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ABSTRACTS

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CLINICAL GENETICS

Abstract 1
SRC_0269

Heterozygous missense variants of SPTBN2 are a frequent cause of congenital cerebellar ataxia

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Introduction: Heterozygous missense variants in the SPTBN2 gene, encoding the non-erythrocytic beta spectrin 2 subunit (beta-III spectrin), have been identified in autosomal dominant spinocerebellar ataxia type 5 (SCA5), a rare adult-onset neurodegenerative disorder characterized by progressive cerebellar ataxia, whereas homozygous loss of function mutations in SPTBN2 have been associated with early onset cerebellar ataxia and global developmental delay (SCAR14). Recently, heterozygous SPTBN2 missense mutations have been identified in a few patients with an early-onset ataxic phenotype. Objectives: We report five patients with non-progressive congenital ataxia and psychomotor delay, 4/5 harboring de novo heterozygous missense variants in SPTBN2 and one patient with compound heterozygous SPTBN2 mutations. Conclusions: With an overall prevalence of 5% in our cohort of unrelated patients screened by targeted next generation sequencing (NGS) for congenital or early-onset cerebellar ataxia, our study indicates that our study indicates that both dominant and recessive mutations of SPTBN2 together with CACNA1A and ITPR1, are a frequent cause of early-onset non-progressive ataxia and that their screening should be implemented in this subgroup of disorders.

Abstract 2
SRC_0321

Neuropsychological and structural MRI correlates in patients with spastic paraplegia type 7

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Objectives: Spastic paraplegia type 7 (SPG7) is an autosomal recessive disorder caused by mutations in the gene encoding paraplegin, a mitochondrial protein of chaperone functions. The SPG7 phenotype is predominantly characterized by pyramidal and cerebellar signs causing progressive paraparesis complicated by ataxia and cerebellar dysarthria; brain MRI typically show signs of cerebellar degeneration, mainly involving the vermis, and a dentate nuclei hyperintensity on T2-weighted sequences is another frequent feature. Other associated signs or symptoms are represented by extrapyramidal signs, optic nerve atrophy and cognitive impairment due to frontal executive dysfunction or to mental retardation and recently, a case report emphasized an impaired emotional communication as another clinical manifestation linked to SPG7 mutations.
Material and Methods: To better characterize the cognitive and affective profile associated with SPG7 mutations and their correlates with the pattern of neurodegeneration of the cerebellar structures, we studied a small cohort of SPG7 patients by applying a specific cognitive assessment combined with neuroimaging studies using voxel-based morphometry.
Results: According to Schmahmann's syndrome Scale, all patients were affected by the Cerebellar Cognitive Affective Syndrome evidencing a specific cognitive profile together with a low Intelligence Quotient; accordingly, MRI analysis showed a diffuse cerebellar grey matter reduction.
Conclusions: Overall, the present study gives new insights about the neuropsychological profile and the neuroanatomical correlates in SPG7.

Abstract 3
SRC_0330

The Classification of Autosomal Recessive Cerebellar Ataxias: A consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force

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Objective: There is currently no accepted classification of recessive cerebellar ataxias, a group of disorders characterized by important genetic heterogeneity and complex phenotypes. The objective of this task force was to build a consensus and develop a clinical and pathophysiological classification for recessive ataxias.
Methods: The work of this task force is based on a scoping systematic review of the literature that identified recessive disorders characterized primarily by a cerebellar motor syndrome and cerebellar degeneration. The task force regrouped 12 international ataxia experts who decided on general orientation and specific issues.
Results: We identified 59 disorders that are classified as primary recessive ataxias. For each of these disorders, we present geographical and ethnical specificities along with distinctive clinical and imagery features. The primary recessive ataxias were organized in a clinical and a pathophysiological classification, and we present a general clinical approach to the patient presenting with ataxia. We also identified a list of 48 complex multisystem disorders in which ataxia is a secondary feature, but which should be included in the differential diagnosis.
Conclusion: This classification is the result of a consensus among a panel of international experts, and it promotes a unified understanding of recessive cerebellar disorders for clinicians and researchers.

Abstract 4
SRC_0356

Body mass index and peripheral insulin sensitivity in spinocerebellar ataxia type 3/Machado-Joseph disease (BIGPRO study)

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Background and Objective: Body mass index (BMI) and peripheral sensitivity to insulin (PSI) are altered in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). Contradictory associations have been described with disease progression or with mutation severity. We aimed to review our previous results by expanding our sample size of SCA3/MJD subjects studied so far.
Methods: we performed case–control observations in 2007 (group 1, described in DOI: 10.1002/mds.23428 and 10.1007/s12311-011-0326-6); 2011-2013 (group 2, described in doi: 10.1007/s12311-015-0719-z); and 2017-2018 (group 3, BIGPRO study, bigpro.webnode.com). BMI was calculated as [weight/(height)2]. PSI was studied by means of HOMA2-%S, estimated by Calculator v2.2.2. For asymptomatic carriers (SARA < 3), time from onset (corrected by age) was estimated as described elsewhere (doi: 10.1111/ene.13779). SARA, ICARS, SCAFI, CCFS, NESSCA, INAScount, age, age at onset, time to/after onset and the CAG repeat length at the expanded allele (CAGexp) were obtained. HOMA2-%S and CAGexp were logarithm10 transformed for parametric analyses.
Results: BMI of carriers were lower than controls - 24.9±4.6 in symptomatic (n=138) and 24.7±4.7 in pre-symptomatic (n=47) subjects and 26.8±5.3 in controls (n=109) (p=0.004, ANOVA with Tukey). Similarly, logHOMA2-%S of carriers were higher than controls – 4.76±0.39 in symptomatic (n=44) and 4.78±0.38 in pre-symptomatic (n=34) subjects and 4.51±0.43 in controls (n=39) (p=0.007, ANOVA with Tukey). No differences were found between symptomatic and pre-symptomatic subjects. Although BMI was correlated to age at onset, age, logCAGexp and HOMA2-%S on SCA3/MJD carriers, only HOMA2-%S explained BMI on linear regression (r=0.500, p<0.05). BMI was unrelated to time to/after onset, SARA, NESSCA, ICARS, INAScount, SCAFI or CCFS. logHOMA-%S was not correlated with any of these variables but BMI (r=-0.48, p<0.0001) – similarly as seen in controls.
Conclusion: Although low BMI and high PSI are clearly associated with the carrier status in SCA3/MJD and are quite interrelated, they did not seem to present good potential to be used as biomarkers of neurological progression in SCA3/MJD.

CLINICAL ATAXIAS

Abstract 5
SRC_0280

Epstein-Barr Virus associated-Cerebellitis in a Young Adult: Case Report and Patient Perspective

Mark YZ Wong, Eng-King Tan

Background: Acute cerebellitis (AC) is a rare neurological manifestation of Epstein-Barr Virus (EBV) infection, with the majority of cases often reported in pediatric populations. Much less is known about EBV-related AC in adults, which may have a variety of presentations. The pathophysiology of the disease is still not clear.
We present an informative case of a 21-year-old patient with EBV-AC, following a course of misdiagnosis and management. Furthermore, as the first author of this report (MYZW) is the affected patient, we also present the course from the patient perspective
Case Presentation: A 21 year old Asian male initially presented to the A and E department with incoordination, gait difficulty and slurred speech, with a prior sore throat and inner ear infection a week ago. Initial MRI, CT-scan, CSF examinations and serology revealed no abnormalities and patient was discharged with a "functional disorder". Patients neurological symptoms declined and he was re-admitted to our hospital with severe dysarthria, dysmetria, dysdiadochokinesia, hypomeric saccades and a wide based ataxic gait. Repeat MRI revealed leptomeningeal enhancements without parenchymal signal abnormality, and immunologic serum tests showed raised EBV capsid IgM and IgG levels, consistent with the recent URTI. Patient responded well to a 5 day course of IV immunoglobulins.
Conclusion: EBV-AC is rare in adults, and clinical guidelines are not fully established. Nonetheless, this condition should be considered in the differential diagnosis for patients presenting with signs of cerebellar ataxia. Due to the lack of established biological and radiological markers, it is thus equally important to consider neurological examinations and medical history when establishing a proper diagnosis.

Abstract 6
SRC_0352

Nocebo in cerebellar ataxia; a systematic review and meta-analysis of placebo-controlled clinical trials

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Introduction: Nocebo, the negative counterpart of the placebo phenomenon results in the induction of adverse events following the administration of an inert substance. Nocebo has been demonstrated to be associated with low treatment compliance in clinical trials, thus affecting treatment outcomes. This study sought to determine the prevalence of nocebo in cerebellar ataxia.
Methods: A systematic literature search was conducted on Pubmed for randomized controlled trials (RCTs) for cerebellar ataxia treatments. The number of drug-related AEs and the number of withdrawals due to drug intolerance in the placebo group were statistically analysed.
Results: The literature search identified 214 studies, of which 6 studies fulfilled the inclusion criteria. Approximately 1 in 20 (4.8%, 95% CI 2.2% - 10.0%) placebo-treated patients withdrew treatment due to AEs and approximately 1 in 7 (13.8%, 95% CI 5.4% - 31.1%) placebo-treated participants reported at least one AE. Participants in cerebellar ataxia trials reported similar AEs across both treatment groups (active and placebo).
Conclusion: Our results demonstrate that the nocebo effect in cerebellar ataxia is amongst one of the lowest among the neurological diseases.

Abstract 7
SRC_0357

Cerebellar ataxia is a common neurological manifestation of primary Sjogren's syndrome

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Objectives: Primary Sjogren's syndrome (pSS) is a common autoimmune disease characterised by xerophthalmia and xerostomia. The aim of this study was to identify the prevalence and type of neurological dysfunction in pSS.
Methods: The study sample comprised 166 patients. All patients fulfilled the 2002 ACR-EULAR combined criteria for pSS. Patient information was obtained retrospectively between August and December 2018. Data collected included demographics, clinical, serological, glandular, extraglandular, neurophysiological and brain imaging.
Results: The mean age was 61 with mean age at diagnosis of pSS 51 years. 152/166 (92%) were female. 156/166 (96%) had anti-nuclear, 146/166 (88%) had anti-Ro and 81/166 (49%) had anti-La antibodies. Extraglandular features included: interstitial lung disease 7/166 (4%), renal tubular acidosis 5/166 (3%), non-Hodgkin's lymphoma 5/166 (3%) and myositis 1/166 (<1%).
Neurological symptoms were reported in 96/166 (58%) of patients. The most common were sensory and poor balance. Nerve conduction studies were done in 65 patients. Symmetrical sensorimotor axonal neuropathy was found in 11/65 (17%) and sensory ganglionopathy in 8/65 (12%). Twenty seven patients presented with balance problems and underwent MRI brain and spectroscopy of the cerebellum. Of these 18 (67%) had abnormal spectroscopy (low NAA/Cr ratios), 11 (41%) had cerebellar atrophy. Eight (38%) also had a sensory ganglionopathy.
Conclusions: Neurological symptoms are common in pSS (58%). Sensorimotor axonal neuropathy or sensory ganglionopathy are the commonest types of neuropathy seen. Ataxia was present in 27 patients (16% of the total population of pSS) with some having pure cerebellar ataxia and others having in addition sensory ganglionopathy. As not all patients were assessed by a neurologist or underwent neurophysiology and brain imaging we believe that these figures may be an underestimate.

Abstract 8
SRC_0360

Brain atrophy in patients with alcohol-use disorder

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Introduction: Alcohol misuse is a major cause of morbidity and mortality with significant health and economic consequences. Although alcohol excess has been shown to cause effects on the brain, the exact mechanisms that lead to alcohol related brain injury (ARBI) remain unclear. This study aimed to determine the prevalence and patterns of brain atrophy in patients with alcohol use disorder (AUD).
Material and methods: Retrospective study analysing brain imaging characteristics in patients with AUD. Patients were identified from a Sheffield Teaching Hospitals, UK audit of 153 anonymised patients admitted acutely in 2012-13 to A&E with an AUD. Clinical data included number of A&E visits, indication of CT brain scans and mortality rate. Image analysis was based on validated referenced radiological CT brain atrophy visual rating scales, rated on a scale from 0 (no atrophy) to 3 (severe atrophy). Inclusion criteria to enable analysis of brain atrophy progression, were patients who had at least 2 CT brain scans at 1 year apart.
Results: Fifty-two (34%) patients were deceased (mean age of death 53 years) between the previous (2012) and present (2018) study. Six hundred and fifty-two CT brain scans had been done between 2012-2018 in 126 patients. Trauma was the most frequent indication. Following inclusion criteria, radiological analysis was undertaken in 87 patients. Brain atrophy progressed from 93% to 95% prevalence between the first and most recent scan (mean interval 59 months). Results for regions assessed are based on the most recent CT. Cerebellar atrophy (85%) was the most prevalent area of brain atrophy followed by atrophy affecting the medial temporal lobes (69%) and frontal lobes (66%). Ventricular enlargement was seen in 59%, posterior cortical atrophy in 53% and white matter lesions in 32%.
Conclusions: Brain atrophy is highly prevalent in patients with AUD. There is a need to increase awareness of ARBI aiming for early diagnosis and prevention.

Abstract 9
SRC_0361

Deferiprone in the treatment of ataxia due to superficial siderosis

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Introduction: Superficial siderosis (SS) is a rare neurological condition characterised clinically by progressive ataxia and deafness, and radiologically by curvilinear low signal intensities on blood-sensitive MRI sequences. It accounts for 1% of progressive ataxias and is a result of haemosiderin deposits within the cortex (preferentially the cerebellum), spinal cord, leptomeninges or subarachnoid space. Risk factors include CNS surgery and head injury. Treatment options include repairing the bleeding source (if identified) and/or treating haemosiderin accumulation with iron-chelating agents. Deferiprone crosses the blood-brain barrier, specifically targeting haemosiderin.

Objective: To describe the clinical course and radiological features of patients with SS followed up at the Sheffield Ataxia Centre (SAC), treated with deferiprone.
Methods: We retrospectively reviewed clinical and radiological data of patients with SS attending the SAC and included those patients treated with deferiprone.
Results: The treatment cohort, consisted of 3 male and 1 female patient (mean age of 52 years and mean treatment duration of 45.75 months). Decision to treat was based on severity of ataxia with three out of 4 patients having mild ataxia (able to walk without walking aid) and one having moderate ataxia (uses walking aid). The youngest improved clinically and radiologically. One patient progressed. Two stabilised but one of the 2 stopped treatment due to anaemia. Deferiprone was tolerated well and only discontinued in the anaemic patient. None exhibited neutropaenia or trace element deficiency. The patient with clinical improvement underwent cochlear implantation with good results.
Conclusions: The results suggest that deferiprone can be beneficial in some patients with SS with reduction in haemosiderin on MRI and/or clinical stabilisation. It is possible that early diagnosis and treatment may be associated with better outcomes.

Abstract 10
SRC_0362

Anti-GAD ataxia: A single centre experience in managing 40 patients over 25 years

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Objectives: To provide clinical and imaging data on patients with progressive cerebellar ataxia associated with high levels of anti-GAD antibodies (anti-GAD ataxia).
Methods: Retrospective review of all patients with anti-GAD ataxia managed at the Sheffield Ataxia Centre over the last 25 years.
Results: We identified 40 patients with anti-GAD ataxia (anti-GAD>2000 U/ml, normal <5). This suggests a prevalence of 2% amongst 2000 patients with ataxia. Mean age at onset of ataxia was 54 years (range 18-85) and mean duration 8 (range 1-20). Gaze evoked nystagmus was seen in 25%, limb ataxia in 33% and gait ataxia in 100%. 10 patients (25%) had severe ataxia (wheel-chair bound), 11 (28%) moderate (need walking aid) and 19 (48%) mild ataxia (can walk unaided). 43% of patients had type 1 diabetes, 35% had autoimmune thyroid disease and 18% had pernicious anaemia. 23/40 (58%) patients had gluten sensitivity (GS) or coeliac disease (CD) (15+8).
Baseline MR imaging was available in 37 patients, showing mild or no atrophy in 31, moderate in 5 and severe in 1. The atrophy affected the vermis in 17 (46%) cases and the hemispheres in 21 (57%). MR spectroscopy was abnormal at presentation (vermis and/or hemisphere) in 70% of patients, and showed improvement with treatment in 13/15 (87%) who had follow up imaging. 17/23 with GS or CD went on to a strict gluten free diet and in 16/17 (94%) the ataxia improved. Immunosuppression in 12 patients included mycophenolate (9), IVIgs (3), cyclophosphamide (1) and rituximab (1). 10 (83%) responded, 1 did not and one has only just started the treatment.
Conclusions: There is considerable overlap between anti-GAD ataxia and gluten ataxia (GA). For those patients with both anti-GAD and GS or CD, strict gluten free diet can be an effective treatment of the ataxia. Patients with anti-GAD ataxia with GS or CD that do not respond to gluten free diet and those with anti-GAD ataxia without GS or CD show good responce to immunosuppression.

MOLECULAR PATHOGENESIS (INCLUDING ANIMAL MODELS)

Abstract 11
SRC_0263

Exploring the regulation of frataxin expression by neurotrophic factors in mouse cerebellum after physical exercise

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Friedreich's ataxia is a predominantly neurodegenerative disease caused by recessive mutations that ultimately lead to a deficiency of frataxin (FXN) protein. It mainly affects the spinocerebellar system, thus leading to lack of motor coordination and loss of balance. However, little is known about the regulation of frataxin gene expression under different physiopathological situations. Our group has recently shown the prominent role of neurotrophic factors (specifically the Brain-derived Neurotrophic Factor; BDNF) to elicit neuroprotection against frataxin deficiency both in vitro and in vivo. Compelling evidence has pointed out a link between physical activity and the expression of neurotrophic factors in the nervous system through several molecular mechanisms In this work, we aim to explore the link between physical exercise, neurotrophic factors and frataxin gene expression in the mouse cerebellum. To achieve this, we subjected our mice to a spontaneous exercise protocol lasting 8 weeks, allowing us to identify, between the "runners" a sub group of "high runners" in order to check for "activity-amount" specific effects. We tested, through qPCRs, the levels of mRNAs of the factors we have previously demonstrated are involved in frataxin regulation such as BDNF, Neurotrophin 3 (NT3) and Sonic Hedgehog (SHH) as well as FXN itself. Our results show an increment in the levels of mRNAs for NT3 and SHH, while we were not able to detect significant changes in FXN or BDNF levels. Then we checked FXN protein levels by performing an ELISA assay, showing a significant increment in FXN protein in an amount directly related to the physical activity performed by the mouse. Similar, but not significant, results for BDNF protein levels were found. To search for more possible mediators of the effect of physical exercise on FXN protein level, we analyzed the levels of multiple cytokines using a protein array, which have led to the identification of several potential candidates for FXN upregulation. In view of these data, we suggest that physical exercise up-regulated FXN protein possibly through a posttranscriptional mechanism. A more thorough knowledge of the mediators and molecular mechanisms underlying FXN upregulation may provide some clues for new therapeutic approaches to curb neurodegeneration in Friedreich's ataxia.

Abstract 12
SRC_0271

Sustained benefits of deep brain stimulation in the Car8wdl mouse model of cerebellar motor disease: A focus on the ataxia phenotype

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Deep brain stimulation (DBS) is a surgical treatment for movement disorders that involves the delivery of electricity to specific brain regions that support motor function. A number of brain targets—including the thalamus and basal ganglia—are being investigated for treating movement disorders such as Parkinson's disease, dystonia, and tremor. However, the efficacy of treating ataxia with DBS remains underexplored despite its pressing need for therapies. Currently, ataxias that develop as a result of genetic mutations, infection, stroke, or brain trauma, rely on physical, occupational, and speech therapy to improve the patients' quality of life. These therapies are not always effective because patients typically have difficulties retaining the improvements that they do make. To address this problem, our lab developed a DBS paradigm that targets the cerebellar nuclei in mouse models of human motor disease. We tested the efficacy of the cerebellum as a target for dystonia and found that high-frequency stimulation delivered to diseased mice improved posture, but only during its application. When DBS was turned off, the abnormal postures returned. Targeting DBS to the cerebellar nuclei of ataxic mice (Car8wdl) also improved movement. Surprisingly, these motor improvements persisted long after DBS was stopped, but were specific to the frequency of stimulation and the age of the animal. We then combined our DBS treatment paradigm with measurements from various behavioral assays to assess how stimulation impacts motor function. We found that cerebellar DBS may (1) promote motor learning, (2) evoke long-lasting improvements to gait, and (3) impact muscle firing. Together, our data suggest the possibility that particular frequencies of DBS support permanent motor recovery in ataxia by influencing brain and muscle health. Future studies will be aimed at deciphering the specific cell types and circuits that promote plasticity in the brain as well as the muscles.

Abstract 13
SRC_0294

The effect of lactational perfluorooctanesulfonate (PFOS) exposure on cerebellar development and motor coordination later in adulthood

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Background: Perfluorooctane sulfonate (PFOS) is a persistent organic pollutant and was commonly used in industries and consumer products. PFOS has been detected in breast milk, serum and umbilical cord blood. Although previous studies have illustrated the significant neurotoxicity of PFOS, the underlying mechanism remains unclear. The purpose of this study is to examine the effect of early lactational PFOS exposure on motor coordination later in adulthood, and further disclose the molecular mechanisms involved.
Methodology: PFOS solution (0.1, 0.25 and 1 mg/kg) was orally administered in different time periods to dams during the post-partum days (P) 1 to 14 (P1-P14), so that pups would be exposed through breast milk. After post-natal 8-10 weeks, we performed Rotarod test using male offspring. We also measured the mRNA levels of specific genes responsible for proper cerebellar development and function using the cerebellum samples of PFOS-exposed and control mice at post-natal days (PND) 2, 7, 14, 21 and 28 by quantitative real time PCR.
Results: PFOS-exposed mice showed significant decreases in time-to-fall latency compared to control group. PCR analysis showed a significant decrease in mRNA levels of genes responsible for cerebellar function and neurodevelopment, mainly on PND 14.
Conclusion: Our study revealed that post-natal PFOS exposure has profound long-lasting effect on cerebellar development, and consequently leads to motor coordination deficiency. Furthermore, we found that PFOS peak effect in cerebellum is around P14.

Abstract 14
SRC_0300

A Zebrafish Model of Ataxia Telangiectasia

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Ataxia-Telangiectasia (AT) is a life-limiting, neurodegenerative disorder phenotypically characterised by ataxia, infertility, increased sensitivity to ionising radiation and, an increased incidence of cancers, particularly lymphomas. AT is caused by recessively inherited, loss of function mutations in the ATM gene, the product of which primarily functions as a protein kinase that is activated in response to DNA damage. Activated ATM then initiates DNA repair or directs the cell towards apoptosis.
While there are currently a number of rodent models that exhibit many of the disease phenotypes they are not suitable for high throughput screening studies. Therefore, we propose a zebrafish model. Using CRISPR/Cas9, zebrafish with a 5 bp deletion in exon 6 of the ATM gene have been generated (atmSH477). This results in a frameshift mutation, leading to a premature stop codon (p.Glu256GlyfsTer19).
AtmSH477 homozygous zebrafish are viable and have no obvious behavioral abnormalities at 9 months of age. Clutches of these atmSH477 zebrafish have abnormal sex ratios with all observed atm null fish being male. These atmSH477 males are also infertile, a key phenotype shared with AT patients and rodent models.
Investigations into this infertility at 7 months old reveal that atmSH477 zebrafish have atypical testis that contain primarily immature spermatids. Histological sections of the testis also show them to be neoplastic, containing irregular growth of Sertoli cells (support cells) and disorganisation of the seminiferous tubules. By 18 months, the Sertoli cell tumors present as multilobular, soft, cream-colored, masses, present within the caudal abdominal cavity and become pronounced enough that the overall morphology of the fish is significantly distorted.
The atmSH477 zebrafish model is also currently being investigated for recapitulation of other aspects for the AT disease such are radiosensitivity, decrease in the DNA damage response (DDR) and atrophy of the cerebellum

Abstract 15
SRC_0305

Genetic modelling of SCA13 in zebrafish cerebellar Purkinje neurons

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Objectives: Purkinje cells (PCs) are primarily affected in neurodegenerative Spinocerebellar ataxias (SCAs). Linking pathological molecular effects with impaired function and organismic behavior requires genetic regulatory elements specifically targeting PCs. Because cerebellar anatomy and function is evolutionary conserved, zebrafish represent an excellent model to study SCAs in vivo.
Results and Conclusions: We have isolated a 258bp cross-species PC-specific enhancer element that can be used in a bidirectional manner for bioimaging of transgene-expressing PCs with variable copy numbers for

tuning expression strength. Emerging ectopic expression at high copy numbers can be further eliminated by repurposing microRNA-mediated posttranslational mRNA regulation.
Mutations in the human potassium channel KCNC3 result in autosomal dominant Spinocerebellar Ataxia Type 13 (SCA13) with pronounced Purkinje cell degeneration. Expression pattern analysis revealed that the zebrafish kcnc3a but not the kcnc3b homolog is expressed in zebrafish cerebellar Purkinje cells. Single cell RT-PCR showed that the X12 variant of kcnc3a is the predominantly expressed splice isoform.
Subsequently, we generated a transgenic SCA type 13 model, using a zebrafish-variant (kcnc3aX12R335H) mimicking the human pathological SCA13R420H mutation. Purkinje cell specific expression of kcnc3aX12R335H resulted in cell-autonomous progressive PC degeneration linked to cerebellum-driven eye-movement deficits as observed in SCA-patients. This underscores that investigating PC-specific cerebellar neuropathologies in zebrafish allows for interconnecting bioimaging of disease mechanisms with behavioral analysis suitable for therapeutic compound testing.

Abstract 16
SRC_0323

Cerebellum: a target of perinatal hypoxia

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Perinatal hypoxia (PH) is a common injury involved in 1/3 of neonatal deaths. It has already been shown that it affects many cerebral regions inducing neurodevelopmental disorders. However, cerebellum involvement to these deficits has been neglected to date. Yet it could also be a target of PH due to its immaturity at birth. Moreover, deficits observed in children after PH have been correlated to cerebellar functions, suggesting that this structure could be affected by PH.
Thus we aimed to identify the effects of two types of PH on cerebellar development: (i) an intermittent hypoxia (IH) consisting of 2-minute cycles of hypoxia and reoxygenation repeated over 6 hours on mice from postnatal day 2 to 12 (P2 to P12), referring to apnea of prematurity; and (ii) a continuous hypoxia (CH) of 5% of O2 during 40 minutes on P6 and P12 mice, mimicking a perinatal respiratory delay.
We first showed that ROS production increases after IH and CH, indicating that hypoxia actually affects cerebellum. The oxidative stress induced by CH causes an increased apoptosis but no histological or behavioral defaults. Yet, caspases-3/7 activity decreases after IH, suggesting that cerebellum may trigger a long-term neuroprotective process to compensate an early apoptosis due to the O2 privation. Moreover, IH induces a reduced thickness and a disorganization of the cerebellar cortex. Finally, these histological changes are combined with development retardation including less weight gain and delays in righting and grasping reflexes.
To conclude, this work validates our PH models but shows that each one has specific effects on cerebellar development: continuous hypoxia acts in the short-term while intermittent hypoxia has profound structural impacts. Analyzes are in progress to determine if the alterations in young mice are compensated in adults. In the long term, our data aim to correlate cerebellum alterations with functional deficits observed in children after PH to improve their health care.

Abstract 17
SRC_0329

Distributed organization of functional cerebrocerebellar mossy fibers pathways in the mouse

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The cerebellar cortex receives afferents from many mossy fiber sources that essentially provide information from either the sensory systems of the body or from the cerebral cortex. Widespread cerebral cortical information originates from layer V pyramidal cells, which, mostly by way of the pontine nuclei, can reach the cerebellar cortex (Legg et al., 1989). Our understanding of the functional organization of the cerebral afferents to the cerebellar cortex and its integration with other precerebellar sources of information has been hampered by the complex organization of both the corticopontine as well as that of the pontocerebellar projections (Ruigrok et al., 2015). Only more recently, with the advent of viral tracers, has it become possible to study the relation between both cortices in a more direct way (Kelly and Strick, 2003; Suzuki et al., 2012; Gao et al., 2018). Yet, the detailed characterization of mossy fiber pathways deriving from specific cerebral regions remains largely unknown.
Here, using an anterogradely transported AAV1 virus that allows for a single transneuronal step (Zingg et al., 2017), we have studied the distribution of labeled mossy fibers resulting from viral injections into different functional cerebral cortical areas of the mouse.
The results show that injections into different cortical regions result in a specific distribution of labeled mossy fiber rosettes. Patches of labeled rosettes were observed in multiple lobules and always in several mediolaterally separated patches. We conclude that information from single functional cortical areas is distributed to several, non-adjacent, areas of the cerebellar cortex.

Abstract 18
SRC_0335

Region-specific deficits of Purkinje cell development in Atxn1[82Q] mice

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Purkinje cells are primary players in the pathology of spinocerebellar ataxia 1 (SCA1). Disease progression in humans and animal models exhibits degeneration of Purkinje cells. Furthermore, in animal models, Purkinje cells also feature abnormal physiology, molecular expression and connectivity prior to severe neuropathology. Two aspects of Purkinje cells with respect to disease progression in SCA1 deserve more investigation. 1) It has been shown that a delay of the expression of the mutated form of the protein Ataxin1 that induces the disease, decreases the severity, strongly suggesting a role for development in SCA1. 2) A great deal of evidence shows that Purkinje cells are heterogeneous in their gene expression, circuit connectivity and propensity for degeneration. Here, we aim to investigate these two features in a mouse model of SCA1. We determined the developmental onset of Purkinje cell dysfunction in SCA1 and observed that several physiological functions and morphological features are abnormal from a very young age, before cellular degeneration and behavioral phenotypes. Furthermore, we identified the regional differences in the dysfunction of Purkinje cells in SCA1 and found that these differences are mirrored by behavioral defects. Overall, our data provide novel insight in the effects of mutant Ataxin1 on the cerebellum and demonstrate how a mutation affecting all Purkinje cells can lead to differential and behaviorally-specific effects.

Abstract 19
SRC_0336

Cerebellar degeneration induces behavioural response to a spatial task in mice with retinal degeneration

Jan Barcal, Filip Tichanek, Zuzana Petrankova, Jan Cendelin

Objectives: C3H Lurcher mutant mice are a model of cerebellar and retinal degenerations. These mice permit to study the behaviour of mice lacking Purkinje cells in conditions of eliminated visual orientation. The aim of the work was to assess motor and spatial performance of Lurcher mice and wild type mice, both with or without the retinal degeneration.
Material and methods: Spatial navigation was tested using the water maze test with stable position of a hidden escape platform and a starting point that allowed both allothetic and idiothetic navigation. Motor skills were tested on a rotarod. Finaly, visual evoked potentials were examined.
Results and conclusions: Lurcher mice had shorter fall latencies in the rotarod test. Presence of the retinal degeneration did not have any impact on the motor performance neither in Lurcher nor in wild type mice. Both wild type and Lurcher mice with the retinal degeneration were not able to find the platform in the water maze. Lurcher mice with the normal retina also failed in the maze task and their performance was similar to mice with the retinal degeneration. Only wild type mice with the normal retina ware able to learn to find the platform. Thus, vision disability was not a significant factor limiting spatial performance in C3H Lurcher mice. Performance in the water maze positively correlated with motor skills in Lurchers. While blind wild type mice developed immobility responses, Lurcher mice maintained a high swimming activity throughout the entire test. Such abnormal behaviour could be due to stress-induced behavioural disinhibition that is supposed in Lurcher mice. Despite total inability of the mice with the retinal degeneration to use visual navigation, these mice generated visual evoked potentials.
This work was supported by the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic, the Charles University Research Fund (project number Q39).

Abstract 20
SRC_0337

Baclofen improves motor performance in cerebellar mutant mouse Lurcher

Jan Cendelin

Objectives: Lurcher mutant mice suffer from a severe hereditary cerebellar degeneration, which manifests by ataxia and cognitive and affective disorders including behavioural disinhibition and increased stress reactivity. To assess a hypothesis that behavioural abnormalities could influence performance of Lurcher mice not only in specific behavioural and cognitive tests but also in motor tests.
Materials and methods: Adult Lurcher mutant and healthy wild type mice of the B6CBA strain were treated with intraperitoneal injection of Baclofen (2 mg/kg or 4 mg/kg), an anxiolytic and myorelaxant substance, or saline 30 minutes before starting the examinations. The mice were examined in the open field and elevated plus maze to assess their activity and exploratory behaviour. Then they were tested on an accelerating rotarod for 5 days. The muscle strength was also measured.
Results: As expected, Baclofen reduced motor and exploratory activity in both Lurcher and wild type mice. Saline-injected Lurcher mice had more entries into the open arms of the elevated plus maze compared with wild type mice, but Baclofen reduced this difference. Fall latencies in the rotarod test were significantly shorter in Lurcher mice than in wild type mice. While in wild type mice the performance on the rotarod was not influenced by Baclofen, in Lurcher mice a significant dose-dependent increase of latencies was observed. On the other hand, Baclofen had no impact on muscle strength.
Conclusions: These findings suggest that poor performance of Lurcher mice in the rotarod test is not only a result of cerebellar ataxia but also by disinhibition or hyperactivity. These phenomena could be reduced by anxiolytic treatment.
This work was supported by the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic, the Charles University Research Fund (project number Q39).

Abstract 21
SRC_0339

Oscillatory motor network activity during rest and movement in the Harmaline rodent model of tremor

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Essential Tremor (ET) is the most common movement disorder that is characterised by uncontrollable shaking induced by posture or movement of the affected limb, typically the arms and hands. Converging literature has suggested that ET may be associated with pathological synchronous activity in the motor network at the tremor frequency (4-12Hz; Schnitzler et al, 2009). Furthermore, cumulating evidence also suggests that pathological changes in the cerebellum may play a key role in the origins of abnormal oscillatory activity ET (Louis, 2016). However, the underlying neurophysiological mechanisms which generate a tremor that occurs during voluntary contraction of muscles (known as an 'action tremor') are unknown. Electromyography (EMG) assessments of action tremor in ET have shown that abnormalities arise in the timing of EMG burst patterns recorded from the wrist during ballistic wrist movements, which is followed by a continuation of rhythmic EMG bursts at the tremor frequency. Neural correlates of motor network activity during rest and action in ET have not been examined. Harmaline is a neurotoxin which produces a tremor in rodents that is phenotypically similar to ET, by increasing climbing fibre activation to produce pathological oscillations within the olive-cerebellar pathway (De Montigny & Lamarre, 1973). This study aimed to examine the effect of harmaline on oscillatory motor network activity during rest and movement. To measure this, surface electroencephalography (EEG) over the sensorimotor cortex, local neuronal activity from thalamic and cerebellar medial nuclei, along with EMG activity, were recorded simultaneously in awake behaving rats, before and after systemic administration of harmaline (10mg/kg, I.P). Analyses reveal a change in oscillatory activity in the motor network for periods of movement compared to resting, providing new insights into the role of the cerebellar-thalamo-cortical network interactions in action tremor.

Abstract 22
SRC_0340

Hyper-excitability and hyper-plasticity disrupt cerebellar signal transfer in the IB2 KO mouse model of autism

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Autism spectrum disorders (ASD) are pervasive neurodevelopmental conditions that often involve mutations affecting synaptic mechanisms. Recently, the involvement of cerebellum in ASD has been suggested but the underlying functional alterations remained obscure. Herein, we exploited a combination of whole-cell patch-clamp recordings with voltage sensitive dye imaging (VSDi) in acute cerebellar slices in WT and IB2 KO mice to investigate single-neuron and microcircuit properties. The IB2 gene (chr22q13.3 terminal region) deletion occurs in virtually all cases of Phelan–McDermid syndrome, causing autistic symptoms and a severe delay in motor skill acquisition. The granular layer of these mice revealed severe alterations in synaptic transmission, neuronal excitation and long-term synaptic plasticity. A 2.5-times larger NMDA receptor-mediated current in IB2 KO granule cells enhanced synaptic plasticity (WT = 20.4 ± 4.2 %, n=12 vs. IB2 KO = 107.7 ± 44.4, n=9; $p<0.05$) along with the excitatory/inhibitory (E/I) balance (WT = 0.98 ± 0.27, n=6 vs. IB2 KO = 2.78 ± 0.32, n=7; $p<0.01$). At the same time, the spatial organization of granular layer responses to mossy fiber inputs shifted from a "Mexican hat" to a "stovepipe hat" profile, with stronger excitation in the core (WT = 12.9 ± 1.7 μm vs. IB2 KO = 29.5 ± 4.9 μm, n=5 for both; $p<0.01$) and limited inhibition in the surround (WT/KO ratio IWT/KO = 2.83 ± 0.17, n=5). The IB2 KO mouse model therefore configures a complex cerebellar synaptopathy centered on NMDA receptor gain of function, that in several respects resembles alterations also observed in cortical minicolumns. The profound changes of signal processing at the cerebellar input stage unveil a possible new mechanism contributing to the pathogenesis of autistic-like behavior.

Abstract 23
SRC_0344

Mitochondrial-targeted sulfide delivery molecules reverse oxidative damage in Friedreich's ataxia fibroblasts

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Friedreich's Ataxia (spinocerebellar ataxia; FRDA) is a rare autosomal recessive monogenic disease caused by mutations in the Frataxin gene. Clinical manifestations include limb muscle weakness, loss of coordination and heart disorders (atrial fibrillation, tachycardia and hypertrophic cardiomyopathy). Frataxin is a mitochondrial matrix protein required for Fe-S protein assembly in electron transport chain (ETC) constituents need for cellular bioenergetics/ ATP generation. Defective frataxin results in mitochondrial iron accumulation, an overproduction of mitochondrial oxidants (resulting in oxidative stress), impaired ETC activity and ATP synthesis, and mtDNA damage. Effective therapeutic interventions are currently lacking. Several approaches to diminish oxidative stress with antioxidants, including those targeted mitochondria (e.g. idebenone) or to provide ETC co-factors (e.g. nicotinamide derivatives) have been attempted, but have not progressed clinically; possibly because these drugs either combat oxidative stress or impaired ETC activity, but not both. To address this problem, we have developed a series of novel slow release hydrogen sulfide (H_2S) delivery molecules which selectively target H_2S (MtH_2SD) to mitochondria. H_2S can bypass defects in ETC complex I and provide electrons to complex II/III to stimulate ETC activity and ATP generation, preserving/restoring cellular bioenergetics *in vivo*. Our first-in-class molecule (AP39) has shown considerable therapeutic efficacy in animal models of mitochondrial dysfunction (e.g. neuroprotection *after* stroke and cardiac arrest, and myocardial infarction) and increased cerebellar, caudoputamen, cortex and hippocampal levels of H_2S indicating blood brain barrier penetration. Furthermore, AP39 (0.017-0.17 mg/kg) *reversed* neurological damage and brain atrophy, spatial memory defects and improved mitochondrial bioenergetics in a murine model of Alzheimer's disease. With the above observations in mind, we evaluated the effects of several classes of our mtH_2SD in fibroblasts obtained from FRDA patients and unaffected carriers (Coriell Institute, USA). Mitochondrial and cytoplasmic oxidants were assessed by *in situ* fluorimetry using MitosoxRed and DCF-DA respectively. ATP levels were measured by luminescence and viability by Trypan Blue. MtH_2SD (each 50 nM) significantly lowered mitochondrial and cytoplasmic oxidant production, improved cellular viability and increased ATP levels under basal conditions, and after glutathione-depletion (using BSO; 10 μM). MtH_2SD also increased ATP levels after complex I inhibition caused by rotenone (1 μM) treatment. These preliminary studies suggest that modulation of mitochondrial H_2S may represent a novel therapeutic opportunity in FRDA and related ataxias.

Abstract 24
SRC_0348

Novel SCA19/22-associated KCND3 mutations disrupt human KV4.3 protein biosynthesis and channel gating

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Objectives: Mutations in the human voltage-gated K+ channel subunit KV4.3-encoding KCND3 gene have been associated with the autosomal dominant neurodegenerative disorder spinocerebellar ataxia types 19 and 22 (SCA19/22). The precise pathophysiology underlying the dominant inheritance pattern of SCA19/22 remains elusive. Using cerebellar ataxia-specific targeted next generation sequencing technology, we identified two novel KCND3 mutations, c.950G>A (p.C317Y) and c.1123C>T (p.P375S) from a cohort with inherited cerebellar ataxias in Taiwan. The patients manifested notable phenotypic heterogeneity that includes cognitive impairment.
Material and Method(s) when relevant: We employed in vitro heterologous expression systems to inspect the biophysical and biochemical properties of human KV4.3 harboring the two novel mutations, as well as two previously reported but uncharacterized disease-related mutations, c.1013T>A (p.V338E) and c.1130C>T (p.T377M).
Result(s) and Conclusion(s): Electrophysiological analyses revealed that all these SCA19/22-associated KV4.3 mutant channels manifested loss-of-function phenotypes. Protein chemistry and immunofluorescence analyses further demonstrated that these mutants displayed enhanced protein degradation and defective membrane trafficking. By co-expressing

KV4.3 wild-type with the disease-related mutants, we provided direct evidence showing that the mutants instigated anomalous protein biosynthesis and channel gating of KV4.3. We propose that the dominant inheritance pattern of SCA19/22 may be explained by the dominant-negative effects of the mutants on protein biosynthesis and voltage-dependent gating of KV4.3 wild-type channel.

Abstract 25
SRC_0349

Downregulation of n-myc protein levels independent to the sonic hedgehog signaling pathway contributes to granule cell developmental impairment in lysosomal acid phosphatase 2 (Acp2) mutant mice cerebellum

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A lysosomal acid phosphatase 2 (Acp2) mutant mouse (naked-ataxia, nax) has a severe cerebellar cortex defect with a reduction in number of granule cells in the cerebellum. Since the Sonic Hedgehog (Shh) - N-Myc pathway is important for granule cell precursor proliferation and differentiation we examined SHH and N-Myc expression in nax and wild type mice. Using a combination of in vivo and in vitro immunohistochemistry, Western blotting, and RTPCR, we show that the proliferation defect of granule cells is associated with N-Myc downregulation, but independent of SHH protein expression. N-Myc protein expression was significantly reduced in the nax cerebellum whereas N-Myc gene expression in cerebellum was not significantly different between wild type and nax mice. It is suggested that the reduction of granule cells in the cerebellum of nax mice is due to dysregulation of the N-Myc pathway. One explanation for the reduction of N-Myc is increased activity of the ubiquitin ligase Huwe1 followed by increased proteasomal degradation.

Abstract 26
SRC_0350

G protein-coupled receptors 17 (GPR 17) upregulation delayed differentiation and impaired migration of oligodendrocyte in Acp2 mutant cerebellum

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Myelin formed by oligodendrocytes in the central nervous system is an essential structural component of brain function and neural circuitry. Extracellular and intracellular signaling pathways regulate oligodendrocytes proliferation, migration, differentiation and myelination. In this study we describe the oligodendrocytes development and molecular changes in lysosomal acid phosphatase 2 mutant (Acp2-/-) mouse (aka, nax: naked and ataxia) during early postnatal cerebellar development. By using immunohistochemistry and RNAseq we identified that the MBP and G-protein coupled receptors 17 (GPR17) are upregulated. GPR17 is important in oligodendrocyte differentiation during late stage of the developmental process. GPR17 upregulation inhibited differentiation of the pre myelinating - oligodendrocytes to myelinating - oligodendrocyte in nax cerebellum. In addition, GPR17+ oligodendrocytes are excessively migrated to the molecular layer in nax cerebellum. This study suggests that the GPR17 play a key role in regulating migration of the oligodendrocytes while controlling differentiation of the oligodendrocyte which is impaired in nax cerebellum.

Abstract 27
SRC_0363

Severe malformation of the fourth ventricle choroid plexus in Zfp423 mutants

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The choroid plexus (ChP) is a secretory tissue that produces cerebrospinal fluid (CSF) and secretes it into the ventricular system. CSF flows from the lateral to the third ventricle, and then through the cerebral aqueduct to the fourth ventricle. Recent studies have uncovered new, active roles for this structure in the regulation of neural stem cell maintenance and differentiation into neurons. Zfp423, encoding a Kruppel type zinc finger transcription factor essential for cerebellar development and mutated in rare cases of Joubert syndrome and other ciliopathies, is expressed in the roof plate (RP), from which the ChP arises, and in mesenchymal cells giving rise to the leptomeninges. Zfp423 mutants display a marked reduction of the fourth ventricle ChP. Markers of ChP development and function are sharply downregulated in our mutants. A detailed immunohistochemical analysis has ruled out drastic differences in markers of the vascular tree, meninges, roof plate or basal lamina, while revealing a complete lack of multiciliated ChP ependyma. Markers of BMP and Wnt signaling were not obviously altered in the mutant hindbrain. However, by RNA sequencing, we revealed a near-complete absence in the mutant hindbrain of master genes promoting the differentiation of monociliated neurogenic apical progenitors into ChP multiciliated ependymal cells. Conditional inactivation of Zfp423 in RP derivatives is required to gauge the cell-nonautonomous effects of this gene on cerebellar neurogenesis.

NEUROIMAGING

Abstract 28
SRC_0277

Dysmetria in cerebellar degeneration is accompanied by compensatory gray matter increase in premotor cortex and Supplementary Motor Area

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Patients with cerebellar cortical degeneration exhibit a range of motor deficits including ataxia of stance and gait, limb ataxia and dysarthria. Gray matter decrease in the cerebellar cortex has been shown to correlate with the severity of ataxia, but as of now, few studies investigated possible compensatory changes in cerebral areas. METHOD: Thirty patients with pure cerebellar cortical degeneration (mean age 57 SD 12, range 18-73; 16 women) and 30 age- and gender-matched healthy controls (mean age 56 SD 12, range 21-71; 18 women) performed horizontal elbow flexion movements at three different target amplitudes (10°, 25°, 50°) using a single-joint manipulandum. In addition, active and passive limb position sense acuity at the elbow joint was assessed using the same

apparatus. At the day of the experiment, high-resolution T1-weighted magnetic resonance images (MRI) were acquired at a 3T MRI scanner in all participants. Voxel-based analysis (VBM) was performed considering the cerebellum in SUIT space, and considering the whole brain in MNI space. RESULTS: First, the goal directed elbow movements showed dysmetria in cerebellar patients as revealed by significantly increased relative joint position errors (RJPE). Second, proprioceptive acuity was preserved in cerebellar patients for both passive and active elbow movements. Third, gray matter density of the cerebellar cortex was reduced in cerebellar patients, but gray matter density of the cerebellar nuclei was significantly increased. Forth, a significant increase of gray matter volume was observed in right SMA and left premotor cortex. Whereas decrease of cerebellar gray matter showed a significant negative correlation with RJPE, increase of SMA and premotor cortex gray matter showed a significant positive correlation with RJPE. CONCLUSION: Our findings show that cerebellar cortical degeneration is accompanied by a secondary, possibly compensatory increase of gray matter volume in cerebral cortical areas.
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Abstract 29
SRC_0284

Imaging of the cerebellar nuclei in spinocerebellar ataxia type 6

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Spinocerebellar ataxia type 6 (SCA6) is a more pure form of cerebellar degeneration which affects primarily the cerebellar cortex. A previous study of our group using susceptibility weighted imaging (SWI) at an ultra-high-field-MRI of 7 Tesla (7T) showed that the cerebellar nuclei were also affected (Stefanescu et al., Brain 2015). SWI, however, has the tendency to overestimate iron rich structures such as the cerebellar nuclei due to blooming effects. Therefore we assessed the cerebellar nuclei in a larger group of SCA6 patients (n = 25) as well as age- and sex-matched healthy controls using quantitative susceptibility mapping (QSM), which should allow an improved depiction of the nuclei. Furthermore, we did not only apply a 7T MRI but also a 3T MRI which is widely available. Ataxia rating scales were conducted to determine disease severity.
QSM allowed a reliable delineation of the dentate nucleus at both field strengths. However, the smaller cerebellar nuclei were seen less reliably especially in patients. Volumes of the dentate, globose and fastigial nuclei were significantly reduced in patients compared to controls. Linear correlation analysis revealed significant negative correlations of dentate and globose volumes with respect to clinical ataxia scores. As voxel size has a strong influence on the determined volumes, we also compared the surface of the dentate nuclei which was similar between 3T and 7T exams.
In conclusion, QSM allowed a reliable identification of the dentate nuclei not only at 7T MRI but also at a conventional field strength of 3T. Imaging of the smaller cerebellar nuclei was possible but especially in patients limited. Our previous finding of atrophy of the cerebellar nuclei in SCA6 was confirmed. The dentate surface is a more objective marker for atrophy than the volume because it is independent of voxel size.
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Abstract 30
SRC_0343

Multiple Imaging Modalities for Evaluation High Dose Stereotactic Radiosurgery for Cerebellum Target

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Objectives: Neuro function and structure of Cerebellum are still lack of enough knowledge to be described due to limitation of different resources such as imaging modalities availability, direct clinical data, and qualified researchers. Most of current studies was utilized Magnetic Resonance Imaging (MRI) and diagnostic computer tomography with contrast agents. Modern Linear accelerator X-ray for stereotactic radiosurgery usually equipped with onboard Cone Beam Computed Tomography (CBCT) imaging system, which is used for target localization before dose. In this study, the sensitivity of on-board CBCT imaging was evaluated through comparing with MRI and CT images for cerebellum stereotactic radiosurgery (SRS) with volumetric perturbation methodology.
Methods and Materials: A cerebellum SRS case was selected for this study. During the patient care procedure, several imaging modalities was utilized. These imaging modalities include MR, CT and CBCT. And these images were taken by Siemens MR Scanner, GE LightSpeed RT System, and On-board-imager (OBI) on Truebeam Linear accelerator from Varian Medical System. The volumetric perturbations were generated by the percentage of prescription dose for the treatment. The percentages range from 120%, 100%, 80%, 60%, 40% and 20%. The collected images information include volume, minimum Hounsfield Unit (HU), maximum HU, mean HU, standard deviation of HU in selected volumes. The second order standard deviation method was applied to compare the sensitivity of among these imaging modalities for these volumes of interest.
Results: In this study, based on the selection volumes , which were 24.37cc, 34.01cc, 45.72cc, 67.79cc, 132.19cc and 383.73cc, the corresponding differences of second order standard deviation for CT to MR were 119.01, 91.67, -34.42, -133.08, -237.01, and -256.05; for CBCT to CT were-17.22, -40.38, -54.24, -75.72, -98.51, and -92.90; for CBCT to MR were 101.797, 51.29, -88.664, -208,795, -335. 518, and -348.95.
Conclusion: Modern Linac system for SRS provided OBI for CBCT imaging for evaluation cerebellum patient under SRS procedure. And the procedure could embed an instantly post treatment CBCT imaging for cerebellum response evaluation. Further development could apply selecting spectrum of imaging system for precise analysis of microscopic structure of cerebellum.

DEVELOPMENTAL BIOLOGY/ELECTROPHYSIOLOGY/FUNCTION

Abstract 31
SRC_0262

The role of the Cerebellum in understanding Social Action Sequences

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Recent neuroimaging research has revealed that the posterior cerebellum plays a critical role in social reasoning, and in particular in understanding beliefs. One hypothesis is that the cerebellum is responsible for the understanding of sequences of motions and actions, and the automatization of these action sequences. Automatization of actions in their correct order is a prerequisite for understanding the social actions of others and their mental state, including their beliefs.
In order to investigate this hypothesis, we tested for the first time patients with generalized cerebellar degenerative lesions on a number of tests of social and affective understanding, and compared their performance with matched control volunteers. One of the tests involved the picture sequencing test in which participants have to generate the correct order of social actions depicted in cartoons (Langdon & Coltheart, 1999). In line with our hypothesis, only this test showed clear deficits in cerebellar patients, in particular when dealing with cartoons depicting false beliefs.
Subsequently, we extended the picture sequencing test with true belief events, as well as with an analogous verbal version of all events and conditions, which we termed the stories sequencing test. While under an fMRI scanner, participants conducted both tests. As expected, the results showed that under both tests, false and true belief stories activated the posterior cerebellum (Crus 1 and 2) much stronger than social scripted and mechanical routines, which did not differ significantly from each other

Abstract 32
SRC_0267

The social cerebellum: New sequencing tasks and cerebello-cortical connections

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An increasing number of studies highlighted the importance of the cerebellum in social functioning, most often the posterior part (i.e., Crus 1 and 2). One hypothesis states that the basic function of the cerebellum – to develop and construct internal models of sequences involving motor elements for the planning and execution of movements – extended during human evolution to the development and construction of internal models of purely mental element which facilitates (social) event sequence processing. We introduce new tasks to investigate cerebellar involvement in the processing of different types of sequences, in which participants generated the correct chronological order of new or well known (non-)social event stories. The results of a functional magnetic resonance imaging study, showed strong posterior cerebellar activation during order generation for all event types compared to passive viewing or reading events, and even more so for new social events compared to routine (non-) social events. Using dynamic causal modelling, we reveal direct contra- and ipsilateral closed-loop connections between the bilateral posterior cerebellum and the bilateral temporo-parietal junction, a cortical area involved in social mentalizing. These results confirm that the posterior cerebellum plays a critical role in the understanding and construction of the correct order of new action sequences relevant for social cognition, and shows strong connection with social regions in the cortex. The false and true beliefs did not generate much differences either.
Together, these results suggest the prominent role of the cerebellum in sequencing social actions. This might be an important, but hereto neglected, capacity to understand social actions, such as in social narratives, gossip as well as in social interaction and cooperation.

Abstract 33
SRC_0268

The role of secretin in cerebellar development and motor learning functions

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Backgrounds: Secretin is one gastrointestinal peptide hormone with prominent functions in the digestive system. In recent decades, the neuropeptide role of secretin is emerging with its identification in multiple brain regions including the cerebellum. Objectives: We aim to study the regulatory role of secretin in early postnatal development and motor learning function within cerebellar cortex. Material and Methods: By generating Purkinje cell-specific secretin gene knockout (Sct cKO) mice, we described the postnatal neurogenesis, migration, apoptosis and dendritic arborization of cerebellar cortex. Motor reflexes and motor learning functions were examined in juvenile and adult mice, followed by patch clamp recordings. Results: Secretin knockout leads to impaired proliferation, apoptosis and migration of granular cell precursors plus defects of Purkinje cell dendritic formation, both of which were associated with developmental retards of motor reflexes. Adult Sct cKO mice presented impaired motor learnings. Moreover, inhibitory postsynaptic transmission of Purkinje cells was mediated by secretin and secretin receptor. Conclusion: Secretin modulates cerebellar associated motor functions probably via its influences on postnatal neurodevelopment and synaptic transmissions.

Abstract 34
SRC_0270

Extinction of cognitive associations is preserved in patients with cerebellar disease

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In the present study extinction and renewal of cognitive associations were assessed in two experiments in patients with focal and degenerative cerebellar disease. Subjects had to learn by trial and error the association between different food items and the occurrence of stomach ache yes or no. In the first experiment, focus was on renewal effects. Patients with chronic cerebellar stroke [n = 14; mean age 50.9 ± 12 years], patients with degenerative cerebellar disease (n = 16; mean age 58 ± 12 years), age-, sex-, and education matched controls (n = 20; mean age 53.7 ± 10.8 years) and young controls (n = 19; mean age 23.2 ± 2.7 years) were tested. Acquisition and extinction of food-stomach ache associations took part in two different contexts (that is, restaurants). In a subsequent test phase, food stimuli were presented in both contexts and no feedback was given. This allowed

testing for renewal of the initial association in the acquisition context. Acquisition and extinction effects were not significantly different between groups. Significant renewal effects were present in young controls only. In the second experiment, focus was on extinction. To control for age effects, 19 young subjects with chronic surgical lesions of the cerebellum (mean age 25.6 ± 6.1 years), and 24 age-, sex- and education-matched healthy controls were tested. Acquisition and extinction of food-stomach ache associations took part in the same context. In the extinction phase, the association with stomach ache yes or no was reversed in part of the food items. Acquisition and extinction were not significantly different between groups. Both cerebellar patients and controls were able to unlearn the initial associations. The main finding of the present study was preserved extinction of learned cognitive associations in patients with chronic cerebellar disease. Findings agree with previous observations in the literature that cognitive abnormalities are frequently absent or weak in adult cerebellar patients. This does not exclude a contribution of the cerebellum to extinction of learned associations. For example, findings may be different in more challenging cognitive tasks, and in patients with acute cerebellar disease with no time for compensation.

Abstract 35
SRC_0273

Celsr3 is required for Purkinje cell maturity and cerebellar function

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Celsr3 encodes a transmembrane receptor containing a seven-transmembrane motif. Previous studies show that Celsr3 is critical for brain wiring during development, and conditional inactivation of Celsr3 in the forebrain, brain stem, spinal cord and hippocampus results in the deficits of local network formation. However, its role in the cerebellum remains elusive. In this work, we first studied Celsr3 expression pattern in the cerebellum using Celsr3-GFP mice followed with double immunofluorescent staining and found that Celsr3 was highly expressed in both somas and neurites of calbindin-positive Purkinje cells at different stages postnatally. Mice with conditional inactivation of Celsr3 (Celsr3 cKO mice) in Purkinje cells after birth showed deficits in motor coordination, learning and emotional behaviors using Rotarod, Erasmus ladder, gird and elevated plus maze tests. In Celsr3 cKO mice, however, the gross morphology of the cerebellum was comparable to that in control mice, including the volume, monolayer organization of Purkinje cells and neurite distribution. Anti-synaptophysin 38 and -postsynaptic density protein95 immunostaining displayed that the synapse density was significantly decreased in the cerebellar molecular layer in Celsr3 cKO mice. Mutant Purkinje cells showed the reduction of mEPSP frequency using whole-cell recordings on acute cerebellar slices and the decreased dendrite volume using individual cell labeling and tri-dimensional reconstruction, compared to those in the control group. In conclusion, our work provides the first evidence that Celsr3 is required for Purkinje cell maturity and cerebellar function.

Abstract 36
SRC_0288

Long-term effects of cerebellar transcranial direct current stimulation (tDCS) on associative motor learning

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Objective: Transcranial direct current stimulation (tDCS) has been reported to accelerate acquisition of conditioned eyeblink responses (CR), a form of associative motor learning which depends on the integrity of the cerebellum. The aim of the present study was to investigate long-term effects of cerebellar tDCS.
Methods: Eyeblink conditioning was performed on four days (day 1, 2, 8, 29) using standard parameters. On day 1, one group of 20 young, healthy subjects received anodal cerebellar tDCS, another group sham stimulation in a randomized double-blinded design.
Results: CR incidence did not significantly differ between the anodal and sham groups on any of the days. At the end of the fourth day extinction trials were presented. Extinction was significantly faster in the anodal group compared to sham [block effect: $p < 0.001$; learning phase effect (Acquisition on day 1 vs. Consolidation on day 2,8,29 vs. Extinction on day 29): $p < 0.001$; Mixed Model Analysis. There was a stimulation effect during extinction with an increased reduction of the CRs in the anodal group compared to sham (stimulation x learning phase effect: $p = 0.032$; stimulation x learning phase x block effect: $p < 0.001$). The size of the CRs (CR-Area) increased in both groups on day 1. A further increase was shown on the other days (block effect, lerning phase effect: $p < 0.001$). This increase was significantly reduced in the anodal group compared to sham (stimulation effect: $p = 0.015$).
Conclusions: In conclusion, we were unable to replicate previous findings of accelerated CR acquisition using cerebellar anodal tDCS. Cerebellar anodal tDCS, however, appeared to interfere with retention of learned responses.

Abstract 37
SRC_0296

Early trigeminal ganglion afferents enter the cerebellum before the Purkinje cells are born and target the nuclear transitory zone

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In the standard model for the development of climbing and mossy fiber afferent pathways to the cerebellum the ingrowing axons target the embryonic Purkinje cell somata (around embryonic ages (E)13-E16 in mice). In this report we describe a novel earlier stage in afferent development. Immunostaining for a neurofilament-associated antigen (NAA) reveals the early axon distributions with remarkable clarity. By using a combination of DiI axon tract tracing, analysis of neurogenin1 null mice, which do not develop trigeminal ganglia, and mouse embryos maintained in vitro, we show that the first axons to innervate the cerebellar primordium as early as E9 arise from the trigeminal ganglion. Therefore, early trigeminal axons are in situ before the Purkinje cells are born. Double immunostaining for NAA and markers of the different domains in the cerebellar primordium reveal that afferents first target the nuclear transitory zone (E9-E10), and only later (E10-E11) are axons, either collaterals from the trigeminal ganglion or a new afferent source (e.g., vestibular ganglia), seen in the Purkinje cell plate. The finding that the earliest axons to the cerebellum derive from the trigeminal ganglion and enter the cerebellar primordium before the Purkinje cells are born, where they seem to target the cerebellar nuclei, reveals a novel stage in the development of the cerebellar afferents.

Abstract 38
SRC_0303

Can cerebellar-dependent motor responses modulate extinction of conditioned fear?

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Impaired extinction of learned fear responses likely plays a role in the pathophysiology of anxiety disorders. Possible ways to improve extinction learning are therefore of general interest. Studies in animals have shown that at the beginning of eyeblink conditioning unspecific fear responses are learned, only to be superseded by specific cerebellar-dependent motor responses. Magal and Mintz (Eur J Neurosci, 2014) have provided initial evidence that the cerebellar nuclei suppress the amygdala. Our aim was to test if extinction of conditioned fear can be improved by concurrent eyeblink conditioning in humans.
Four groups of 20 young and healthy right-handed men participated in a two-day experiment. On day 1, three groups underwent differential fear acquisition followed by delay eyeblink conditioning. Extinction was tested on day 2 in three different ways: Group 1 – extinction of learned fear responses followed by extinction of conditioned eyeblink responses, Group 2 – fear and eyeblink extinction trials alternated, Group 3 - fear and eyeblink extinction trials overlapped. Group 4 served as control group with fear acquisition on day 1 and extinction of learned fear responses on day 2.
Differential fear acquisition was observed in all groups based on skin conductance responses. Additionally, all participants in Groups 1-3 acquired conditioned eyeblink responses. On day 2, there were significant effects of extinction of learned fear responses in all groups. Between-group differences were significant with attenuated extinction of learned fear responses in Group 2 The present results show an interaction between the extinction of learned fear and motor responses. Against expectations, however, extinction of learned fear responses was impeded by the alternating presentation of extinction trials. Future studies need to test if the concomitant acquisition or expression of conditioned eyeblink responses improves extinction of fear.
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Abstract 39
SRC_0308

Differences in cerebellar activation to visceral and somatic pain stimuli in healthy women

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There is increasing evidence that the cerebellum plays a role in pain processing. The aim of the present study was to evaluate possible differences in cerebellar processing of visceral and somatic pain. Functional magnetic brain imaging (fMRI) data collected as part of a previous 3T MRI study were reanalyzed utilizing an advanced normalizing method of the cerebellum. 22 healthy female subjects received 10 visually cued visceral pain stimuli and 10 visually cued somatic pain stimuli in a pseudorandomized order. Pressure controlled rectal distensions and cutaneous thermal stimuli applied to the ventral forearm were individually calibrated and matched for perceived pain intensity. Differences between pain modalities were analyzed during the anticipation and the presentation of the pain stimuli. During pain anticipation, no difference between pain modalities was found. During pain presentation, there was significantly more cerebellar activation to visceral compared to somatic stimuli. The difference was most prominent during the ascending phase of pain stimulation. Activation included the vermal, intermediate and lateral parts of the anterior and posterior cerebellum with a focus on lobules I-VI and VIII. The present data show that the involvement of the cerebellum in pain processing differs between pain modalities. Recruitment of the cerebellum is more pronounced in visceral pain compared to somatic pain, likely because of the higher salience of visceral pain.
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Abstract 40
SRC_0311

Neural evidence of the cerebellum as a state predictor

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Computational studies suggest that the cerebellum predicts current and future states of the body and its environment using internal forward models. Sensory feedback signals have delays in reaching the brain, ranging between tens to hundreds of milliseconds. It is well known that feedback control based on time-delayed inputs may result in ataxic unstable movements. Therefore, the brain needs to predict a current state from a previous state using forward models. Here we provide neural evidence that the cerebellar circuit can predict future inputs from present outputs, a hallmark of an internal forward model.
To test the forward-model hypothesis, we analyzed activities of 94 mossy fibers (inputs to the cerebellar cortex), 83 Purkinje cells (output from the cerebellar cortex to dentate nucleus), and 73 dentate nucleus cells (cerebellar output), all recorded in the cerebrocerebellum of a monkey performing step-tracking movements of the wrist joint (Ishikawa et al., PLoS ONE, 2014; Kakei et al., Science, 1999). We found that activities of one population could be reconstructed as a weighted linear sum of those of preceding populations. Furthermore, activities of mossy fibers (cerebellar inputs) in a near future (~100 ms) could be predicted as a weighted sum of current activities of dentate cells (cerebellar outputs), thereby proving that the cerebellar outputs contained predictive information about the future cerebellar inputs. The linear equations derived from the cerebellar neuron activities resembled those of a predictor known as Kalman filter composed of prediction and filtering steps. Overall, out results support the forward-model hypothesis of the cerebellum (Tanaka et al., Cerebellum, 2019).

Abstract 41
SRC_0314

Activity patterns in cerebellar cortical microcircuits during goal-directed movement

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A fundamental principle of cerebellar organization is its division into a series of longitudinally oriented modules. Each module is defined by its climbing fibre input from a specific subdivision of the contralateral inferior olive, which targets one or more longitudinal zones of Purkinje cells within the cerebellar cortex. In turn, Purkinje cells within each zone project to specific regions of the cerebellar or vestibular nuclei. Within zones, smaller units known as 'microzones' have been identified electrophysiologically in anaesthetized animals. Within a given microzone, all Purkinje cells have climbing fibre-mediated input with similar receptive fields. Microzones and their associated input–output connections are thought to represent the basic operational units of the cerebellum. However, little is known about their function in awake, behaving animals. The aim of the present study is to examine microzones in the forelimb part of the C3 zone (lobule V) 'in action' by recording from single cerebellar neurones located in different microzones during performance of a visually guided forelimb reach/retrieval task in cats. Results demonstrate the activity of most cerebellar cells are modulated at some point in the task, and that the pattern of modulation is not necessarily related to location of peripheral receptive field, with classes of microzones showing diversity in their response profiles. Our results suggest that specific features of a given movement are not uniform for a given micozone but as their output to their target cerebellar nuclei is the sum of a range of different patterns, this may represent a mechanism by which the cerebellum monitors different aspects of a skilled movement, determined by a combination of prior experience and ongoing differences in patterns of inputs.

Abstract 42
SRC_0319

Cerebellar astrocytes are born through a remarkably ordered developmental program and can contribute to ataxic motor features through Sox2-dependent alterations

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In the cerebellum, astrocytes are characterized by a typical heterogeneity, closely related to specific functional features essential for the correct development and functioning of this brain area. However, the ontogenesis of such astroglial diversity remains poorly explored, and to what extent astrocyte defects may specifically contribute to cerebellar disfunctions in ataxia still needs to be fully clarified. By combining in vivo clonal analyses employing StarTrack plasmids and Confetti mice with proliferation studies, we investigated cerebellar astrogliogenesis and demonstrated that the major astrocyte types derive from embryonic and postnatal progenitors with diverse lineage potentials. Moreover, astrocytes heterogeneity appeared to emerge according to an unprecedented and remarkably orderly developmental program, likely driven by deterministic components as suggested by in silico simulations. Searching for intrinsic determinants involved in cerebellar astrocytes development, we focused on Sox2, transcription factor required for the development and maintenance of neural stem cells and whose loss was associated to CNS defects, in which glial cells had been involved. In the cerebellum, Sox2 is active from early embryogenesis in neural progenitors and, namely, is maintained postnatally within one of the main astrocyte types, Bergmann glia (BG), essential for Purkinje neurons functionality and correct motor control. Cre-mediated Sox2 deletion in the whole embryonic cerebellum reproduced ataxic features, with reduction of the cerebellar vermis and a progressive mislocalization of BG during postnatal development. Importantly, Sox2 conditional deletion in postnatal astrocytes reproduced BG defects and caused similar, although milder, ataxic features. These results define a role for Sox2 in cerebellar development and functioning, and identify a functional requirement for Sox2 within postnatal BG, of potential relevance for ataxia in mouse mutants, and in human patients.

Abstract 43
SRC_0320

Unravelling the cerebellar role in social cognition: new evidence from functional connectivity study in cerebellar patients

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Objectives. In the context of social cognition, recent evidences have showed the cerebellar involvement in function-specific mentalizing and mirroring processes (Van Overwalle & Marien, 2016). According to these findings, some areas of the cerebellum are preferentially recruited for social mentalizing. In particular, a mentalizing area in the posterior cerebellum, specifically Crus II, has been shown to contribute to more complex and abstract forms of social processing, together with mentalizing areas located in the cerebrum including the dorsal medial prefrontal cortex (mPFC), the temporo-parietal junction (TPJ) and the precuneus. The present study investigated the patterns of functional connectivity (FC) alterations within this mentalizing cerebello-cerebral network associated with cerebellar damage and cerebellar patients' social performances. To this aim, patients with neurodegenerative disease of the cerebellum and a group of healthy subjects have been enrolled. Material and Methods. All participants underwent an MRI acquisition protocol at 3T including resting-state fMRI scans for functional connectivity analysis. Patients' social cognition profile was also assessed. According to results of Van Overwalle and Marien (2016), 5 regions of interest were used to obtain a connectivity matrix for each subject. The network-based statistics (NBS) tool developed by Zalensky et al. (2010) was performed to assess within-group differences in FC between mentalizing cerebellar and cerebral "nodes". Results and Conclusions. When compared to controls, patients showed a specific pattern of altered FC from dmPFC and left and right TPJ to posterior cerebellar Crus II. The present results suggest that FC changes between function-specific cerebello-cerebral mentalizing nodes may specifically account for social impairment in patients affected by cerebellar damage.

Abstract 44
SRC_0322

Cerebellar contribution to affective processing revealed by non-invasive brain stimulation

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Growing evidence suggests that the cerebellum plays a critical role in non-motor functions, contributing to cognitive, affective and social processing. Recently, we have carried out a series of experiments using Transcranial Magnetic Stimulation (TMS) to investigate the possible causal contribution of the (left) cerebellum in affective processing. We targeted the left cerebellar hemisphere in light of prior evidence specifically pointing to this region as crucial in emotional processing. TMS is largely used in cognitive neuroscience to investigate causal structure-function relationships.
In a first study, participants were presented with facial emotional expressions that had to be explicitly discriminated or that were incidental for the task at play (i.e., face gender discrimination). Cerebellar TMS affected both explicit and implicit emotional processing, whereas it was not detrimental for judging neutral face features (ruling out unspecific effects of stimulation on visual discrimination).
In a following study, we extended the investigation to the role of the cerebellum in emotion processing by considering bodies (rather than faces) as stimuli. Indeed, growing evidence suggests the importance of body signals in conveying affective information. Interestingly, cerebellar TMS interfered with body emotion discrimination but only when the emotion expressed was anger. Thus, our results show that the causal role of the cerebellum in processing emotional stimuli generalizes to emotional body postures, although body emotions of different valence seem to elicit cerebellar activity to a different extent.
Overall, our findings point to a critical role of the cerebellum in affective processing, with important clinical implications. Indeed, cerebellar dysfunctions have been associated to psychiatric disorders (such as schizophrenia and autism), and cerebellar TMS has already been successfully tested as a therapeutic tool for psychiatric syndromes.

Abstract 45
SRC_0324

Cerebellum and mental state recognition: Anodal cerebellar tDCS enhances the mentalizing process in patients affected by cerebellar atrophy.

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Recent clinical studies in patients with cerebellar damage evidenced impairments in basic emotions and in mental states recognition (Sokolov et al. 2018). It has been proposed that the cerebellum plays a role in these two aspects of the mentalizing process by its connections with limbic and associative areas (Van Overwalle et al. 2014). In 2012, Ferrucci et al. demonstrated that the transcranial direct current stimulation (tDCS) over the cerebellum improves the emotion recognition processing in healthy subjects. However, no study investigated these aspects in patients with cerebellar disease. Aim of the present study was to investigate the effect of the cerebellar tDCS on the mentalizing process when the cerebellum is damaged.
The ability to attribute mental states to others was tested before and after the cerebellar tDCS, by using a computerized version of the 'Reading the mind in the Eyes test' (Baron-Cohen et al. 2001), that includes also perceptive and motor stimuli. Two patients affected by cerebellar atrophy underwent 3 counterbalanced experimental sessions in which anodal, cathodal or placebo stimulation was applied. A repeated measures analysis of variance for accuracy and RT was run, considering 3 main factors: condition, time and stimulus type. The post hoc test was applied when appropriate ($p<0.05$).
The cerebellar patients showed a selective improvement in mental states recognition processing after the anodal cerebellar tDCS, as revealed by the RTs reduction between the baseline and post-stimulation session ($p<0.005$) for the mental states stimuli. No significant effect was found in the cathodal and placebo conditions and for perception and motor stimuli. These findings show for the first time a direct cerebellar contribution in the first automatic stage of the mentalization and suggest that the anodal tDCS over the cerebellum might constitute an effective strategy to modulate this ability in patients with cerebellar dysfunctions.

Abstract 46
SRC_0328

On the social role of the cerebellum: a focus on the understanding of social sequences in patients affected by cerebellar neurodegenerative disease

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Objective: The literature on patients with cerebellar disease established a role of the cerebellum in detection and generation of motor and cognitive sequences. It has been advanced the cerebellum might play a role in understanding the sequencing of social actions in order to build efficient human relations. The sequencing of actions is a prerequisite for social understanding, since it may contribute to handling social environmental stimuli in order to understand and predict behaviours. Such a process includes the ability to infer intentions and beliefs, referred to as Theory of Mind. According to the theory of a cerebellar role in social sequencing, deficits in social mentalizing were reported in patients with cerebellar disease. To test the hypothesis of a cerebellar role in understanding social events specifically when a sequential processing is required, we compared the performances of patients affected by cerebellar neurodegenerative disease with those of healthy matched controls.
Material and methods: All participants were administered two advanced social tests: "The Faux Pas test", assessing the ability to infer mental states by means of cognitive and affective processes not requiring sequences reconstruction; the "Picture Sequencing Test" and "Stories Sequencing Test", that need the generation of correct chronological order of social events involving mental states attribution and non-social events displayed on a tablet, illustrated in cartoons or phrases. All patients underwent a brain MRI, a neurological and a cognitive-affective assessment.
Results and Conclusion: The results showed cerebellar patients' impairments in the ability to reconstruct social actions compared to the non-social ones, particularly when involving false belief reasoning. These preliminary results confirm a cerebellar function in modulating theory of mind ability when understanding social sequences is necessary, thus giving more insight into the role of the cerebellum in social domain.

Abstract 47
SRC_0331

Modulation of cerebellar and basal ganglia loops affects vestibular perception in Parkinson's Disease

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Vestibular information is critical for postural control in Parkinson's Disease (PD), where falls are the lead cause of morbidity and mortality. The cerebellum processes vestibular information and interacts with basal ganglia via subthalamo-ponto-cerebellar and cerebello-thalamic projections, which deep brain stimulation (DBS) can modulate. In this study, experimentation and computational modeling were used to investigate how DBS affects balance in PD.
Individuals with subthalamic nucleus (STN) DBS for PD who had an abnormal percept of motion (spinning, vertigo) were identified. Symptoms were systematically examined at various DBS settings. Also, vestibular perception was examined in a two-alternative-force-choice psychophysics task using a six degree-of-freedom motion platform. Post-DBS brain imaging was fused with an atlas of deep white matter tracts derived from MR tractography. Using volume of tissue activated (VTA) models, the percent activations of cerebello-thalamic, internal capsule, hyperdirect, medial lemniscus, lenticular fasciculus, ansa lenticularis, and subthalamopallidal tracts were generated.
In the force choice task, STN DBS changed the participants' perception of linear motion. Also, modeling determined that self-motion perception occurred when DBS locations closest to dorsal STN were active. Such modulation consistently activated 90-100% of the cerebello-thalamic tract. In addition, activations of lenticular fasciculus and ansa lenticularis were variable ranging from null to >90%, as was activation of hyperdirect pathway (53-100%).
The results suggest that vestibular modulation by STN DBS relies on two mechanisms: orthodromic stimulation of cerebello-thalamic fibers, and anterograde modulation of subthalamo-ponto-cerebellar projections (via direct stimulation of the subthalamus or via ansa lenticularis modulation). While suggesting the involvement of the cerebellum, these results suggest possible DBS targets to modulate balance function in PD.

Abstract 48
SRC_0338

Transmembrane protein 240, mutated in spinocerebellar ataxia 21, is involved in cerebellar afferent connections to Purkinje cells

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Missense mutations and a stop mutation in transmembrane protein 240 (TMEM240) have been reported as the causative mutations of spinocerebellar ataxia 21 (SCA21). The aim of the present study was to explore the expression of TMEM240 in mouse brain at the tissue, cellular and subcellular levels. Immunofluorescence labeling highlighted TMEM240 protein expression in different areas of the brain with higher values in hindbrain and cerebellum. Focusing on cerebellum, TMEM240 is detected in the white matter and in the cerebellar cortex, mostly in Uvula and Nodulus lobules. In the cerebellar cortex, the protein is localized in all three layers, in different cerebellar neurons, and especially in Purkinje cells. Interestingly, TMEM240 is involved in climbing, mossy and parallel fiber afferents projecting to Purkinje cells as evidenced by co-immunostaining with VGLUT1 and VGLUT2. Next, we investigated synaptic expression of TMEM240 by co-immunostaining with Synaptophysin. This synaptic expression was validated by electron microscopy localizing TMEM240 at the post synaptic side of synapses around the Purkinje cell soma. Finally, similar expression was observed in human cerebellum. Our study suggests that TMEM240 might have a crucial role in cerebellar network, especially in synaptic inputs converging to Purkinje cells. The present data provide new characterization of TMEM240 expression in normal mice brain, leading to future ways to explore the physiopathological mechanisms underlying SCA21.

Abstract 49
SRC_0341

Realistic Models of Cerebellar Stellate Neurons Predicts Intrinsic Excitability and the Impact of Synaptic Inputs

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The cerebellar stellate cells (SC) are inhibitory interneurons located in the molecular layer (ML) of the cerebellum. These cells receive excitatory inputs from parallel fibers (pf) and their branched axons make inhibitory synapses with Purkinje cells and other SCs. We reconstructed a multi-compartmental biophysically realistic SC model in Python-NEURON (Python 2.7; NEURON 7.5) to investigate the SC electrophysiological properties. 3D morphologies of mouse neurons were reconstructed from fluorescent images obtained with a confocal microscope and analyzed with Neurolucida. Ionic channels were located on the morphology compartments according to immunohistochemistry data. The maximum ionic conductances (Gi-max) were tuned to match the firing pattern revealed by electrophysiological recordings in mice cerebellar slices using patch-clamp techniques. SC discharges elicited by step current injections were used as templates to extract the features needed to assess the fitness function for the optimization procedure. Gi-max tuning was performed by automatic parameter estimation algorithms, using the multi-objective genetic algorithm in Blue Brain Python Optimisation Library (BluePyOpt). Optimized models reproduced the experimental results, showing spontaneous firing, an almost linear I/O relationship following positive somatic current injections, sag in hyperpolarizing direction following negative current injections, synaptic responses and PSTH following pf inputs and synchronization through gap-junctions. The optimization technique gave satisfactory results, reproducing SC electrophysiological behaviors. The model provided a valuable tool to further investigate the SC function in cerebellar network activity.
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Abstract 50
SRC_0342

Long-lasting response changes in deep cerebellar nuclei in vivo correlate with low-frequency oscillations

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The deep cerebellar nuclei (DCN) have been suggested to play a critical role in sensorimotor learning and some forms of long-term synaptic plasticity observed in vitro have been proposed as a possible substrate. However, till now it was not clear whether and how DCN neuron responses manifest long-lasting changes in vivo. Here, we have characterized DCN unit responses to tactile stimulation of the facial area in anesthetized mice and evaluated the changes induced by theta-sensory stimulation (TSS), a 4 Hz stimulation pattern that is known to induce plasticity in the cerebellar cortex in vivo. DCN units responded to tactile stimulation generating bursts and pauses, which reflected combinations of excitatory inputs most likely relayed by mossy fiber collaterals, inhibitory inputs relayed by Purkinje cells, and intrinsic rebound firing. Interestingly, initial bursts and pauses were often followed by stimulus-induced oscillations in the peri-stimulus time histograms (PSTH). TSS induced long-lasting changes in DCN unit responses. Spike-related potentiation and suppression (SR-P and SR-S), either in units initiating the response with bursts or pauses, were correlated with stimulus-induced oscillations. Fitting with resonant functions suggested the existence of peaks in the theta-band (burst SR-P at 9 Hz, pause SR-S at 5 Hz). Optogenetic stimulation of the cerebellar cortex altered stimulus-induced oscillations suggesting that Purkinje cells play a critical role in the circuits controlling DCN oscillations and plasticity. This observation complements those reported before on the granular and molecular layers supporting the generation of multiple distributed plasticities in the cerebellum following naturally patterned sensory entrainment. The unique dependency of DCN plasticity on circuit oscillations discloses a potential relationship between cerebellar learning and activity patterns generated in the cerebellar network.

Abstract 51
SRC_0345

A role for the cerebellum in semantic memory: a TMS study

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Several studies showed a cerebellar involvement in cognitive non-motor functions. Overall, prediction seems to be the underlying cognitive function linked to the cerebellum. It has also been argued that the same cognitive process - with a different temporal orientation - might underlie prediction and memory. Several studies showed that memory and prediction share common neural substrates, but the cerebellar involvement in domains like these is not yet clear. Here we used transcranial magnetic stimulation (TMS) to investigate the role of the right cerebellar hemisphere (an area linked to semantic prediction) in semantic memory. We found that TMS over the right cerebellar hemisphere impaired participants' ability to recognize the meaningfulness of noun-adjective pairs. Specifically, TMS over the right hemisphere resulted in reduced accuracy of semantic meaningful word pairs such as "red apple" with comparison to non-meaningful word pairs such as "federal cow". Overall, our data suggest that the right cerebellar hemisphere plays a causal role in semantic memory, thus suggesting common neural substrates for memory and prediction.

Abstract 52
SRC_0353

Relation of Internal Models with Motor Control

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The cerebellum learns information coming from external environment, so that arm movements are precisely and quickly controlled. Here, we aimed to clarify relationship between motor learning measuring the clinical indexes in the prism adaptation task and motor control measuring arm movements during the finger chase in the clinical tests.
We developed a computational model and conducted its simulation. In the prism adaptation task, participants wearing the prism goggles repeatedly reached toward the target on the touchscreen on the basis of the target position. We analyzed the horizontal differences between the touch and target positions and calculated the adaptability index (AI) representing capability of cerebellar motor learning. In the finger chase, the participants were requested to follow to a moving target presented on a display with a pointer reflecting his/her index finger. We analyzed the errors which are the differences between the finger-pointer position obtained by our system including the Kinect v2 sensor and the target position on the display were measured in real-time.
The simulation reproduces behaviors of healthy subjects and cerebellar patients (SCA6 and SCA31) in the prism adaptation task. The computational model predicts that the internal models changes during the adaptation. This suggests that AI representing capability of cerebellar motor learning indicates the amount of change of these internal models. In the finger chase, the trajectories of patients' index fingers were different from those of the target movements. The errors of cerebellar patients are significantly larger than those of healthy subjects. We also found that the AIs in the prism adaptation task significantly correlated not horizontal errors but vertical errors in the finger chase. It is suggested that low AI indicates impairment of internal models for gravity information.

Abstract 53
SRC_0359

Representation of self-motion in the lateral vestibulo-cerebellum of rat

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Orientation and navigation are based on the body representation in space, which is fed and updated by the sensory flows, notably from the vestibular system that measures head movements. This system collects two types of information, the rotation and the translation (acceleration) of the head. However, these signals contain ambiguities, the gravity being perceived as an acceleration, that the central nervous system must solve as soon as they enter in the vestibulo-cerebellum (VC) and in the vestibular nuclei (VN). Here we focus on the existence of two integration loops in the nodulo-uvular complex to disambiguate the vestibular signal and examine their activity for natural, self-generated movements.

First, previous electrophysiological recordings in the team showed that median Purkinje cells are widely sensitive to rotation and gravity. However, it is also necessary to extract the linear acceleration of the head from vestibular inputs. So, we first verified that receptive fields of some lateral Purkinje cells present a sensitivity for acceleration. These results are consistent with the existence of a differential integration of gravity along the medio-lateral axis in the nodulo-uvular complex. Second, according to the literature, we know that the rotational and translation inputs are segregated in the cerebellum, in the nodulus and in the uvula respectively. But, reciprocal projections from those two structures via the vestibular nuclei allow to merge the vestibular inputs since projections from one project back to the other. Anterograde injections in the nodulo-uvular complex, suggest that there is a regionalization of the Purkinje cells projections depending of their localisation in the vestibulo-cerebellum. Thus, another integration in the rostrocaudal axis allows the extraction of the gravity from the acceleration signal.
Altogether, these anatomical and electrophysiological results suggest the existence of a double integration of the vestibular signal along the rostrocaudal axis via the vestibular nuclei and along the mediolateral one in the nodulo-uvular complex.

Abstract 54
SRC_0364

Realistic Models of Cerebellar Stellate Neurons Predicts Intrinsic Excitability and the Impact of Synaptic Inputs

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The cerebellar stellate cells (SC) are inhibitory interneurons located in the molecular layer (ML) of the cerebellum. These cells receive excitatory inputs from parallel fibers (pf) and their branched axons make inhibitory synapses with Purkinje cells and other SCs. We reconstructed a multicompartmental biophysically realistic SC model in Python-NEURON (Python 2.7; NEURON 7.5) to investigate the SC electrophysiological properties. 3D morphologies of mouse neurons were reconstructed from fluorescent images obtained with a confocal microscope and analyzed with Neurolucida. Ionic channels were located on the morphology compartments according to immunohistochemistry data. The maximum ionic conductances (Gi-max) were tuned to match the firing pattern revealed by electrophysiological recordings in mice cerebellar slices using patch-clamp techniques. SC discharges elicited by step current injections were used as templates to extract the features needed to assess the fitness function for the optimization procedure. Gi-max tuning was performed by automatic parameter estimation algorithms, using the multi-objective genetic algorithm in Blue Brain Python Optimisation Library (BluePyOpt). Optimized models reproduced the experimental results, showing spontaneous firing, an almost linear I/O relationship following positive somatic current injections, sag in hyperpolarizing direction following negative current injections, synaptic responses and PSTH following pf inputs and synchronization through gap-junctions. The optimization technique gave satisfactory results, reproducing SC electrophysiological behaviors. The model provided a valuable tool to further investigate the SC function in cerebellar network activity.

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