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P1 - Shifted Parvalbumin Interneuron States Elicit Post-Traumatic Stress Disorder-like Memory in Autism

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Autism Spectrum Disorder (ASD) presents with enhanced sensitivity to stress, yet vulnerability to trauma in this condition remains poorly explored. In this study, we aimed to investigate the predisposition to Post-Traumatic Stress Disorder (PTSD) and its protracted impact in ASD. We demonstrated a reciprocal relationship between the two disorders. Indeed, we revealed that exposure to a mild stressful event induces PTSD-like memory in two mouse models of ASD, unlike in control conditions. Remarkably, PTSD-like memory exacerbated two key core traits associated with ASD (social impairments and repetitive movements). We determined that the susceptibility to developing PTSD-like memory in ASD stemmed from prefrontal cortex hyperactivation and changes in fine-tuning of the parvalbumin interneuron firing. These alterations were associated with the dysregulated expression of activity-dependent proteins: the Etv1/Er81 transcription factor, the parvalbumin protein, and the stress-related Neurokinin Receptor 3. Finally, we showed that PTSD-like memory formation in ASD could be prevented by normalizing parvalbumin interneuron activity through the activation of the Neurokinin 3 Receptor. Overall, this study reveals multi-level neurobiological mechanisms that explain the increased vulnerability of developing PTSD in ASD. It provides a framework for examining the impact of stress-induced traumatic memory and interneuron adaptation in autism to ultimately increase the success of therapeutic interventions.

P2 - Epigenetic mechanisms in autism spectrum disorder control neuronal plasticity in the adult mouse brain

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Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders characterized by deficits in social interaction and communication, as well as the presence of repetitive and stereotyped behaviors. The heterogeneous clinical presentation is mirrored by high genetic variability. Indeed, during the last decade, hundreds of different genes have been identified as risk factors for ASD. Although the high genetic heterogeneity, these genes converge in common biological pathways and their identification might help for the development of potential treatments[1]. Among these shared pathways, of particular interest is the regulation of gene expression, essential to orchestrate the transcriptional programs that underlie the maturation of developing neurons and the plasticity of adult neurons[2]. Both structural and functional plasticity of neurons requires a fine regulated transcription of new genes and dysregulation of transcription in either the developing or the adult brain leads to aberrant brain development and impaired cognitive functions.

The aim of this study is to unravel the role of a class of ASD genes, involved in transcription regulation, in modulating neuronal plasticity in the adult mouse brain.

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P3 - Motor anticipation capacities in ASD children: the experience of a double-pointing task

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Autism Spectrum Disorder (ASD) is a neurodevelopmental psychiatric condition characterized by difficulties with social interactions and communication, repeated and stereotypical movements or restricted interests. Altered motor behaviours have also always been observed in ASD children[1]. But, to this day, they are still neglected during rehabilitation phases. Recent studies on animal models have suggested that ASD could be related with a cerebellum dysfunction[2]. Because the cerebellum is particularly involved in the control of anticipation, we proposed to compare the production of sequential pointing movements in ASD and neurotypical (NT) children. Precisely, we focused on motor anticipation of a second movement which occurs during the production of the first part of the sequence (first pointing).

Using a digitizer, 34 NT (18 girls) and 27 ASD children (9 girls), 6-12 years divided into three age groups (6-7 years, 8-9 years, 10-11 years). They've had to point to a target first horizontally situated at a 14cm and then, to another one vertically situated at a 10cm height. These two targets were presented ten times on each side. Concerning the second target, two target widths were used (0,5cm and 4cm). A movement endpoint tolerance was used (from the center of the target: radius +0,2mm). The analyses have been concerned with the velocity of the first movement (V P1). In each group, two subjects were excluded because their results were at +- 2SD of the mean.

Results show an effect of the age group ($p = .05$), a strong significant effect of the group ($p < .01$) and a margin interaction between age group and target width (F (1, 2) = 2.93, $p = .06$). No interaction effect exists between group, age group and target width ($p = .64$).

Thereby, as NT do, during a double pointing task, ASD children can anticipate the difficulty incoming during the production of a current movement and this motor anticipation capacities increase with age. Although their developmental trajectory mimics that of NT children, they stay more slower in each of the conditions. Consequently, motor anticipation capacities of ASD children seems preserved but they present global motor slowness. These results will be discussed with the cerebellum dysfunction theory in ASD.

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P4 - Reversal of neurological and glial deficits by painless Nerve Growth Factor in a mouse model of Rett Syndrome

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Rett syndrome is a rare genetic neurodevelopmental disease, affecting 1 over 10,000 females born worldwide (Chahrour and Zoghbi, 2007), caused by sporadic mutations in the X-chromosome-located methyl-CpG-binding protein 2 (MeCP2) gene (Amir et al., 2000). Despite the great effort put forth by the scientific community, a therapy for this devastating disease is still needed. Here, we tested the therapeutic potential of a painless mutein of the Nerve Growth Factor, called *human NGF painless* (hNGFp) (Cattaneo and Capsoni, 2019), via a non-invasive intranasal delivery in female MeCP2$^{+/-}$ mice. We report that treatment with hNGFp (1) increased the chance of survival, (2) greatly improving behavioral parameters in MeCP2$^{+/-}$ mice. Furthermore, we observed (3) the rescue of a known target population of NGF, cholinergic neurons in the medial septum. Moreover, we reveal (4) a deficit in microglial morphology in MeCP2$^{+/-}$ mice, completely reversed in treated animals. To understand the immunomodulatory activity of hNGFp, we analyzed (5) the cytokine profile after hNGFp treatment in MeCP2$^{+/-}$ mice, to discover that our treatment rescued the expression of key neuroimmune-communication molecules such as Fractalkine (aka CX3CL1) and C-C Motif Chemokine Ligand 1 (CCL1). The overall conclusion is that hNGFp delivered intranasally can ameliorate symptoms in the MeCP2$^{+/-}$ model of Rett syndrome via its pleiotropic activity on both neurons and glia.

P5 - Alteration of mouse cognition and neural circuits formation resulting from mutations in the *Nuak1* gene

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The development of functional neural circuits relies on tightly regulated cellular processes controlled by complex cascades of signaling pathways, culminating in the proper development of axon terminals and synaptic connections. A disruption of these molecular mechanisms can lead to life-altering neurodevelopmental disorders such as autism spectrum disorders (ASD), mental retardation, schizophrenia or cognitive defects. Our team identified previously that the autism-associated protein kinase NUAK1 plays a central role in controlling axonal development in the mouse cortex (Courchet et al. Cell 2013). In addition, we recently described that Nuak1 in haploinsufficient for mouse cortical development (Courchet et al. 2018). Knockout of Nuak1 leads to alterations of cortical connectivity and a wide-array of behavioral alterations including sociability defects, deficits in learning and memory and abnormal sensory gating. Building on this work, we created a humanized mouse line with a mimicking a *de novo* mutation of the Nuak1 gene identified in autistic patients. The targeted knock-in mutation (Q434*) was achieved using the Crispr-Cas9 strategy. By comparison of conditional knock-out and targeted knock-in models, we seek to better characterize the cognitive defects associated to NUAK1 and to identify the alterations in the neural circuits underlying these behavioral alterations. Using a candidate-approach, we obtained evidence that NUAK1 regulates signaling by CREB, a transcription factor, which plays a key role in neuronal plasticity and memory. Our results suggest that the deficit observed in cued- and contextual fear memory is linked to the level of CREB activity at the time of learning.

P6 - Improved discrimination learning after spatio-temporal disruption of Planar Cell Polarity signaling using touch-screen-based test

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To be able to remember past experiences, we need to use two types of memory: one that will allow the "reconstruction" of the memory from sometimes partial information (pattern completion), one that will allow the discrimination of one memory from a very similar one (pattern separation).
Pattern separation (PS) and pattern completion (PC) rely on a key brain structure of episodic memory, the hippocampus. Mechanistically, PS and PC are supported by a hippocampal circuit: the dentate gyrus (DG) and the CA3. Using a conditional knockout, we previously showed that the core Planar Cell Polarity (PCP) protein Vangl2 participate in these processes (Robert et al., 2020). We showed that a specific postnatal deletion of Vangl2 in the DG, impairs the PC and improves the PS processes. In order to bypass the need for Vangl2 deletion and modulate PCP signaling with spatio-temporal resolution, our team developed a molecular construct in order to block PCP signaling, without affecting Vangl2 levels. We injected the virus in the hippocampus of adult animal before testing the mice in PS and PC protocols. For this, we used an innovating and non-aversive technology, called the touchscreen chamber. Our preliminary results show an improvement in the discrimination memory test in the mice model for PCP disruption, supporting our team's previous results.

Key-words: Hippocampus, PCP, behaviour, touchscreen, pattern separation/completion, DG/CA3 circuit

P7 - Core PCP protein Vangl2 shapes the morphofunctional development of the hippocampal mossy fiber synapse and modulates declarative memory processes

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Vangl2, a core protein of the Wnt/PCP pathway, is a known key player in morphogenesis. One of our recent studies has also linked it to the regulation of cognitive function. However, we lack information on the precise role of Vangl2 in different types of synapses associated to specific cognitive processes. Here, we found that the Vangl2 is essential to the development and function of a specific hippocampal connexion, the MFB/TE synapse. We show that Vangl2 is enriched in the postnatal hippocampus, specifically in the DG and CA3. Using 3D reconstruction of both confocal and SBFSEM acquisitions, we show that the early genetic ablation of *vangl2* in mice leads to aberrant morphogenesis of the MFB synapse with long lasting consequences on its structural plasticity. This morphological defe
ct is accompanied by molecular modifications in both pre- and post-synaptic compartments, as well as basal transmission deficits. Lastly, we show that the early loss of Vangl2 leads to specific reference memory deficits in adult animals. Altogether, we show that Vangl2-dependent mechanisms are critical for the correct postnatal morphogenesis and function of the MFB/TE synapse, and altering those mechanisms have long lasting consequences on the flexibility of reference memory. Our data uncover the importance of the PCP pathway in the establishment of hippocampal synaptic connexions and in long term memory.

P8 - Non-cell-autonomous OTX2 transcription factor regulates anxiety-related behavior in the mouse

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The OTX2 homeoprotein transcription factor is required for the proper development of ventral tegmental area (VTA) dopaminergic neurons, which project to limbic structures and medial prefrontal cortex (mPFC)[1,2]. OTX2 is also produced in choroid plexus, from which it is secreted into CSF and transferred to parvalbumin interneurons throughout the cortex, including the mPFC[3,4]. Roles for Otx2 in juvenile and adult control of complex traits such as depression or anxiety have been recently revealed in maltreated children and in mouse models of early-life stress[5,6,7]. We investigated the behavioral consequences of reduced OTX2 levels in Otx2+/- mice and in mouse models for decreasing OTX2 transfer from choroid plexus to parvalbumin interneurons[8]. Both male and female adult mice show anxiolysis-like phenotypes in all models. In Otx2+/- mice, VTA dopaminergic neuron numbers, morphology, metabolic output, and projections remain unchanged. However, parvalbumin expression was reduced in mPFC. This expression could be rescued in part by adult overexpression of OTX2 specifically in choroid plexus, resulting in increased anxiety-like behavior. Taken together, OTX2 synthesis by the choroid plexus followed by its secretion into the CSF is an important regulator of anxiety-related phenotypes in the mouse.

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P9 - Modelling the impact of NRXN1 mutations on neurodevelopmental using patient-derived induced pluripotent stem cells (iPSCs)

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Neurexins are a family of adhesion molecules encoded by NRXN1/2/3 genes, each transcribed by two different promoters to generate the main isoforms NRXN1α/β. NRXN1 play a crucial role in synaptic formation, function, and maintenance. Mutations in NRXN1 have been highly associated with different neurodevelopmental conditions including autism and schizophrenia. Recent studies have linked NRXN1 with a role in regulating early stages of neurodevelopment. However, our understanding of what processes NRXN1 regulates during neurodevelopment is currently unclear. Understanding how variants in the *NRXN1* gene may alter neuronal development, could shed light into how these mutations contribute to increased likelihood for such disorders. Hence, to unravel the molecular mechanism that contribute to autism phenotypes in individuals with NRXN1 mutations, it is necessary to identify the transcriptomic changes during different stages of neuronal differentiation that might drive the cell to acquire an atypical phenotype. To this end, we have generated iPSC lines from individuals with NRXN1 deletions and neurotypical individuals as an in vitro system to re-capitulate different stages of neuronal induction and identify alterations in the gene expression patterns and their functions in cells undergoing neuronal development. Of these lines, we have generated iPSCs from a mother and son pairing with identical NRXN1 deletions, and from a 3rd unrelated individual with a larger, yet overlapping NRXN1 deletion.

Multiple clones from each iPSC line were differentiated towards a forebrain linage, using a dual SMAD inhibition differentiation protocol. We analyzed the expression of NRXN1 main isoforms α and β and other key developmental markers during different time point of neuronal induction. This analysis revealed conserved expression of these genes in control lines. However, NRXN1 isoforms as well as developmental markers showed highly heterogeneous expression in NRXN1 mutated lines. In addition, immature neurons generated from NRXN1 mutant lines, displayed abnormal neurite outgrowth compared to immature neurons generated from control line. RNAseq analysis of immature neurons further revealed that a number of genes are significantly differentially expressed between the control and the NRXN1 mutated derived neurones including the transcription factors SALL1 and RAX, which play important roles in neurogenesis. Additionally, neurones derived from an autistic individual with a NRXN1-mutation show significant reduction in the expression of genes associated with synaptic formation, function, and maintenance, including glutamatergic pathways. These results suggest that NRXN1 mutations could contribute to the molecular events that distinguish the developmental trajectory from typical and atypical development, and thus contribute to an increase likelihood of a neurodevelopmental condition.

P10 - Alterations of cortical connectivity in a mouse model of premature brain injury

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Cortical circuits are built at perinatal times and gradually refined in an activity-dependent manner during the postnatal period of critical plasticity. Although lesions of the CNS occurring during this period recover better than those occurring later in life, they are often associated with long-term cognitive deficits, which suggests that neuronal circuits rewiring, in particular within the cortex, may either be incomplete or inappropriate. Here we used chronic hypoxia, a mouse model of very premature birth, to study the long-term impact of premature brain injuries on glutamatergic neuron's maturation and cortical circuit's formation. Our results reveal gradual and profound alterations of glutamatergic neurons dendritic arborizations following chronic hypoxia, that differentially affect their apical and basal dendritic compartments. Using retrograde tracing, we show that these dendritic alterations are paralleled by a global cortical hyperconnectivity as well as a redistribution of long-distance cortical connections. Finally, testing of sociability reveals an impairment for social novelty in young adult hypoxic mice, which amplifies in adulthood. Altogether, our results highlight how premature brain injuries, such as those resulting from very premature births, impact cortical neuron maturation and connectivity, as well as associated behaviors.

P11 - Role of noise and variability in atypical sensory information processing in autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social impairments, repetitive behaviors, and,sensory deficits. Sensory deficits are almost universally expressed in ASD subjects but have only recently been included as a core diagnostic criterion in the DSM-5. Since atypical sensory responses have a strong neurobiological basis, they can be measured using imaging or electrophysiological approaches – both in humans and mice. Human studies have shown that sensory responses are characterized by an increased variability or noise in the neuronal responses, but mechanistic investigations of these features are still lacking. Here, we probed the role of neuronal noise and response variability for atypical sensory information processing, and their potential use as translational biomarkers and targetable mechanism, in Fmr1 knockout (Fmr1KO) mice. The Fmr1KO mouse model is one of the most well-characterized models for Fragile X Syndrome (FXS) and ASD. To address these questions, we recorded, in vivo, the responses of individual layer 2/3 pyramidal neurons of the somatosensory cortex to tactile stimulation of the hind paw in anesthetized mice. In addition, we measured the spontaneous activity and intrinsic properties of these neurons, enabling us to link alterations in neuronal excitability, noise, and response variability at the neuronal level.

Our results reveal overall enhanced tactile stimulus evoked responses in Fmr1KO mice compared to their WT littermates, as well as an increased variability of these responses to repetitions of the same stimulus. In addition, Fmr1KO mice presented greater baseline fluctuations of the membrane potential together with a higher power for the commonly used frequency band (delta, theta, alpha, beta, gamma). Importantly, we uncovered a correlation between these parameters and atypical sensory information processing, linking stronger neural responses to increased variability and noisier resting membrane potential. These findings characterize complex and nuanced mechanisms of neural dynamics which may be responsible for the unreliable and temporally imprecise sensory information processing in autism. Our results contribute to the development of a new framework for noisy neural sensory sensitivity, in which modern noise theory promotes multiplicative noise has a key player of neuronal and behavioral variability.

P12 - Maternal genotype as a predictor of severity of offspring autistic-like behavior

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Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired social communication and interaction, and by repetitive and stereotyped behaviors. The mechanisms that govern the development and onset of the disease remain elusive. So, it is relevant to investigate the influence of the maternal genotype on the development of its offspring by looking for cognitive, motor and sensorial, and social skills.

In the present work, we used tuberous sclerosis complex 2 (*Tsc2*$^{+/-}$) mice, an established mouse model of ASD, divided in four experimental groups: WT dams with WT offspring; WT dams with *Tsc2*$^{+/-}$ offspring; *Tsc2*$^{+/-}$ dams with WT offspring; and *Tsc2*$^{+/-}$ dams with *Tsc2*$^{+/-}$ offspring. We performed developmental milestones tests to assess pups 'motor ability, sensory system, and pro-social skills from postnatal day (PND) 6 to PND14. Moreover, we recorded maternal-separation elicited ultrasonic vocalizations (USVs) of the pups from PND6 until PND10. Finally, we analyzed maternal instinct through pup retrieval behavior.

We found that regarding developmental milestones tests, mother's genotype significantly influenced surface righting reflex, negative geotaxis and cliff aversion tests. Indeed, the experimental groups whose mother and pups shared the same genotype performed better than the groups where mother and pups differed in their genotypes. However, while the experimental group *Tsc2*$^{+/-}$ mother with *Tsc2*$^{+/-}$ pups performed significantly better in nest seeking test, WT mother with WT pups performed worse. Accordingly, USVs analyses revealed that only the *Tsc2*$^{+/-}$ mother with *Tsc2*$^{+/-}$ pups displayed a more complex vocal repertoire and produced a significantly increased number of vocalizations. This may be hinting towards a genotype-dependent development of social skills.

Again, groups whose mother and pups shared the same genotype display a less anxious maternal behavior, which could in turn be linked to the increased developmental state showed by their pups. This work reveals the impact of maternal genotype in the development of motor, sensorial and social skills of pups highlighting the importance of mother and pup sharing the same genotype.

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P13 - Modulation of oxytocin signaling by immunoglobulin G in aggressive behavior

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Background:
Oxytocin (OT) is a 9 amino acid hypothalamic neuropeptide which activates its receptor (OT-R) triggering intracellular Ca2+ release and internalization. OT plays a major role in promoting social interaction, and deficient OT signalling is linked with stress-related disorders, as aggressiveness. OT-reactive immunoglobulin (Ig) were found in human plasma, correlating with behavioural traits, without knowing if they may modulate OT signalling.
Methods:
We compared IgG biological activity from two groups, control and "aggressive", using HEK 293 cells lines expressing human OT-R.
Ca2+ secretion was assayed using fluorimetry after a 3 minutes incubation with OT (10-7M) or individuals Ig (10-7M) preincubated with OT overnight.
In the same way, OT-R coupled with GFP internalization was followed during 30 minutes with confocal microscopy.
Results:
OT induced a typical Ca2+ releasing with a fast increase and slow decrease kinetics and OT-R internalisation.
IgG/OT proceeded differently: they also triggered a fast increase of Ca2+ liberation with a similar amplitude, but it is followed by a faster return to the baseline. The total Ca2+ secretion, as measured by the area under curve, was decreased by about 50% ($p<0,0001$) compared to OT kinetics, and weaker in aggressive group vs. control ($p<0,0001$).
Internalisation occurs after 5 minutes incubation with OT or IgG/OT, with a slower dynamic for the aggressive group.
Conclusion:
The present data show that IgG/OTactivate OT-R with different kinetics than neuropeptide alone, suggesting that Ig may play a role in OT signalling. The possible relevance of their implication in stress-related disorders remains to be studied.

P14 - Sex dimorphism and circadian cycle as crucial factors for early seizures susceptibility in Tuberous Sclerosis Complex 2 mouse model

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Tuberous sclerosis complex (TSC) is a rare genetic disorder, typically involved in serious neurologic comorbidities, such as severe epilepsy, intellectual disability, and autistic features. Epilepsy is the most common neurological complication in this disorder occurring during infancy or early childhood. $Tsc2^{+/-}$ mice, that display some physiopathology features of TSC, has been a useful model to find new treatments for this disorder. However, little is known about susceptibility to epileptic activity in this mouse model. Given the early onset and prevalence of seizures in TSC, it is crucial to better characterized epilepsy in TSC mouse models during earlier stages of development. Thereby, the purpose of the presented work was to investigate seizure susceptibility in $Tsc2^{+/-}$ mice at juvenile age, given special attention to sex dimorphism and circadian cycle.

$Tsc2^{+/-}$ mice were injected with kainic acid (KA), a potent agonist of the AMPA/kainate receptors, to provoke seizures. Males and females and both non-active (daytime) and active period (nighttime) at post-natal day (P) 30 were studied. The wild-type (WT) littermates were used as controls. Seizure severity was determined according to latency times to the first epileptic event and individual scores over time according to Racine scale for both control conditions (saline, i.p.) and following KA administration (20 mg/kg, i.p.).

Our study demonstrated that juvenile $Tsc2^{+/-}$ mice display increased susceptibility to KA-induced seizures when compared with their WT littermates. Specifically, we observed shorter latency times ($p=0.0446$; Mann Whitney test) and higher Racine scores ($p=0.0597$; Mann Whitney test) in mutant mice. We also showed that seizure susceptibility was differently affected by circadian cycle and biological sex. Indeed, seizure activity was increased during daytime period and for females across all paradigms tested independently of animal's genetic background. As result, only males during nighttime period display significant differences between transgenic and WT mice (Latency times: $p=0.0047$; Racine Scores: $p=0.0488$; Ordinary One-Way ANOVA).

These results put juvenile TSC2 mouse model closely related to the clinical manifestations and supports it use in future TSC-related epilepsy research. Moreover, these results highlight the importance of considering biological sex and circadian time as preponderant factors to study $Tsc2^{+/-}$ juvenile mouse model in development of future therapeutic strategies for TSC-related epilepsy.

P15 - Developmental defects of striatal D2 neurons in a mouse model of Huntington's disease

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Huntington's disease (HD) is an inherited neurodegenerative disorder that typically occurs in midlife with progressive alterations of motor and cognitive functions. This disease is due to the mutation of the gene encoding the Huntingtin protein (Htt) and leads to a severe neurodegeneration in the striatum and cortex. Even if the implication of the Htt mutation in HD is well known, recent studies suggest that Htt mutation is also linked to developmental impairment. Indeed early striatal developmental alterations as hypertrophy and impaired cytoarchitecture have been observed in humans or in rodent models of HD. However this issue remains largely unexplored and these findings raise the question of when do the first disease-related striatal alterations emerge in the disease. To answer this question, we are longitudinally comparing the striatal development between wild type (WT) and the R6/1 mouse model of HD. This mouse line is crossed with a D1-GFP mouse in order to discriminate between direct-pathway (D1-expressing) and indirect-pathway (D2-expressing) MSN subpopulations. This study is performed during the two first postnatal weeks as this period has been shown to be crucial for the maturation of MSN's morphological and electrophysiological properties. Using *ex vivo* whole-cell patch clamp electrophysiology we are recording the intrinsic electrophysiological properties of MSNs as well as the establishment of the cortico-striatal glutamatergic transmission. We are also looking at the morphology of the neurons recorded, especially their dendritic length and complexity and their dendritic spines. Our results suggest that there is a biphasic alteration of D2-MSNs properties in R6/1 mice, highlighted by an early decreased excitability and higher dendritic complexity at postnatal day (P)0-3 that is then replaced by an hyperexcitability and a decreased dendritic complexity at P8-P9. These anatomical and electrophysiological data provide an insight into striatal developmental alterations in a mouse model of HD at very early stages.

P16 - White matter maturation trajectories associated with autistic traits in adolescents

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Autistic traits correspond to the two dimensions of clinical signs characterizing Autism Spectrum Disorder (ASD), but at a subclinical level[1]. They are commonly seen as dimensional in nature, and continuously distributed in the general population[2]. Neuroimaging studies have shown, through the use of diffusion magnetic resonance imaging, an association between microstructural changes in White Matter (WM) and autistic traits in neurotypical children and adults[3] but not in adolescents. Therefore, in this study we would like to examine the relationship between autistic traits and microstructural WM trajectories in adolescents taken from the general population.

Neuroimaging and clinical data were obtained from a large sample of community adolescents recruited around age 14 in middle schools from eight sites in four European countries (www.imagen-europe.com). We analyzed diffusion parameters (e.g. Fractional Anisotropy, FA) using diffusion Magnetic Resonance Imaging, in 674 typically developed participants from the IMAGEN cohort followed four times: 14-15 years, 16-17 years, 18-19 years and 23-24 years. Autistic traits were measured using the Social Responsiveness Scale administrated at 16-17 years.

We found a significant interaction between SRS social motivation score and age on the FA for the global white matter skeleton, the right posterior limb of internal capsule, the right retrolenticular part of internal capsule, the right superior corona radiata, the right sagittal stratum the right external capsule, the left and right cingulum, the right fornix and the right superior longitudinal fasciculus.

Our preliminary findings suggest that social motivation traits influence microstructural changes during adolescence and adulthood within white matter tracts that are close or connect cerebral regions known to be involved in the reward system with the internal and external capsules passing through the basal ganglia and the cingulum bundle projecting from the cingulate gyrus, another key structure of the reward system. These results provide elements to understand processes underlies typical and atypical neurodevelopment and may help in differential diagnosis and care of ASD.

[1] Baron-Cohen et al. 2001
[2] Constantino et al. 2003
[3] Hirose et al. 2014

P17 - Cross-areal plasticity of thalamic axons depends on birth sensitive 5-HT levels

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Primary sensory areas of the neocortex are determined by their connectivity with the thalamus, receiving specific projections from distinct first-order (FO) thalamic nuclei. FO thalamocortical axons (TCA) are oriented during embryogenesis towards their cortical target and display a perinatal waiting period before innervating specific area. If TCA are initially misguided, they show an extraordinary capacity to reorient after birth within the neocortex, thereby reaching their proper cortical target. The roles of such sequential targeting and adaptation steps onto areal map formation in normal and pathological conditions remains to be fully understood. Here, using a mutant mouse model in which the trajectory of embryonic TCA is shifted, we found that TCA postnatal rewiring is preceded by a prenatal apoptosis of FO thalamic nuclei, together enabling the formation of sharp, albeit drastically reduced, primary somatosensory (S1) and visual (V1) areas. We furthermore showed that the remarkable postnatal TCA plasticity occurs within a short time-window and is drastically impaired by preterm birth, leading to a maintenance of misguided axons and a blurring of V1 molecular border. At the molecular level, TCA plasticity was regulated by levels of serotonin, which are reduced by preterm birth. Overall, our study reveals sequential embryonic and postnatal checkpoints that enable concerted adaptations of TCA and cortical areas. It also demonstrated that preterm birth impairs a serotonin-dependent plastic time-window which is essential for the rescue of prenatal miswiring and adaptation of cortical map to incoming sensory inputs.

P18 - Contribution of CACNA1H variants in Autism Spectrum Disorder Susceptibility

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Autism Spectrum Disorder (ASD) is a heterogeneous and highly heritable neurodevelopmental disorder, affecting more than 1% of the population[1]. ASD genetic architecture is complex, consisting of a combination of common low-risk and more penetrant rare variants. Voltage-gated calcium channels (VGCCs or Ca_v) genes are strongly associated with ASD susceptibility, consistent with the importance of calcium signaling in neuronal function[2,3].

In order to further investigate the involvement of VGCCs rare variants in ASD susceptibility, we performed whole genome sequencing analysis in a cohort of 105 families, comprising 124 ASD individuals, 210 parents and 58 unaffected siblings.

We identified 53 rare inherited damaging variants in Ca_v genes, including genes coding for the main subunit and genes coding for the auxiliary subunits, in 40 ASD families. Interestingly, biallelic rare damaging missense variants were detected in the CACNA1H gene in ASD probands from two different families. CACNA1H encodes the T-type $Ca_v3.2$ channel, involved in the regulation of neuronal firing and previously implicated in the ASD phenotype[4,5]. Thus, to clarify the role of the identified CACNA1H variants on calcium channel activity we performed electrophysiological analysis using whole-cell patch clamp technique. Three out of four tested variants were shown to mildly affect $Ca_v3.2$ channel current density and activation properties, possibly leading to a dysregulation of intracellular calcium homeostasis, thus altering calcium-dependent neuronal processes and contributing to ASD etiology in these families.

In conclusion, our data further support the role of CACNA1H in neurodevelopmental disorders and suggest that rare CACNA1H variants may be involved in ASD development, providing a high-risk genetic background.

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P19 - Analysis of complex social behaviour during an extended time period in a valproic acid animal model of autism spectrum disorder

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Autism Spectrum Disorder (ASD) is a progressive neurodevelopmental disorder characterized mainly by deficits in social communication and stereotyped behaviours and interests.

One of the recurrent findings in several ASD animal models are deficits in social interactions. This is generally performed using the three chamber's test paradigm that is simple to implement and use but fails to detect complex social behavior on an extended period of time. Here, we set up a novel procedure entitled the Live Mouse Tracker (LMT) that detects several dozens of complex social behavior during three days in groups of 4 mice. For this we used a well characterised environmental animal model for ASD with valproic acid (VPA) injected to pregnant females at E12.5. Studies were performed on male and females offspring. Comparisons were made within groups of 4 animals with same sex and treatment and within groups of 4 animals with same sex but different treatments (saline versus VPA).

We found that VPA mice showed major social deficits and that are different in nature and magnitude in relation with time (from 1 hour to 3 days) and the time period (day versus night). Social deficits were also different when VPA mice were tested together compared to when they are mixed with saline treated mice. This study points out to severe and various impact of VPA treatment on complex social behavior and stresses the need to explore more in depth this behavior in ASD animal models in relation with sex, time period, time window and group composition.

P20 - Maternal dietary n-3 polyunsaturated fatty acids (PUFAs) deficiency – induced cognitive and microglia activity impairments in the offspring – are partially protected by the genetic restoration of n-3 PUFAs levels during development

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N-3 and n-6 polyunsaturated fatty acids (PUFAs) are essential fatty acids that need to be provided to mammals by dietary means. During the neurodevelopmental period, they accumulate in the membranes of brain cells and play a key role both in brain development and function. The developing brain relies on maternal intake of PUFAs which reach the infant through the placenta during gestation and milk or infant formula during lactation. In the last decades, changes in dietary habits of both developed and developing countries have resulted in a reduction in n-3 PUFAs intake in parallel with an increase in n-6 PUFAs intake. Several studies, including ours, have highlighted the deleterious effects of a maternal dietary deficiency in n-3 PUFAs on the offspring brain development. In particular, we have found that an early-life dietary n-3 PUFAs deficiency alters microglia activity and synaptic refinement[1,2] hippocampal neuronal network activity and myelination processes[3] at weaning. The maintenance of mice under the same n-3 PUFAs deficient diet after weaning further impairs prefrontal cortex, accumbal and hippocampal synaptic plasticity[4,5,6] memory and emotional behaviors[7,8,9,10,2,3] at adulthood. Moreover, these alterations are less prominent when mice are exposed to a n-3 PUFAs deficient diet starting after weaning[5,11] suggesting that n-3 PUFAs levels in the developing brain are crucial in the behavioral trajectory.

In this work, we aimed to determine whether the maintenance of n-3 PUFAs levels in the offspring during development protects them from the deleterious effects of a maternal dietary deficiency in n-3 PUFAs, taking sex into account. To do so, Fat-1 transgenic male mice, expressing the *fat-1* gene from *C.elegans* which allows the conversion of n-6 PUFAs into n-3 PUFAs, were mated to wild-type (WT) female mice exposed to a diet deficient in n-3 PUFAs during gestation and lactation. Then, at weaning, we studied brain PUFAs levels, microglia phagocytosis of synaptosomes and behavioral outcomes of WT and Fat-1 offspring maintained in a n-3 PUFAs deficiency maternal environment. Our results show that n-3 PUFAs levels in the brain of both male and female Fat-1 offspring were higher compared to WT offspring. In addition, hippocampal-dependent working memory abilities were preserved in both male and female Fat-1 offspring. However, no significant difference was detected between the phagocytic activity of microglia Fat-1 and WT, despite differences in the microglia phagocytic activity according to sex. Altogether, our results indicate that the genetic maintenance of n-3 PUFAs levels both in male and female during gestation and lactation protects them from deleterious effects of a maternal dietary n-3 PUFAs deficiency.

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P21 - Post-weaning n-3 PUFA improves memory and synaptic plasticity alterations induced by developmental n-3 PUFA decrease according to sex

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The brain contains n-3 and n-6 polyunsaturated fatty acids (PUFAs), which have distinct biological activities. PUFAs are provided through the diet and aggregate in the brain since the perinatal period. Our previous data show that perinatal dietary n-3 PUFAs deficiency changes amounts of n-3 PUFAs in the hippocampus, alters spatial memory and impairs hippocampal neuronal plasticity in male mice at weaning (P21). Here, we aim at deciphering whether a n-3 PUFAs-sufficient diet reverses the effect of perinatal dietary n-3 PUFAs deficiency taking into account sex.

We carried out several cohorts of animals (male and female CD1 mice) comprising a balanced group on a n-3 PUFAs sufficient diet, a deficient group on a n-3 PUFAs deficient diet and a reversed group : animals are exposed to a n-3 PUFAs deficient diet from gestation until P21, then they are fed with a n-3 PUFA balanced diet. We assessed spatial memory abilities, fatty acids and their metabolites in the hippocampus and plasticity. In addition, a genetically modified mouse model expressing iFat1, a C Elegans gene allowing to convert n-6 into n-3 PUFAs into Camk2-cre positive cells, was created to study whether a specific increase of n-3 PUFAs in glutamatergic neurons counteract the deleterious effect of n-3 PUFAs-deficient diet.

A n-3 PUFAs-sufficient diet given at weaning restores plasticity in both male and female adult mice, while it partially restores hippocampal fatty acids levels and memory.

Perinatal exposition to a deficient diet impairs hippocampal PUFAs levels, memory and plasticity. Interestingly, exposition to a sufficient diet from weaning reversed plasticity alterations and cognition as well as fatty acid levels in the brain but in a different way between the two sexes.

Layé, 2010; Lafourcade et al., 2011; Bazinet et Layé, 2014; Joffre et al., 2014; Delpech et al., 2015; McNamara et al., 2015; Thomazeau et al., 2016; Manduca et al., 2017; Robertson et al., 2017; Layé et al., 2018; Larrieu and Layé, 2018 ; Madore et al., 2020 ; Martinat et al., 2021.

P22 - A BDNF/LKB1/NUAK1 signaling pathway regulates the development and function of cortical circuits in the mouse

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Identifying the molecular mechanism underlying the formation of neural circuits is a critical step to understand the physiopathology of socially-devastating neurodevelopmental diseases. The correct patterning of long-range axonal connections rely on the coordinated activation of cell-intrinsic signaling pathways in response to environmental cues such as trophic factors, guidance molecules and synaptic activity. The kinase LKB1 has been linked to several aspects of axon development (ie. axon formation and terminal axon branching) through the sequential activation of intracellular signaling pathways involving effector kinases such as the autism-linked kinase NUAK1. Yet the extracellular factors ensuring the spatial and temporal regulation of LKB1-dependent signaling in the axon remain largely unknown. We now gathered evidence that a single Serine residue (S431) in the C-terminal end of the protein LKB1 acts as a molecular switch to integrate extracellular neurotrophin signaling. *In vivo* analyses of callosal axon development revealed that S431 phosphorylation is necessary for terminal axonal branching of layer 2/3 pyramidal cortical neurons. Interestingly, branch formation on other regions of the brain such as the layer 5 ipsilateral plexus was largely unaffected by the S431A mutation, suggesting that BDNF conveys spatial specificity to LKB1-mediated signaling. Finally, LKB1 S431A knock-in mice show a range of behavioral alterations, including a decrease in the preference for social novelty (but not social preference), similar to phenotypes previously described for NUAK1 mice. As a whole our results indicate that a LKB1/NUAK1 signaling pathway integrates extracellular BDNF signaling to promote axon branching and participates in the balance between ipsilateral and contralateral axonal projections.

P23 - Novel MPDZ/MUPP1 transgenic models confirm *Mpdz*'s role in social-psychological disorders associated with hearing and vestibular dysfunction.

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Congenital hydrocephalus is a common heritable anomaly. Mutations in MPDZ gene have been reported in patients with autosomal recessive congenital hydrocephalus (HYC2, OMIM #603785) with brain and eye anomalies (heterotopia, coloboma). Some sensory neuronal hearing loss and mild Intellectual Disability we also reported, the later believed to be a consequence of hydrocephalus (Shaheem et al., 2017). Also, genetic variation within Mpdz has been associated with alcohol and sedative dependence in humans, which suggest that it may regulate responses to multiple drug of abuse (PMID35095607).
Mice models recapitulate hydrocephalus deficits, as well as addiction-related phenotypes, but hearing and balance, learning and memory, or other emotional or social deficits were not, or poorly, addressed. We generated two *MPDZ* mice models with an early deletion of the MPDZ/MUPP1 gene, one for the forebrain and bypassing the hydrocephalus phenotype and one for the inner ear, to characterize specifically these deficits.
We subjected our mice models to a series of behavioural tests in relation to neurodevelopmental disorders such as intellectual disability, autism spectrum disorder as well as in relation to emotional and disruptive Disorders. We also analysed them during development in tasks requiring motor coordination, balance and motor skills. Our preliminary data identified the exact nature of emotional, cognitive and social behavioural disorders associated with hearing and vestibular dysfunction specifically linked to the MPDZ gene.

Key-words: Mpdz, Mupp1, hydrocephalus, psychological comorbidities, hearing and vestibular dysfunction.

P24 - Bacterial peptidoglycan-sensing molecules are expressed in the mouse hypothalamus during specific temporal windows of postnatal development

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Pattern-recognition receptors that recognize conserved microbial molecular signatures such as bacterial surface molecules (e.g., peptidoglycans, PGN) have emerged as potential regulators of gut microbiota-brain interactions. PGN-sensing molecules are highly expressed in various brain regions underlying cognitive functions, like prefrontal cortex and hippocampus, during postnatal life. Moreover, the absence of PGN-recognition protein 2 (Pglyrp2) leads to abnormal social development in mice. The hypothalamus is a key brain region involved in the regulation of social behavior, mainly through the production of the neuropeptides oxytocin (Oxt) and vasopressin (Avp). However, little is known about the expression of PGN-sensing molecules in the hypothalamus. Using expression-profiling techniques, we found that two families of PRRs that specifically detect PGN [i.e., PGN-recognition proteins (Pglyrp1-4) and NOD-like receptors (Nod1 and Nod2)] and the PGN transporter PepT1 were highly expressed in the hypothalamus during specific temporal windows of postnatal development in C57BL/6J mice. Specifically, the gene expression levels of Pglyrp2, Nod2 and PepT1 were significantly higher during the first few days of life, thereafter, decreasing to adult levels. In contrast, Pglyrp1 and Nod1 mRNA levels were significantly lower during the first postnatal days than in adults, after which they increased to peak levels at postnatal days 7 and 21, respectively. Interestingly, we did not find any significant sex differences in their expression levels. In addition, there was an age-dependent increase in Oxt and Avp mRNA levels. These findings suggest that the gut microbiota, via the central activation of PGN-sensing molecules, could influence the development and function of the hypothalamus.

P25 - Perinatal Exposure to a pollutant mixture, combined to a mild inflammatory episode induces long lasting motor coordination impairment and emotional disturbances in offsprings

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In recent decades, the number of neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) has steadily increased. It has long been considered that these pathologies were mainly caused by genetic factors but more and more studies tend to show such diseases to be the result of a combination of genetic and environmental factors, a concept commonly referred as the "multiple-hit hypothesis". This assumption suggests that environmental exposures act in concert to "sensitize" brain tissue, making it more vulnerable to other exposures later in life. These environmental influences include toxins / pesticides exposure and/or infection (symptomatic and asymptomatic). The multiple-hit concept is strengthened by an increasing number of studies have shown that early exposure, especially during essential windows of brain development, to such agents is likely to modify the "fate" of brain development through neural and/or inflammatory processes leading ultimately to neurodegenerative disturbances later in life. This also relates to the relatively recent concept of "DOHaD = Developmental Origin of Health and Diseases". Alterations in neural progenitor production, proliferation and migration (among other processes) are strongly suspected to be centrally involved in such a phenomenon. Concomitantly to these brand new theories, numerous studies emphasize the importance to consider "cocktail effects" when risk assessment of environmental contaminants is addressed. Unfortunately, few studies have been implemented to concomitantly address all these issues.

This was the main goal of our study: implementing an experimental protocol «closer» to actual exposure conditions. In order to assess the neurodevelopmental effects, two protocols have been designed: either a chronic maternal pre-toxicant - β-N-methylamino-L-alanine (BMAA) (50 mg/kg), Glyphosate (GLY) (5 mg/kg), and Ammonium Glufosinate (GLA) (0.2 mg/kg) - exposure to a post-natal inflammatory challenge (post-natal day 5 LPS injection at 0.008 mg/kg) (**protocol 1**). At the contrary a prenatal low inflammatory challenge (IP LPS injection at 0.008 mg/kg) - followed by a chronic combined exposure to 3 environmental toxicants (BMAA 50 mg/kg, GLY 5 mg/kg, GLA 0,2 mg/kg; 3x/week) (**protocol 2**) has been settled. It would allow as well as the determination of a link between this co-exposure and the late occurrence of neuropathologies. A battery of tests assessing motor (Rotarod test) and emotional abilities (Openfield Test) was performed at different stages of development.

Behavioral results from **protocol 1** showed in adolescence (from P35 to P42) that a toxicant exposure combined with low inflammatory challenge appears to induce motor disorders. These attend to be confirmed in adulthood (from 3 months) and later during aging (from 14 months). In addition, an altered emotional behaviour has been shown in the Openfield test in these individuals. Interestingly, similar results were obtained from the **protocol 2** when animals were exposed to the mixture postnatally preceded by a maternal mild inflammatory episode, from adolescence to aging. These data suggest that a mild inflammatory event (pre or post-natal) could modulate a multiple toxins exposition during a critical cerebral development phase. These could highlight a part of a new experimental model of ALS with environmental origin that would open pathways from a therapeutic point of view and that would be of crucial importance in understanding this pathology.

P26 - Autistic-like behavioral effects of prenatal stress in the Fmr1-KO mouse model of Fragile X syndrome

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Fragile X Syndrome (FXS) is the most common heritable form of mental retardation and the main monogenic cause of autism spectrum disorder (ASD). FXS is due to a mutation in the X-linked FMR1 gene and is characterized by motor, cognitive and social alterations, mostly overlapping with ASD behavioral phenotypes. The severity of these symptoms and their timing may be exacerbated and/or advanced by environmental adversity interacting with the genetic mutation. We therefore tested the effects of the prenatal exposure to unpredictable chronic stress on the behavioral phenotype of the Fmr1 knock-out (KO) mouse model of FXS, including locomotion, spatial memory, social interaction and communication. Our findings demonstrate the relevance of early environmental stressors in interacting with genetic factors to influence the age-dependent appearance of selected FXS- and ASD-like phenotypes.

P27 - N-3 polyunsaturated fatty acids as an early life nutritional intervention to counterbalance c-section delivery linked gut-brain axis abnormalities and gut dysbiosis

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Early primocolonization patterns play a fundamental role in the bidirectional communication between the gastrointestinal tract (GIT) and the central nervous system (CNS) being a major actor in the gut-brain axis[1]. Perturbations in this critical period can impact neurodevelopment and lead to adverse mental health outcomes later in life[2]. Indeed, human studies have demonstrated that caesarean section delivered (CSD) newborns have an altered microbiota and a higher risk of developing chronic diseases later in life including some neuropsychiatric disorders[3]. Furthermore, it has been found that dietary habits play a crucial role in creating a host-specific gut microbiota, being possible to define preventive strategies that operate by modifying the altered newborn microbiota and that thus limit gut-brain axis disruptions associated with later-life diseases risk. Our central hypothesis is that the microbiota plays a key role in the correlations found between CSD and the risk of later-life disease and that it is possible to modulate early-life microbiota to prevent later life neuropsychiatric disorders using a nutrition intervention based on Docosahexaenoic acid (DHA). DHA is an n-3 polyunsaturated fatty acid (PUFA) with potent immunomodulatory activities, including in the brain and known by being able to modulate the gut microbiota. In contrast to other nutrients, it is also easily transferable from the mother to the pups by the mother milk[4,5]. Our results show that CSD mice show alterations in the diversity and composition of the microbiota at 5 days of life compared to VD mice of the same age, alterations in the structure and permeability of the intestine. In addition, CSD mice have higher levels of circulating and colonic inflammatory markers than VD mice. Taken together, these data data indicate that caesarean section alters the gastrointestinal-microbiota sphere and immunity, including a bias towards a pro-inflammatory status. Behavioural studies show that at weaning, the proportion of CSD pups showing alterations in social behaviour is higher than in VDs, especially in females. Anxiety was measured by the elevated plus maze (EPM) test and revealed a significant effect of delivery mode, independent of sex. In adolescence, a significant effect of parturition mode on social interactions was found. In this case, the proportion of male CSD mice showing interaction alterations was higher than that of VDs, but this trend was not found in females. In the Y-maze test, significant differences in the time spent in the arms were observed in CSD mice compared to VD mice, suggesting that the mode of delivery influences spatial memory. Anxiety measured by the EPM test reveals that CSD mice are more anxious than VD mice, regardless of sex. A number of proinflammatory/microglia activating genes were differentially increased in brain structures of CSD/VD mice irrespective of sex. Taken together, this first set of results suggests that caesarean section has an impact on the behavioural sphere and neuroinflammation early in postnatal life, notably through increased anxiety and inflammatory markers in several brain regions.
We are currently analysing the experiences with DHA nutritional intervention.

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P28 - Phenotype/genotype correlation for TRIO variants in neurodevelopmental disorders: a cellular and molecular approach

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Intellectual Disability and Autism Spectrum Disorders are neurodevelopmental disorders with large genetic components. Deleterious *de novo* mutations in the *TRIO* gene have been identified in different cohorts of individuals with ID and/or ASD, and *TRIO* is now recognized as a risk gene for these disorders.
TRIO is an activator of the GTPase RAC1 and a major regulator of neuronal migration, axon growth/guidance, and synaptogenesis[1]. Mice models with deletion of *TRIO* in the hippocampus and cortex during early embryogenesis present progressive defects in learning ability, sociability and motor-coordination, reinforcing the hypothesis of a contribution of *TRIO* variants to NDDs.

The clinical phenotypes of *TRIO* patients are quite heterogeneous, and it is difficult to establish clear phenotype/genotype correlations. Nonetheless, we have reported an international cohort of 24 individuals with confirmed pathogenic variants in *TRIO* and discovered that these missense variants cluster into 2 mutational hotspots in the *TRIO* sequence[2]. Our functional studies show that Cluster-1 variants (spectrin domain of TRIO) lead to RAC1 hyperactivation, increased neurite outgrowth, and are associated to severe ID and macrocephaly in patients. Cluster-2 variants (RAC1-activating GEF1 domain) lead to an opposite phenotype (hypoactivation of RAC1) and are associated to milder ID and microcephaly. *In vivo*, in the vertebrate *X. tropicalis*, these *TRIO* variants induce defects that are consistent with the human phenotype. Altogether, our data show that spectrin and GEF1 TRIO variants cause opposite modulation of RAC1 activity and we observe a striking correlation between RAC1 activation levels and the head size of the individuals[2]. This work demonstrates a clear phenotype/genotype correlation, with distinct clinical and molecular disorders clustering to these two domains.

More recently, in a new cohort of 25 individuals, we have identified novel pathogenic missense variants in *TRIO*, which reinforce the importance of the spectrin hotspot. Current molecular studies allow us to propose that hyperactivation of RAC1 by variants is due to a release of an autoinhibited basal state of TRIO. We are currently analysing how these pathogenic mutants affect neuronal morphogenesis and development. This work highlights the importance of a tight control of the TRIO/RAC1 signalling in neuronal development, that can be disrupted by pathogenic mutations.

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P29 - Hidden targets of autism spectrum disorders: dissecting the pathophysiology of mutations in the ubiquitin-proteasome system

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In order to enable and maintain the physiological organization and functioning of the cerebral cortex, an internal balance of necessary elements, including protein synthesis and breakdown, are crucial. A prevailing hypothesis suggests that protein levels are altered upon mutations in the ubiquitin-proteasome system (UPS), leading to an accumulation of protein substrates and thus interfering with a usually balanced system. Unsurprisingly, our current understanding supports an involvement of ubiquitin-dependent degradation in the development of autism spectrum disorders (ASDs)[1,2]. Therefore, we aim to decipher effects and consequences of proteasome dysfunction by analyzing the molecular and behavioral changes of a mutant mouse model haploinsufficient for the high risk ASD gene *Wac.*

Wac haploinsufficient animals display hyperactivity, mild sociability defects and aberrant freezing behavior in the contextual fear conditioning task. In addition, *Wac* animals present slight brain abnormalities at juvenile and adult stages. To investigate the effects of Wac loss on brain protein composition and its direct interaction partners, quantitative proteomic analyses are ongoing. The multidisciplinary combination of cellular, molecular und quantitative techniques aims to tackle the role of UPS dysfunction in brain development from multiple angles.

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P30 - Sensory and Cognitive deficits associated with embryonic loss of MPDZ

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Multiple PDZ domain containing protein (MPDZ or Mupp1) is a large cytosolic polarity protein with thirteen PDZ domains present in neurons and epithelial cells. MPDZ is found at the tight junction of epithelial cells (*Marivin et al., 2019*; *Jarysta et al.,* 2021), and at the postsynaptic density of synapses in the brain (*Krapivinsky et al*., 2004; *Jones et al.,* 2009). In both systems, it seems to function as a scaffolding protein, interacting with different partners to control the development and function of the cell.

Mutations in *MPDZ* gene have been reported in patients with autosomal recessive congenital hydrocephalus (HYC2, OMIM #603785) with multiple brain deficits, including mild intellectual disability and certain eye anomalies. Also, genetic variations within *Mpdz* have been associated with alcohol and sedative dependence in both mice and humans, which suggest that it may regulate responses to multiple drug abuse (PMID35095607). Preliminary data from our lab show hearing deficits associated with early deletion of the gene in the inner ear, while *Shaheen et al.,* 2017 report sensorineural hearing loss in one patient carrying 2 heterozygous point mutations in MPDZ gene.

To try and decipher the multi-syndromic effects connected to loss of MPDZ, we created two mice lines with an early deletion of MPDZ, one deleting the gene in forebrain (and thus bypassing the hydrocephalus phenotype) and one deleting in the inner ear. We find that early deletion of MPDZ in the inner ear leads to both apical epithelial defects and basal synaptic disruption of the auditory hair cell suggesting that both defects contribute toward hearing deficits in the mice model. We report learning and memory deficits as well as emotional and sociability deficits from early deletion of MPDZ in the brain.
Taken together, our results suggest that both brain and sensory organ dysfunctions occur in the absence of MPDZ, supporting a peripheral and a central function for MPDZ in hearing and cognition.

P31 - Developmental Landscape of Oxytocin and Vasopressin Networks

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Background:
Oxytocin (OT) and its partner Vasopressin (VP) are two essentials neuropeptides involved in the regulation of species- and sex-specific social behaviors. Decades of research in human and in animal models have demonstrated their direct involvement in social recognition and memory, parental behaviors, social bonding, affiliation and cooperation. As such, they play critical roles in typically developing individuals. They are also thought to be implicated in neurodevelopmental disorders including autism, social anxiety and schizophrenia. Given the importance of the balance between OT/VP over social function, it becomes increasingly important to identify the developmental stages that favor the emergence of such relationship. Yet their spatial co-organization during early postnatal development, which is known to be a sensitive period, is still not clearly defined.
Objective and Methods:
To specifically address the question of whether neurons co-expressing OT and VP exhibit a unique distribution by region and by age stage, we identified the postnatal developpment using high resolution of cellular 3D-imaging of cleared immunolabeled mice brains over four early postnatal (P) stages, from birth (P0), early life (P3, P7, P14) to young adulthood (*Soumier A et al., 2021*)[1].
Results:
Our 3D atlas-based cellular mapping revealed unique anatomical properties of OT and AP neurons in the developing mice brain, showing dramatic differences between and within the two neural networks during very early development. We also found the number of OT neurons doubles according to unique temporal dynamics in selective hypothalamic regions, namely the periventricular and paraventricular nuclei, and in a novel location we named the antero-lateral preoptic. No changes were observed for VP neurons.
Conclusions:
Our findings demonstrate the coexistence of innate (antenatal) and plastic (postnatal) OT/VP circuits, that are triggered by environmental adaption of the social brain.

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P32 - Microglia in early brain development: from ontogeny to impact on inhibitory circuit wiring

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Microglia are instrumental to the development, function, homeostasis and pathologies of the central nervous system. These brain-resident macrophages are generated in the early embryonic yolk-sac, progressively seed and colonize the brain where they self-renew throughout life. They are particularly sensible to systemic signals, such as those derived from inflammation or microbiota at pre- to postnatal stages. We have highlighted a key developmental role of microglia in the positioning of GABAergic inhibitory neurons as well as their subsequent functional integration in the somatosensory neocortex. Transient embryonic microglial depletion, as well as maternal immune activation (MIA), which perturbs microglial activity, modulate fast-spiking Parvalbumin (PV)-expressing neurons that provide perisomatic inhibition and which dysfunctions are at the core of several neurodevelopmental disorders. In particular, we observed an increased inhibitory drive of PV interneurons onto excitatory neurons of the somatosensory cortex, as well as a more widespread horizontal inhibition, revealing a profound miswiring of this major neuronal subtype. Remarkably, this phenotype was specific to juveniles, since PV interneurons showed a reduced inhibitory drive in young adults, consistent with PV deficits described in both autism spectrum disorder rodent models and in patients. Our results provide a novel framework for understanding the impact of microglia and prenatal immune challenges onto the developmental trajectory of inhibitory circuits that leads to pathological brain wiring.

P33 - Impact of Omega-3 Diet on Cerebellar Behavior and Histology in an Environmental Mouse Model of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is characterized by deficits in social communication as well as increased stereotyped and repetitive behavior. Motor and gait impairments are amongst the earliest and most consistent signs of this neurodevelopmental disorder but remain excluded from the diagnosis criteria of the disease[1]. Since the cerebellum is connected to cerebral regions involved in both cognitive and motor tasks, cerebellar dysfunction is highly related to ASD[2]. Recently, omega-3 long chain polyunsaturated fatty acids (PUFA) have been shown to decrease motor symptoms in ASD patients and prevent behavioral deficits in mouse models of ASD[345]. Our main aim is to determine omega-3 long chain PUFA impact on both motor and social behaviors as well as cellular correlates in a well-acknowledged animal model of ASD, the valproic acid model (VPA). Pregnant female mice (C57BL/6J) were injected i.p. either with valproic acid (450mg/kg) or saline solution at embryonic day E12.5. Both dams and offspring were subjected to either omega-3 PUFA long chain supplemented diet or omega-3 precursor PUFA balanced diet from the first day of gestation to the end of the experiment. From P45 on, male and female offspring underwent social and motor behavioral tests before being sacrificed at P60 for histological cerebellar correlates. Our current results indicate that a balanced diet with omega-3 PUFA precursor may be sufficient to alleviate ASD motor and social symptoms and that omega-3 long chain PUFA supplementation brings only limited benefits in these conditions. Omega-3 precursor diet seems to be beneficial regarding Purkinje cell number in VPA-exposed animals; their morphology and localization is currently under investigation. This is an ongoing study that will also investigate lipidomics and fecal microbiota to decipher n-3 PUFA impact on the cerebellum, the metabolism, and the gut physiology.

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P34 – High fat diet-induced obesity decreases social interaction and thermogenic response due to brain redox imbalance in wistar rats

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Introduction:
Obesity is a worldwide public health problem. It causes endocrine, musculoskeletal and behavioral changes in both humans and in experimental models of obesity. However, studies which aim assessing the impact of obesity on behavioral and cognitive changes in females are still scarce.
Objective:
We aimed to analyze the impact of a high-fat diet (HFD) induced-obesity on anxiety-related defensive behaviors, cognitive responses and social interaction in female Wistar rats.
Methods:
Female Wistar rats (n=28; Ethical approval CEUA-8744280818) were randomly divided into two groups: Control Diet (11% fat/n = 14) and High-Fat diet (HFD) (45% fat/n = 14) and subjected to a 9-week nutritional protocol with free access to diet and water. We subjected all animals to the Elevated Plus Maze (EPM) and Open Field (OF) tests. Further, rats were subjected to the Object recognition test (ORT), on short- and long-term duration (60 min and 24hs) and the social interaction test. Rats were euthanized, and collected their brains.
Results:
HFD-induce obesity did not change the anxiety-like defensive behavioral responses in the EPM and OF tests. However, we observed the animals fed the HFD had a longer time of exploration in the new object paradigm when compared to control animals in the short term, with a significant increase in the recognition index in the HFD group when compared to the CD animals. The findings regarding social interaction show a shorter interaction time in obesity-induced as well as the number of interactions. In the social interaction test, the animals fed the HFD had a shorter interaction time and a lower number of interactions. These responses were accompanied by a lower stress reactivity, evidenced by a lower increase in the back temperature, during the social interaction test in the HFD rats when compared to controls. HFD promoted a cerebral redox imbalance in the hippocampus, increasing catalase activity and carbonyl protein, and in the hypothalamus, as it decreased the superoxide dismutase activity.
Conclusion:
HFD impaired social interaction, which was accompanied by a decreased thermogenic response, possibly because of an imbalance in oxidative stress redox. However, it increased object recognition in the short term in obese female rats. Our results increase the understanding of how a HFD affects social behavioral and cognitive process and in female rats.

P35 - The disease-associated synaptic protein synGAP is involved in AMPA receptor organization

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The formation of the synapse as well as their strengthening or pruning is a crucial process during neurodevelopment. Many different proteins are involved in this process and their spatiotemporal expression is finely tuned. Disturbance of this balance due to loss-of -function mutations can have drastic effects on synaptic function and circuit development. The SYNGAP1 gene encodes the synaptic Ras/Rap GTPase-activating protein (synGAP) which is one of the most abundant proteins in the postsynaptic density (PSD) of excitatory synapses. SynGAP interacts with PSD-95, transmembrane AMPAR regulatory proteins (TARPs) and *N-methyl-D-aspartate* (NMDA) receptors at the PSD. The GAP function of synGAP controls the activity of the GTPases Ras and Rap and thus regulates the Ras-MEK-ERK pathway, which is involved in the insertion of AMPARs at the synapse. Over the last decade synGAP has been implicated in neurodevelopment disorders like autism spectrum disorders (ASD), intellectual disability (ID) and epilepsy. Until now the treatment is addressing the symptoms but not the cause. To change this, it is crucial to reveal the underlying molecular mechanism in detail. To understand why loss of synGAP causes an increase of AMPARs at the surface and thus impacts synaptic function we use super-resolution microscopy (SRM). Dual-color direct STochastic Optical Reconstruction Microscopy (d-STORM) enables us to observe alterations in receptor nano-organization as well as co-organization between different synaptic proteins e.g. synGAP, PSD-95 and AMPARs. To investigate changes in AMPAR nano-organization at different stages of development we used primary hippocampal neurons from a heterozygous synGAP mouse line and compared them to neurons from wildtype littermates. Further, we induced long-term depression to study effects of altered synGAP levels on synaptic plasticity and observed an impaired LTD in haploinsufficient neurons. In addition to the SRM approach we performed electrophysiological experiments measuring miniature excitatory post-synaptic currents (mEPSCs) and observed that reduced synGAP levels cause an increased mEPSC amplitude during development. Our goal is to understand the molecular mechanisms underlying changes in synaptic function which are caused by altered synGAP levels in developing neurons.

P36 - BKCa channel as a target to treat auditory impairments in neurodevelopmental disorders

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Auditory impairments, such as hearing loss and hyperacusis (i.e. increased perception of sounds), affect a large part of the human population with a dramatic impact on life quality. These auditory dysfunctions are commonly described in patients with neurodevelopmental disorders (NDDs) and often exacerbate the communication and social deficits typical of these conditions. In subjects with two major NDDs characterized by auditory abnormalities – namely, Fragile X syndrome (FXS) and Williams-Beuren syndrome (WBS) - a reduction in the expression and functionality of a specific population of ion channels, the Big conductance calcium-activated potassium (BKCa) channels, has been reported. This reduction could be linked to the hearing disorders manifested by these patients. Indeed, BKCa channels are highly expressed in the auditory pathway and play a key role in regulating the membrane potential of cochlear hair cells as well as neurons. BKCa channels are therefore potential major therapeutic candidates for auditory impairments in the context of NDDs. Here we tested the effects of a BKCa channel opener molecule (Chlorzoxazone) on the abnormal auditory phenotypes of two mouse models of FXS and WBS, i.e., respectively the Fmr1-KO and CD-1 mouse lines. To this end, we combined acute injections of Chlorzoxazone with behavioural, electrophysiological and molecular analyses, in order to elucidate the role of these ion channels in the etiopathology of acoustic dysfunction. Our results clearly demonstrate that acting on BKCa channels is a valuable therapeutic strategy to treat acoustic dysfunction in these NDDs.