## P.121
## Characterizing the transcriptional profile of L-type calcium channels (CACNA1S and, CACNA1F) in human brain

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Voltage-gated calcium channels (VGCCs) play a significant role in many aspects of brain function including neuronal excitability and synaptic plasticity [1]. At the neuronal level, increases in intracellular calcium in the brain lead to the activation and nuclear localization of transcription factors, followed by increases in gene expression [2]. Large-scale genomic studies implicate that VGCCs, especially L-Type calcium channels (LTCC), are significantly associated with schizophrenia and other psychiatric disorders [3]. However, the molecular mechanisms mediating disorder associations remain obscure. VGCC genes are highly spliced, resulting in functionally-distinct channels which in turn, could profoundly affect the function of VGCCs in human brain [2]. However, the splice profile of VGCCs in human brain is largely unknown.

The aim of this research is to elucidate the coding sequences of the CACNA-genes that encode LTCCs in human post-mortem brain tissues. Here, we present our findings for CACNA1F and CACNA1S in human brain. CACNA1F was previously known to be expressed primarily in retina and CACNA1S is expressed primarily in skeletal muscle but, both were not reported to be expressed in human brain. However, our findings corroborate recent data suggesting that a truncated version of the gene is expressed in human brain. Therefore, we aimed to characterize the truncated isoforms of CACNA1F and CACNA1S.

We examined publicly-available short-read RNASeq data obtained from human brain (produced by the Lieber Institute for Brain Development) for evidence of reads localized to the CACNA1F locus. Guided by this information, truncated isoforms of CACNA1F and CACNA1S were successfully amplified from 8 regions of human post-mortem brain (striatum, thalamus, parietal lobe, cingulate, dorsolateral prefrontal cortex, superior temporal lobe, cerebellum, and occipital lobe) from 6 control subjects using long-range PCR. Nanopore sequencing was then used to reveal the diversity of isoforms of truncated CACNA1F and truncated CACN1S. We identified 152 truncated CACNA1F isoforms expressed in human brain, 21 of which contain unannotated exons. Analysis of CACNA1S is ongoing but the diversity of CACNA1S isoforms across individuals and brain regions will be presented using Principal Components Analysis plots.

We have demonstrated for the first time the presence of a truncated isoforms of CACNA1F and CACNA1S mRNA in human brain. The functional significance of these isoforms is unknown, and will be investigated in our future studies. They are unlikely to encode a functional VGCCs, since they lack the necessary transmembrane domains. However, CACNA1C and CACNA1D have been reported to encode transcription factors from their 3' ends [4]. Finally, our findings highlight how little remains known about the complement of full-length mRNA isoforms present in human tissues. The research will provide a comprehensive catalogue of the VGCC transcript isoforms present across the healthy, adult human brain and will provide an initial insight into the functional significance of key transcript isoforms.

### References

[1] Nanou, E., Catterall, W.A., 2018. Calcium channels, synaptic plasticity, and neuropsychiatric disease. Neuron 98, 466–481.
[2] Simms, B.A., Zamponi, G.W., 2014. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. Neuron 82, 24–45.
[3] Harrison, P.J., Tunbridge, E.M., Dolphin, A.C., Hall, J., 2019. Voltage-gated calcium channel blockers for psychiatric disorders: genomic reappraisal. Br. J. Psychiatry. 24, 1–4.
[4] Gomez-Ospina, N., Tsuruta, F., Barreto-Chang, O., Hu, L., Dolmetsch, R., 2006. The C terminus of the L-Type voltage-gated calcium channel Cav 1.2 encodes a transcription factor. Cell 127, 591–606.

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## P.122
## The involvement of hypothalamic-pituitary-adrenal and monoaminergic systems genes in developing aggressive behaviour

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**Introduction:** Despite frequent comorbidity of aggressive behavior (AB) with several psychopathologies and criminal antisocial behaviours, it is present in everyday life even at high extent thus representing an important social problem causing significant costs to society. It is known that AB is significantly hereditary, but specific gene-environmental (G × E) mechanisms mediating the genetic risk for aggression remain unclear.

**Aim of the study:** The present study aimed to estimate both the main effect of polymorphic variants and haplotypes of oxytocin receptor (*OXTR: rs53576, rs237911, rs7632287, rs2254298, rs2228485, rs13316193*), arginine-vasopressin receptor (*AVPR1A: rs1042615, rs3803107; AVPR1B: rs33911258*), monoamine oxidase B (*MAOB:*

*rs6651806*), serotonin transporter (*SLC6A4: 5-HTTLPR, rs1042173*) and dopamine receptor (*DRD4, rs1800955*) genes and G × E-interactions in individual differences in AB in both clinical forms and mentally healthy individuals considering modulating effect of environmental factors.

**Methods:** The study included 623 mentally healthy individuals (81,11% women; 19.53±1.75 years) of Caucasian origin (225 Russians, 218 Udmurts, 141 Tatars and 39 mixed ethnicity) from Russia. Aggression was assessed using the Bass-Perry's Aggression Questionnaire (BPAQ). In addition, 189 individuals with clinical forms of AB (ICD-10) who committed serious crimes (7% women; 41.53±14.41 years) of different ethnicity (89 Russians, 63 Tatars and 34 Bashkirs), and 254 mentally healthy individuals without any familial history of psychopathologies corresponding to clinical group (12% women; mean age 37.10±18.38 years; 117 Russians, 91 Tatars and 45 Bashkirs) were included in this study. SNPs genotyping was performed using PCR-based KASP genotyping technology on "CFX96" DNA Analyzer (BioRad, USA). Statistical analysis included multiple linear/logistic regression followed by FDR-correction (or permutation test) for multiple testing (PLINK v.1.09). Genotypes and 21 environmental parameters served as independent factors and aggression level as dependent variable.

**Results:** Statistical analysis revealed an association of *OXTR rs2228485 G*-allele (PFDR=0.046) and *OXTR rs237911 G*-allele (PFDR=0.046) with a decreased aggression in healthy individuals of the Tatar ethnic group, while *SLC6A4 5-HTTLPR L*-allele (PFDR=0.046) was associated with an increased aggression level in mentally healthy individuals. Multiple regression analysis demonstrated that smoking (P=0.029) and paternal overprotection (P=0.014) significantly modulated association of *OXTR rs2228485* and aggression level in the total sample of mentally healthy individuals, while severe somatic diseases (P=0.035), alcohol abuse (P=0.034), familial history of psychopathologies (P=0.025) and income level (P=0.023) significantly modulated association of *OXTR rs2228485* and aggression level in individuals with clinical forms of aggression. Haplotype analysis revealed an association of *OXTR G*G*G*-haplotype (*rs53576-rs2228485-rs237911*) and decreased aggression level (PPERM=0.020) in mentally healthy individuals of Tatars origin. Interestingly, in individuals with clinical forms of aggression *G*T*-haplotype (*rs53576-rs2228485*) was associated with an increased aggression risk (PPERM=0.049), while familial history of psychopathology enhanced this association (PPERM=0.046). Moreover, a modulating effect of age (P = 0.003; PFDR = 0.044) on the association of *AVPR1B rs33911258 G*-allele with a decreased risk of clinical aggression was determined, while familial history of psychopathology modulated association of *SLC6A4 5-HTTLPR L*-allele and lower risk of AB.

**Conclusion.** The present study provides evidence that *OXTR, AVPR1B* and *SLC6A4* genetic variants may contribute to AB susceptibility together with environmental factors in clinical and non-clinical manifestations of AB.

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## P.123
## Effect of R-(+)-methanandamide on neural progenitor proliferation in stress condition

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The endocannabinoid system has been largely studied for its involvement in the regulation of cell fate. In particular, it has been shown that both CB1 and CB2 cannabinoid receptors are present in neural progenitor/stem cells and might control these cells proliferation, differentiation and survival [1]. However, previous data have reported both neuroprotective and neurotoxic effects of cannabinoid drugs in vitro, depending on the specific cannabinoid agonist, concentration and the neuronal cell line used [2]. Moreover, the endocannabinoid system and the stress response appear to be mutually modulated. Indeed, acute and chronic stress differently regulate the levels of endocannabinoids in vivo [3]. Furthermore, in vitro studies of neuronal treatment with non-endogenous cannabinoid agonists produce different outcomes in the cell viability depending on the exposure to stressful conditions [2]. Our study investigates whether incubation of human hippocampal progenitor cells (HPCs) with the selective CB1 agonist, R-(+)-Methanandamide (mAEA), influences human HPCs fate in the context of stress exposure (modelled by treatment with cortisol, as per our previously published work [4]).

The multipotent human hippocampal progenitor cell line HPC03A/07 was used to evaluate the effects of mAEA and stress. Cells were incubated with cortisol at 100 uM and/or mAEA at either 100 nM or 1 uM, under proliferating conditions, for 3 days. The number of proliferating cells was assessed with Ki67, whereas apoptotic cells were evaluated with caspase 3 (CC3) immunostaining. Two-way ANOVA with Bonferroni post-hoc test was used to assess differences among groups.

Treatment with cortisol induced a reduction in the number of Ki67+cells, when compared with vehicle treatment (-9%, F=51.07, $p<0.001$), whereas treatment with mAEA (both 100 nM and 1 uM) did not significantly alter the number of Ki67+cells. Interestingly, co-treatment of cortisol with mAEA (both 100 nM and 1 uM) induced a larger reduction in Ki67+cells compared with cortisol treatment alone (-17%, $p<0.01$; -20%, $p<0.01$, respectively). With respect to apoptosis, treatment with cortisol induced an increase in CC3+cells when compared to vehicle (+78%, F=26.80, $p<0.01$). Interestingly, mAEA (both 100 nM and 1 uM) alone did not affect the number of CC3+cells; however, as per the decrease in Ki67 signal, co-treatment of cortisol with mAEA (1uM only) significantly increased the number of CC3+cells with respect to cortisol treatment alone (+50%, $p<0.05$).

Our findings show that the distinct effects of mAEA on neuronal progenitor/stem cells fate depend on the physiological conditions (with or without stress) in which HPCs are proliferating. Indeed, in presence of stress, mAEA treatment caused a decrease in proliferation and an increase in apoptosis which was much stronger than treatment with