis (CCD).

Methods
Twenty-five participants with symptomatic unilateral cerebrovascular steno-occlusive disease underwent a BOLD-CVR and an acetazolamide challenged (15O)-H2O-PET study. CCD and cerebellar asymmetry index were determined from PET and compared to BOLD-CVR quantitative values. Neurologic status at admission and outcome after 3 months were determined with NIH Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores.

Results
For both the BOLD-CVR and PET examination, a significant cerebellar asymmetry index was found for participants exhibiting CCD (CCD+ vs CCD−: for BOLD-CVR 13.11 ± 9.46 vs 1.52 ± 4.97, p< 0.001; and for PET 7.31 ± 2.75 vs 1.68 ± 2.98, p< 0.001). The area under the curve for BOLD-CVR was 0.89 (95% confidence interval: 0.75–1.0) with 0.91 sensitivity and 0.81 specificity to detect CCD. Participants exhibiting CCD were in poorer clinical condition at baseline (CCD+ vs CCD−: NIHSS 7 vs 1, p= 0.003; mRS 3 vs 1, p= 0.001) and after 3-month follow-up (NIHSS 2 vs 0, p= 0.02; mRS 1 vs 0, p= 0.04). Worse performance on both scores showed an agreement with a larger BOLD-CVR cerebellar asymmetry index. This was not found for PET.

Conclusions
BOLD-CVR demonstrates similar sensitivity to detect CCD as compared to (15O)-H2O-PET in patients with symptomatic unilateral cerebrovascular steno-occlusive disease. Furthermore, participants exhibiting CCD had a poorer baseline neurologic performance and neurologic outcome at 3 months.
Electrophysiological differences between upper and lower limb movements in the human subthalamic nucleus

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Objective
Functional processes in the brain are segregated in both the spatial and spectral domain. Motivated by findings reported at the cortical level in healthy participants we test the hypothesis in the basal ganglia of Parkinson's disease patients that lower frequency beta band activity relates to motor circuits associated with the upper limb and higher beta frequencies with lower limb movements.

Methods
We recorded local field potentials (LFPs) from the subthalamic nucleus using segmented "directional" DBS leads, during which patients performed repetitive upper and lower limb movements. Movement-related spectral changes in the beta and gamma frequency-ranges and their spatial distributions were compared between limbs.

Results
We found that the beta desynchronization during leg movements is characterised by a strikingly greater involvement of higher beta frequencies (24-31 Hz), regardless of whether this was contralateral or ipsilateral to the limb moved. The spatial distribution of limb-specific movement-related changes was evident at higher gamma frequencies.

Conclusion
Limb processing in the basal ganglia is differentially organised in the spectral and spatial domain and can be captured by directional DBS leads. SIGNIFICANCE: These findings may help to refine the use of the subthalamic LFPs as a control signal for adaptive DBS and neuroprosthetic devices.
Hybrid Operating Room Settings for Treatment of Complex Dural Arteriovenous Fistulas.

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Objective
Dural arteriovenous fistulas (dAVFs) are abnormal direct shunts between the occipital or meningeal artery and a meningeal vein or dural venous sinus. Treatment strategies include endovascular, microsurgical, stereotactic radiosurgical, or combined interventions. With few previous reports focused on dAVF treatment in a hybrid operating room (hOR), the authors reviewed their 6-year experience in this unique setting for these complex fistulas.

Methods
Patients with complex cerebral dAVFs underwent endovascular and microsurgical treatment in the hOR. In this retrospective review, 8 consecutive patients with cerebral dAVFs (Borden type 2 or higher) underwent endovascular and microsurgical treatment. Demographic characteristics, symptoms related to the dAVF, preoperative angiographic features, preinterventional therapies, intraoperative digital subtraction angiography (iDSA), and postoperative clinical and radiologic findings were reviewed.

Results
Of these 8 patients, 5 patients underwent multiple embolizations (up to 3) and hybrid procedures, with no procedure-related complications. After microsurgical resection, iDSA revealed remnants of the fistula, which was then immediately re-resected, in 2 patients. At closing of the hybrid procedure, iDSA revealed no fistula remnants in 7 patients (88%). At mean follow-up examination (58 months), 5 patients (62%) had cure of the dAVF, confirmed by noninvasive angiography. Two patients (25%) experienced a recurrence of the dAVF within 5 months.

Conclusions
Our hybrid techniques achieved high rates of dAVF obliteration, with all 8 patients achieving good or excellent outcomes and symptom relief. Angiographic follow-up within 6 months after the hybrid procedure is recommended for all patients even when intraoperative findings do not show remnants.
Dimethyl fumarate persistence-rates and reasons for discontinuation: a retrospective study based on real world data from Denmark and Switzerland

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Introduction
Dimethyl fumarate (DMF) is commonly used to treat Multiple Sclerosis (MS). Drug discontinuation rates have been reported both higher and lower than in the phase three trials. We aim to investigate rates of persistence, reasons for discontinuation and treatment duration in different MS centers in Denmark (DK) and Switzerland (CH).

Methods
We retrospectively assessed medical records from 665 MS patients (DK/CH: 452/213) treated with DMF on post marketing label. Continuous variables are provided as mean and standard deviations and categorical variables as frequencies and analyzed with Mann-Whitney or Chi² test respectively.

Results
We found an overall (CH+DK) discontinuation rate of 30.1% (200/665) due to disease activity, pregnancy or adverse events (AEs) and respectively a discontinuation rate of 32.3% (146/452) and 25.4% (54/213) in DK and CH (p=0.07). In patients who discontinued DMF we found an overall treatment duration of 15.3 (±11.0) months and respectively comparing DK and CH we found a treatment duration of 15.8 (±10.3) months and 14.1 (±12.7) months (p=0.11). Primary reasons for discontinuation was lymphopenia (43/200; 18.1 months (±9.5)), disease activity (39/200; 18.9 months (±11.6)), gastrointestinal discomfort (36/200, 6.6 months (±8.3)) and flushing (23/200, 16.5 months (±10.6)). 115 patients of 200 (57.5%) discontinued because of side effects (pregnancy and disease activity excluded). No differences were found when comparing CH and DK regarding time to discontinuation due to disease activity (p=0.54), whereas in CH patients stopped slightly earlier due to side effects (CH: 10.2 (±10.5) vs. DK: 14.0 (±10.6), p=0.05). Primary reasons for non-persistence within the first 3 months of treatment were gastrointestinal discomfort (16/28 (57.1%)) followed by flushing and skin reactions (both 3/28 (10.7%)). Main reasons for discontinuation between 3-12 months were gastrointestinal discomfort and lymphopenia (each 13/56 (23.2%)) followed by disease activity (8/56 (14.3%)). After 12 months most patients stopped DMF due to lymphopenia (30/116 (25.9%)) and disease activity (29/116 (25.0%)).

Discussion
Discontinuation of DMF due to AEs is frequent and has several reasons. We observed no major differences on average between CH and DK. Management programs should be aware that reasons for non-persistence are dependent on treatment duration in order to achieve higher persistence rates.
Causes and Outcome of acute Meningitis, Meningoencephalitis and Encephalitis, a retro- and prospectiv Analysis of 215 patients

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Background
Meningitis (M) and Meningoencephalitis/Encephalitis (M/E) are often caused by infectious agents. Whereas long-term sequelae are relatively well documented for bacterial M, literature on course of and outcome after viral M/E are sparse. Despite being frequently reported in clinical routine Sleep-Wake-Disturbances (SWD) such as excessive daytime sleepiness (EDS), fatigue and disturbed nighttime sleep have been scientifically neglected in this context so far.

Aims
To systematically review incidence, causes, clinical presentation and outcome (including SWD) of acute M/ME/E in adults presenting to our hospital.

Methods
The digital patient data record system of the Inselspital and the clinical database of the institute of infectious diseases (IFIK) was screened for diagnosis M/ME/E during the period of 1.1.2016-31.10.2018. Patient records were reviewed and in case of definite diagnosis of M/ME/E, patients were contacted via telephone for a follow-up interview and asked to fill out and return questionnaires.

Preliminary Results
After screening of the medical records from 459 patients, 216 were eligible for our study. Thereof 36 were diagnosed for E, 108 ME and 72 for E. A cause was detected in 66%, suspected in 24% and unknown in 10% of cases. The most frequent cause of infectious M was enterovirus in 51%, bacterial infections in 22%, tick borne encephalitis virus (TBE) and Varicella zoster virus (VZV) both in 11% and Herpes simplex virus II (HSV2) in 3%. For ME/E most frequent causes were TBE (51% ), HSV 1 (9%), VZV (10%) and bacterial infections (17% ). The telephone interview was performed at a mean time point of 13 months after M and 17 months after ME/E. 45% of M survivors and 61% of ME/E survivors still reported neurological complaints, such as memory deficits (25% vs 26%), cognitive deficits (17% vs 22%) and headache (21% vs 31%). After ME/E epileptic seizures were reported in 29% of cases. EDS was reported by 16% of M and 43% of E patients. Disturbed nighttime sleep was reported by 12% resp. 13% of cases.

Conclusion
The presented data are preliminary results from our retrospective study with a prospective follow-up. Further analysis is still ongoing. Most frequent causes of M were enterovirus infections, of ME/E was TBE infections. Interestingly, a high percentage of both M and M/E survivors reported persisting neurological complaints, as well as SWD.
Patterns Of Care For Ruptured Aneurysms Of The Middle Cerebral Artery - Analysis Of A Swiss National Database (Swiss SOS)

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Objective
To determine patterns of care and outcomes in ruptured intracranial aneurysms of the middle cerebral artery (IA-MCA) in a contemporary national cohort of aneurysmal subarachnoid hemorrhage (aSAH) patients.

Methods
This is a retrospective analysis of the prospectively collected 2009 – 2015 dataset from a nationwide multicenter registry on all aSAH cases admitted to a tertiary neurosurgical department in Switzerland (Swiss SOS). Patterns of care and outcomes at discharge and 1-year follow-up of IA-MCA patients were analyzed and compared against a control group of aSAH patients with ruptured IA in non-MCA locations. Clinical and radiological independent predictors of favorable disability outcome (mRS ≤ 3) were identified, and their effect size was determined by calculating adjusted odds ratios (aORs) using multivariate logistic regression.

Results
Among 1866 consecutive patients in the Swiss SOS database, 413 (22.1%) patients harbored an IA-MCA. Patients with IA-MCAs presented with higher admission WFNS grades (p=0.007), showed a substantial higher rate of concomitant ICH (41.9% vs. 16.7, p < 0.001) and experienced significantly more frequently DCI compared to those with non-IA-MCA (38.9% vs. 29.4%, p=0.001). Surgical treatment was the dominant treatment modality within IA-MCA patients; significantly higher when compared to IA of other locations (81.7% vs. 36.7%). MCA location of the aneurysm was a strong, independent predictor of microsurgical aneurysm occlusion therapy (aOR 8.49, 95%CI 5.89-12.25, p < 0.001).

Even though IA-MCA patients were less likely to die during the acute hospitalization (aOR 0.52, 95%CI 0.30-0.91, p=0.022), the rate of favorable disability outcome was lower within the IA-MCA cohort compared to non-IA-MCA (55.7% vs 63.7%; p=0.003). At the 1-year follow-up, 68.5% and 69.6% of IA-MCA or non-IA-MCA patients had a favorable disability outcome (p=0.676).

Conclusions
Microsurgical occlusion currently remains the predominant treatment choice for about 80% of ruptured IA-MCAs in Switzerland. Although patients with IA-MCAs presented with worse admission scores, a greater rate of concomitant ICH and DCI, in-hospital mortality was lower and long-term disability outcomes were comparable to patients with ruptured IAs in other locations.
Is contrast media really needed for the MRI follow-up of intracranial aneurysms treated by detachable coils?

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Aims
Following recent concerns about deposition of gadolinium compounds in the basal ganglia and also to reduce healthcare costs, there is a general trend to limit the use of gadolinium contrast media in MR studies, especially in younger patients who need regular follow-ups as is the case with treated aneurysms. The aim of this study was therefore to evaluate the need for contrast media in the MRI follow-up of intracranial aneurysms treated with detachable coils.

Methods
In this retrospective study, we retrieved a list of patients who underwent brain MRI in 2017 for the follow-up of intracranial aneurysms treated with detachable coils by conducting a search in the thesaurus feature of our RIS. At our institution, patients who have undergone endovascular treatment of intracranial aneurysms, benefit from a yearly MRI follow-up to evaluate for recanalisation of the aneurismal sac. As in most institutions, this is investigated using both non-contrast and post gadolinium 3D TOF sequences. Aneurysms in which treatment was completely successful (no residual patent lumen) were excluded. The greatest dimension of the patent lumen of the remaining treated aneurysms was subsequently measured in the non-contrast and contrast 3D TOF sequences. In order to detect significant differences between the two measurements, a paired T test was used with a two-tailed 0.05 significance level.

Results
Our search retrieved 25 patients meeting the inclusion criteria (8 males, 17 females; mean age, 55.8 years; age range, 28.3-78.8 years). Preliminary results based on the measurements performed on this limited number of patients show that there is no statistically significant difference between the greatest dimension of the patent lumen of treated aneurysms measured in the non-contrast and post contrast 3D TOF sequences (p = 0.288)

Conclusions
These preliminary results show no statistically significant difference between the size of the patent lumen of aneurysms treated by detachable coils measured in non-contrast and post contrast 3D TOF. We see no reason why a larger series would not confirm and reinforce these findings. We therefore conclude that in the follow-up of aneurysms treated by detachable coils the administration of gadolinium does not provide significant added value and should therefore be abolished. This would avert all the possible complications associated with the administration of gadolinium, reduce image acquisition time and cut down on healthcare costs.
Linear and nonlinear interrelations show fundamentally distinct network structure in preictal intracranial EEG of epilepsy patients

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Resection of the seizure generating tissue can be highly beneficial in patients with drug-resistant epilepsy. However, only about half of all patients undergoing surgery get permanently and completely seizure free. Investigating the dependencies between intracranial EEG signals adds a multivariate perspective largely unavailable to visual EEG analysis, which is the current clinical practice. We examined linear and nonlinear interrelations between intracranial EEG signals regarding their spatial distribution and network characteristics. The analyzed signals were recorded immediately before clinical seizure onset in epilepsy patients who received a standardized electrode implantation targeting the mesiotemporal structures. The linear interrelation networks were predominantly locally connected and highly reproducible between patients. In contrast, the nonlinear networks had a clearly centralized structure, which was specific for the individual pathology. The nonlinear interrelations were over-represented in the focal hemisphere and in patients with no or only rare seizures after surgery specifically in the resected tissue. Connections to the outside were predominantly nonlinear. In all patients without worthwhile improvement after resective treatment, tissue producing strong nonlinear interrelations was left untouched by surgery.

Our findings indicate that linear and nonlinear interrelations play fundamentally different roles in preictal intracranial EEG. Moreover, they suggest nonlinear signal interrelations to be a marker of epileptogenic tissue and not a characteristic of the mesiotemporal structures. Our results corroborate the network-based nature of epilepsy and suggest the application of network analysis to support the planning of resective epilepsy surgery.
Tele-rehabilitation in Post-Stroke Aphasia

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Background
Stroke affects about 16,000 patients each year in Switzerland, of which 30% develop aphasia. Aphasia is an impairment of language functions (i.e. speech comprehension, speech production, reading, and writing) caused due to brain damage and differs in levels of severity. Current methods to treat aphasia include the speech and language therapy (SLT). In Switzerland, the frequency of therapist-mediated SLT is limited to one session of 45 minutes weekly whereas findings highlight positive effects of higher training frequencies. One promising new approach to increase training frequency and duration is to complement face-to-face SLT with home-based tele-rehabilitation SLT (tele SLT). In tele SLT, patients train independently at home while therapists remotely supervise the training process, select exercise types and adjust the difficulty levels. To provide a system to train the different language modalities, the University of Bern developed a well-accepted tablet-based rehabilitation application called Bern Aphasia App (BAA) which is currently in clinical testing.

Aim
The aim of the study is to investigate the effect of a high dosed tablet-based SLT by using the BAA on different language modalities of chronic aphasic outpatients.

Methods
In this ongoing study, aphasia out-patients are recruited and randomly assigned to two different treatment arms, where both groups train for 2 hours each day. In the experimental group 80% of the training time is allocated to tele SLT and remaining 20% to tablet-based cognitive training and vice versa in the control group. Exercises are allocated on a weekly basis according to the performance of the patient. Patients' language skills are evaluated at three time-points (pre-, post-test and 8-week follow-up).

Results: SUS scores for the patient interface are 98/100 for patients, 92.7/100 for healthy, and 68/100 for the therapist interface.

Conclusion/Outlook
In Switzerland, aphasia outpatients receive lesser frequency of therapy than guidelines recommend. Hence, positive results in this clinical trial would have a great socioeconomic impact, as well as increase the quality of life of the affected patients. Furthermore, with tablet-based applications (e.g. BAA) both, patients and therapists, can benefit from an intuitive, cost efficient touch-based reliable product which fits well with the current trend of moving health treatment from hospital to home.
The effects of transcranial direct current stimulation (tDCS) and exercise on cognition and motor in patients with chronic stroke

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Background
Chronic stroke is one of the most common causes of long-term neurological disability. The recovery of hand function is extremely important for stroke survivors but intensive physiotherapy, the current ‘gold’ standard intervention is expensive and time consuming, in short supply and inherently limited by the activity of the residual cortex.

One potential adjunct therapy is transcranial Direct Current Stimulation (tDCS) to the ipsilesional primary motor cortex (M1). Anodal transcranial Direct Current Stimulation (A-tDCS) is a non-invasive brain stimulation technique that involves passing a 2mA current through the brain via two scalp electrodes, with one centred over the ipsilesional M1.

Method
We report a randomised, double-blind placebo-controlled trial using A-tDCS as an adjunct to physiotherapy in 22 patients with chronic stroke. Patients received one-hour long standardised upper limb training intervention across 20 consecutive working days, with tDCS applied during the first 20 minutes each day. They were then assessed using BI, MRS, MAS and MOCA on enrolment day, one month and three months after the intervention. Patients also had structural (using 3D T1) and functional MRI (motor task in block design). BOLD and VBM analysis were carried out to estimate clusters of activation and measures of grey matter volume.

Conclusion
Overall improvements in function were seen in the A-tDCS group reflecting meaningful long-lasting functional benefits. A-tDCS is a relatively cheap, well-tolerated and easy-to-use approach. The results suggest that it could rapidly become part of routine clinical practice and guide therapeutic developments.