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I. **Vanaveski, T**., Singh, K., Narvik, J., Eskla, K.-L., Visnapuu, T., Heinla, I., Jayaram, M., Innos, J., Lilleväli, K., Philips, M.-A., & Vasar, E. (2017). Promoter-Specific Expression and Genomic Structure of IgLON Family Genes in Mouse. Frontiers in Neuroscience, 11. Published 2017 Feb 2. https://doi.org/10.3389/fnins.2017.00038

II. **Vanaveski, T**., Narvik, J., Innos, J., Philips, M.-A., Ottas, A., Plaas, M., Haring, L., Zilmer, M., & Vasar, E. (2018). Repeated Administration of D-Amphetamine Induces Distinct Alterations in Behavior and Metabolite Levels in 129Sv and Bl6 Mouse Strains. Frontiers in Neuroscience, 12, 399. Published 2018 Jun 12. https://doi.org/10.3389/fnins.2018.00399

III. **Vanaveski, T**., Molchanova, S., Pham, D. D., Schäfer, A., Pajanoja, C., Narvik, J., Srinivasan, V., Urb, M., Koivisto, M., Vasar, E., Timmusk, T., Minkeviciene, R., Eriksson, O., Lalowski, M., Taira, T., Korhonen, L., Voikar, V., & Lindholm, D. (2021). PGC-1α Signaling Increases GABA(A) Receptor Subunit α2 Expression, GABAergic Neurotransmission and Anxiety-Like Behavior in Mice. Frontiers in Molecular Neuroscience, 14, 588230. Published 2021 Feb 01. https://doi.org/10.3389/fnmol.2021. 588230

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I. VT participated in writing, data interpolation and analysis, tissue sampling and qPCR assay and performed in silico analysis

II. VT participated in writing, data interpolation and analysis, animal experiment, tissue collection, and data analysis

III. VT participated in writing, data interpolation and analysis, animal experiment, tissue collection, qPCR, and data analysis

ABBREVIATIONS

AAA–aromatic amino acid
αAAA–α-aminoadipic acid
ADHD–attention deficit hyperactivity disorder
AMPH–amphetamine (D-isomer)
ASD–autism spectrum disorder
BCAA–branched-chain amino acid
BPD–bipolar disorder
CNS–central nervous system
DA–dopamine
DLPFC–dorsolateral prefrontal cortex
$GABA_A$–γ-aminobutyric acid receptor type A
GPI–glycosylphosphatidylinositol anchor
KYN–kynurenine
MDD–major depressive disorder
MetS–metabolic syndrome
mIPSC–miniature inhibitory postsynaptic currents
PPARGC1α (PGC1α)–Peroxisome proliferator-activated receptor-γ coactivator-1α
$PPAR_\gamma$–Peroxisome proliferator-activated receptor
PV–parvalbumin
SCZ–schizophrenia
sIPSC–spontaneous inhibitory postsynaptic currents
SST–somatostatin
VIP–vasoactive intestinal polypeptide

INTRODUCTION

Mental disorders are heterogeneous conditions arising from various genetic and environmental insults. The underlying pathophysiology of any given mental disorder is diverse and results in broad clinically significant impairments in an individual's behaviour, emotional regulation, or cognition. A concept of mental disorder varies across a diverse set of cultures and may refer to various individual and societal problems. Classification of a mental disorder is ambiguous because of the overlap with commonly expressed characteristics and should be considered with a degree of flexibility in mind.

> "There are no people anywhere who don't have some mental illness. It all depends on where you set the bar and how hard you look. What is a myth is that we are mostly mentally well most of the time."
> — Mark Vonnegut (Just Like Someone Without Mental Illness Only More So)

Susceptibility genes are related to a presentation of a mental disorder on synaptic, cellular, ensemble, network, pathway, or higher-order levels. Discovery of a mechanistic connection between susceptibility genes and the phenotype they represent has been cumbersome; the scarcity of practical models is one of the main reasons behind it. There is an ever-increasing need to translate human disease phenotypes into a more convenient set of endophenotypes—more defined quantifiable measures of heritable biological traits, which then can be used for hypothesis testing across a diverse group of models. The task is elusive as the heterogeneity of mental disorders poses a major challenge for identifying their neurobiological underpinnings. Nevertheless, societal pressure to be free from economic costs and a detrimental social burden related to mental disorders is a powerful driver of scientific research. Annual direct and indirect economic loss related to mental disorders is estimated at ~1 trillion euros in the European Union alone (Gustavsson et al., 2011). However, the burden of human suffering is only beginning to be accepted as a measure (Vigo et al., 2016).

A priority of neuropsychiatric disease research in the past quarter-century has been a discovery of early markers in efforts to predict disease onset and prevent its progression. The scientific community has approached predictive marker discovery from diverse angles. Some scientific groups have concentrated on data-driven solutions, such as genome-wide association studies, while others have selected a few genes and manipulated their expression in biological models. We have found that association studies demonstrate a great promise in discovering risk loci on a genomic level, but offer little biological insight, whereas animal models are preferred to achieve in-depth insight but are time-consuming and labour-intensive. Animal models have enormously expanded our knowledge in the past few decades. However, our ability to translate this knowledge wealth into effective therapies has not kept up. Perhaps, all the low-hanging fruit have been picked, and an ever-increasing complexity characterises the journey ahead.

The work discussed here combines many relatively new methods and approaches. To summarize them chronologically, we started our research with IgLON family member 3–IgLON3 or LSAMP. In one of our experiments, a fearful stimulus—a predator odour, increased *Lsamp* expression in the amygdala of rodents (Kõks et al., 2004). The predator odour, such as a cat, is hardcoded in rodent fear circuits (Gross and Canteras, 2012). Thus, the experiment indicated a connection between Lsamp and anxiety. Our clinical findings endorsed this linkage, highlighting an association between *LSAMP* polymorphisms and suicidality, major depressive disorder, and panic disorder (Must et al., 2008; Koido et al., 2012). Further study revealed a correlation between *Lsamp* and *Bdnf* expression—a major growth factor related to synaptic plasticity and suicidality in humans (Dwivedi et al., 2003; Heinla et al., 2015). Development of the Lsamp mutant strain further unveiled the potential of the IgLON family. Lsamp mutants demonstrated a diminished response in many evolutionary conserved behavioural domains, such as predator avoidance and social structure maintenance; both are critically crucial for rodent and human survival (Innos et al., 2011; Philips et al., 2015). The plot thickened fast, which fuelled our interest in other family members. Therefore, we set out to characterise the gene expression of five members of the IgLON family, including the expression levels of twin transcripts of *Lsamp*, *Opcml* and *Ntm* in the mouse brain (Vanaveski et al., 2017).

The chronologically second manuscript was motivated by a clinical discovery showing changes in the metabolic profile of first-episode psychosis patients (Kriisa et al., 2017). The discovery drove us to model metabolic changes in mice with an exciting twist; we did not limit ourselves to the dominantly preferred Bl6 strain but also included a possibly predisposed Sv129 strain in the mix (Narvik et al., 2018). Our mission was to induce a psychosis-like state in both strains by pharmacological manipulation using a dopamine-enhancing drug—amphetamine. Interestingly, medical research, including that of mental disorders, relies predominantly on the Bl6 strain and corresponding sub-strains. The Bl6 strain, however, is rather full of life, perhaps reflecting more of a healthy human population than a predisposed one. We found that these strains display different adaptations on metabolic and behavioural fronts (Vanaveski et al., 2018). This paper highlights the feasibility of studying an organism's metabolic profile as there are fewer active metabolites than gene and protein products. Therefore, metabolomics is a promising approach for sound biomarker discovery and accelerates our understanding of complex biological systems.

Chronologically, the third manuscript revolved around the regulatory role of mitochondrial energy production. Our interest here was driven by PPARGC1α (PGC1α), a master regulator of mitochondrial biogenesis—a promising target for therapeutic intervention. The increased expression of PPARGC1α shows an interplay between energy regulation and mitochondrial dysfunction (Piccinin et al., 2021; McMeekin et al., 2021). Although modest overexpression of *Ppargc1α* shows promise in cellular models, it led to adverse side effects in the rodent model. For some time now, we have known that the brain is more of a mosaic with different distinct regions that come together in a complex and selective manner

to give rise to consciousness. Therefore, therapeutic interventions must be specific, perhaps even down to a specific microcircuitry. As GABAergic circuitry has a notable role in the hierarchical management of neural circuit function, therapies could be developed to re-adjust specific GABAergic circuits, which can readjust the pathology on a broader scale. Our model revealed a crosstalk between energy metabolism and GABAergic neuroinhibition, offering new venues for exploration (Vanaveski et al., 2021).

1. REVIEW OF LITERATURE

1.1. The role of genetics in mental disorders

Neuropsychiatric disorders display a variable heritability of ~88% for attention deficit hyperactivity disorder (ADHD; Larsson et al., 2014), ~83% for autism spectrum disorder (ASD; Sandin et al., 2017), ~85% for bipolar disorder (BPD; McGuffin et al., 2003), ~81% for schizophrenia (SCZ; Sullivan et al., 2003), ~37% for major depressive disorder (MDD; Sullivan et al., 2000) and ~32% for generalised anxiety disorder (GAD; Shimada-Sugimoto et al., 2015). The heritability of highly burdensome neuropsychiatric disorders negatively correlates with their population prevalence. For example, autism/BPD/SCZ have high heritability and low prevalence, ~0.5–3% in the general population (Elsabbagh et al., 2012; Clemente et al., 2015; Charlson et al., 2018; Ayano et al., 2019). Presumably, these disorders are determined by relatively higher-impact negative variants in the fringe of the genetic distribution, whereas prevalent disorders, such as MDD and anxiety disorders (MDD, ~14% and anxiety disorder, ~32% prevalence, respectively) share a high overlap with what is considered a normal human phenotype (Merikangas et al., 2010). Therefore, the genetic variants of burdensome neuropsychiatric disorders are subjected to a strong negative selection and are fiercely filtered out from the general population, whereas the variants of prevalent disorders display a lower cost on fitness and remain in the population, enabling a higher rate of a re-emergence of these disorders in future generations (Doi et al., 2009). Perhaps these prevalent disorders, although unwanted, are an intrinsic part of the human experience.

The neuropsychiatric disorders display a variable distribution of low to high-risk variants; for example, ~41% of adult individuals with 22q11.2 deletion syndrome meet the criteria for a psychotic disorder, accounting for ~1% of all SCZ cases (Bassett and Chow, 2008). The high-impact genetic variant is seconded by many lower-impact variants arising from other genetic loci, such as those 108 discovered from a comprehensive study of SCZ (Ripke et al., 2014). Possible combinations of these and still unknown loci would give rise to a wide selection of incrementally different phenotypes or results in a spectrum. The high-impact variants of SCZ are predominantly *de novo* in nature (Singh et al., 2016). *De novo* mutations are concentrated in genes predominantly expressed in the brain and overlap with the genes identified in other neurodevelopmental disorders (Rylaarsdam and Guemez-Gamboa, 2019; Howrigan et al., 2020). However, *de novo* mutations demonstrate a relatively low incidence rate to explain absolute disease risk (Kong et al., 2012; Campbell and Eichler, 2013). Therefore, we can expect a broad distribution of disease genotypes, with a few high-impact mutations, likely *de novo* in one extreme, and a summation of many low-impact mutations, likely generational in another extreme. The genetic variation translates hereafter into a spectrum of disease-associated phenotypes.

An incomplete penetrance characterises the complex role of genetics in neuropsychiatric disorders; for example, the concordance rate of autism among monozygotic and dizygotic twin pairs is >90% and >50%, respectively (Tick et al., 2016). In contrast, SCZ concordance among monozygotic and dizygotic twin pairs is 41–65% and 0–28%, respectively (Cardno and Gottesman, 2000). Thus, it is striking that monozygotic twins with identical genetic material are not always determined to share the same clinical diagnosis. However, they may still be classified as subthreshold or placed in other related diagnostic categories (Cross-Disorder Group of the PGC, 2013; Mekori-Domachevsky et al., 2017). Poor diagnostic outcomes could be explained by complex genetic mechanisms, such as variable expressivity, epistasis, and pleiotropy; or result from epigenetic mechanisms, such as nucleic acid base pair and histone modifications (Paaby and Rockman, 2013). Genetic research has identified at least 109 pleiotropic loci associated with neuropsychiatric disorders, possibly with agonistic and antagonistic effects on a susceptibility of developing one disorder over another (Lee et al., 2019). Many pleiotropic regions, such as 22q11.2, are associated with several disorders (Maillard et al., 2015; Lin et al., 217). Mutations in these pleiotropic regions gain a functional significance during expression, where down-regulation or up-regulation of gene products will determine the developing disorder (Gandal et al., 2018). Here, genetic vulnerability is additionally shadowed by epigenetic mechanisms, masking disease susceptibility and severity (Kuehner et al., 2019). Therefore, it is unsurprising for 22q11.2DupS to display a high rate of ASD (14–25%) and 22q11.2DS to demonstrate a high rate of schizophrenia (∼25%; Van et al., 2017; Michaelovsky et al., 2019).

Susceptibility predictions become multifactorial with prevalent disorders like anxiety disorders and MDD. MDD, for example, displays a variable onset, recurrence, comorbidity, and severity. Variability in symptoms would not indicate a lack of a genetic component but instead hint at the maladaptive role of many low-risk low-impact variants in the genetic background (Legge et al., 2019). MDD is associated with allostatic load, a process defined by thousands of genes (Athira et al., 2020). A cumulative wear and tear of the body, or the perception of wear and tear, possibly leads to a cascade of stress-related changes. Eventually, these changes induce systemic pathologies such as inflammation, prothrombotic state, or insulin resistance, resulting in co-morbid illnesses such as coronary artery disease, osteoporosis, or diabetes (Gold, 2015). Paradoxically, such adaptation could be considered evolutionarily beneficial, at least in narrow niches. Predisposed individuals may be more sensitive to the stressors in a harsh environment and, therefore, more likely to thrive in bottleneck scenarios. Mood disorders are associated with other mental disorders through endophenotypes, such as mood instability or affective lability (Polderman et al., 2015; Høegh et al., 2020; Ward et al., 2020; Rao et al., 2021). Such endophenotypes are not exclusive to a selected disorder but reflect some common ground in many mental disorders. The underlying dysfunction in mood instability implicates GABAergic neurotransmission, mitochondrial energy production, and synaptic architecture (Kendall et al., 2021). GABAergic neurotransmission has also been implicated in

depression and anxiety, reflecting a widespread vulnerability of the GABAergic system (Nuss et al., 2015). Mitochondrial dysfunction has been implicated in neurodevelopmental disorders, such as early onset mood and psychotic disorders, as well as neurodegenerative disorders (Manji et al., 2012; Wu et al., 2019). Developmentally, synaptic architecture has been implicated in early brain development and later in neural circuit maintenance in many neurodevelopmental disorders (Washbourne et al., 2015). Mood lability endophenotype could predispose an individual to a more debilitating disease state with worse clinical and socio-economic outcomes (Patel et al., 2015).

Genetic variants of a polygenic disorder form a spectrum from low- to high-impact extremes. While high-impact mutations seem more expedient on a clinical level, their cumulative impact is relatively insignificant at the population level. They are, perhaps, reflecting a trade-off the whole of humanity has and will continue to suffer from. The disorder spectrums overlap with what is considered normal, resulting in minor differences between individuals and translating into small effect sizes on the modelling front. Individual predisposition is determined more likely by genetic variants inherited from parents and less likely by *de novo* mutations, underlining that translational research must account for an experimental strain's genetic background. The genetic predisposition is individual, shadowed by genetic and epigenetic mechanisms; therefore, the success of modelling depends on sample size. Moreover, most experimental animals live in impoverished environments, whereas people in society have significant enrichments in their routine lives. One can argue that enrichment in human lives borders with stimulatory madness. These facts reflect the difficulty of modelling polygenic disorders in animal models. To add to the complexity of the task, although the disease variants are unwanted on the individual level, their removal may not be justified on a population level, as on a population level, these variants may prove to be a net positive. In our attempt to handle such complexity, we have turned to animal models and endophenotypes (Gottesman and Shields, 1973). Endophenotypes are more defined quantifiable measures of heritable biological traits, reflecting a function of a discrete biological system in the path between genes and complex behavioural outcomes (Gottesman and Gould, 2003; Dick, 2018). Although vague, this approach enables the dissemination of the complexity of a human disorder in a more workable manner (Gould and Gottesman, 2005). Faced with numerous unknowns, we attempted to explore new avenues by emphasising GABAergic neuroinhibition, mitochondrial dysregulation and synaptic architecture.

1.2. Dysfunction of inhibitory neurotransmission

The spatiotemporal patterns of neural activity give rise to neural oscillations or brainwaves. This evolutionarily conserved phenomenon reflects dynamic brain states and fails only in disorders, such as during epileptic seizures (Dehghani et al., 2016). Deviations from these oscillatory patterns are rapidly recalibrated to sustain consciousness (Lennert et al., 2021). The underlying mechanism of

oscillations is based on an interplay of excitatory and inhibitory neural cells in a web of neural ensembles. Individual neurons in these ensembles maintain a balance between excitatory and inhibitory synaptic inputs. They also maintain certain flexibility of homeostatic control by modulating excitatory and inhibitory post-synaptic strength, altering a probability of presynaptic neurotransmitter release and adjusting intrinsic membrane excitability (Turrigiano et al., 2011). Neurons in these ensembles have somewhat unique roles derived from their molecular composition and neuronal architecture. In the hippocampal and cortical structures, we can distinguish between excitatory neurons and many GABAergic interneurons, which can be further subdivided as parvalbumin (PV), somatostatin (SST), and vasoactive intestinal polypeptide (VIP) expressing neurons. Most interneurons fall into these three broad non-overlapping categories (Huntley et al., 2020). GABA, as a neurotransmitter, is present in these inhibitory neurons and is used by inhibitory cells to elicit inhibitory neurotransmission. GABAergic neuroinhibition is highly energy-dependent and has a fundamental hierarchical role in coordinating neural activity (Kann et al., 2014).

Numerous disorders, such as SCZ, display excitatory and inhibitory dysfunction and desynchronisation; for example, SCZ patients experience a decline in gamma oscillations (Kehrer et al., 2008; Grent-'t-Jong et al., 2018). The decrease in gamma oscillations seems to be part of a normal ageing process and is a marker of cognitive decline with or without neurodegenerative disorder diagnosis (Murty et al., 2020; Murty et al., 2021). Oscillatory coherence between different neural ensembles or higher-order structures could be considered a quality control mechanism (Hakim et al., 2018). At local level, interneurons selectively pattern neural ensembles by feedback inhibition, resulting in high and low-activity excitatory counterparts (Lisman et al., 2012). Due to low or unspecific interneuron activity, functional patterns are not shaped, and ensemble results in nonsensical output. Loss of function at the level of ensembles could translate into a functional loss at higher order, such as impoverished speech, anhedonia, avolition, or general intellectual disability in a brain-region-dependent manner (Umesh et al., 2018; Li et al., 2021).

ASD patients also display altered neural connectivity in excitatory and inhibitory circuits (Gao and Penzes, 2015). This data indicates a fragmented brain with hypo- and hyper-connectivity features, leading to enhanced or diminished functionality depending on the brain region, resulting in high and low-functioning individuals (Keown et al., 2013; Catani et al., 2016). Low-functioning ASD patients are more likely to develop dementia, especially in a subpopulation with intellectual disabilities (Geurts and Vissers, 2012; Vivanti et al., 2021). Both SCZ and ASD demonstrate an accumulation of *de novo* high penetrance high-impact variants in synaptic genes, reflecting a brain-wide vulnerability of higher-order cognitive functions (Awadalla et al., 2010). The exposure of cognition may be considered a shared endophenotype, whereas other more disorder-specific variants lead to disorder-specific endophenotypes. For example, ASD and SCZ show a broad overlap of deficits in social communication and socio-emotional reciprocity, whereas ASD patients, in particular, also experience alpha band asymmetry

during social reward anticipation (Stavropoulos and Carver, 2018; Trevisan et al., 2020). ASD also displays variable E/I balance, where some behavioural outcomes, such as higher social ability, correlate with a higher E/I ratio (Bruining et al., 2020). A deviation from E/I balance and standard oscillatory patterns may cause conflicts in and between different brain regions, resulting in nonsensical output or other dysfunctional states, such as epileptic seizures, a common comorbidity in ASD (Buckley and Holmes, 2016). Such endophenotypes may derive from the vulnerabilities of interneurons because of their high allostatic and synaptopathological load (Ruden et al., 2021). For example, PV^+ interneurons balance the E/I ratio in cortical circuits and are highly vulnerable (Ferguson and Gao. 2018).

The treatment of a subpopulation of ASD patients, notably those with ADHD comorbidity, has relied on mood enhancers, such as lithium, improving energetic and behavioural outcomes (Mintz and Hollenberg, 2019). Lithium treatment in bipolar disorder increases neuroinhibition and moves the brain into an increased inhibitory state, modulating mood and behavioural outcomes. Such an effect reflects a possible shared dysfunction between mood lability and energy regulation or production mechanisms (Malhi et al., 2013). The notion could indicate an inability of neurons to sustain network operations, as a progressive increase in network activity will increase the demand for GABAergic neuroinhibition and related energetic costs (Patel et al., 2005). Lithium seems to have some positive effects on healthspan in healthy as well as in those with BPD diagnosis, coupled with similar effects on their life-span (Nespital et al., 2021). Lithium also relieves some schizophrenia spectrum disorder patients, such as those related to affective phenotype (Cipriani et al., 2013; Puglisi-Allegra et al., 2021). In addition, it suppresses psychostimulant-induced sensitization by acting on some common mechanisms shared by SCZ and BPD (Ago et al., 2011; Puglisi-Allegra et al., 2021). The previous notions could be seen as lithium's ability to buffer resilience in the brain by enhancing inhibitory neuroplasticity and -protection (Puglisi-Allegra et al., 2021). Lithium may achieve neural resilience by upregulating growth factors, such as BDNF (brain-derived neurotrophic factor), via increasing autophagy, especially mitophagy, and reducing inflammatory response (Machado-Vieira et al., 2009; Nassar and Azab, 2014; De Paula et al., 2016; Tomoda et al., 2021). BDNF modulates cortical interneuron development dominantly in the cortex and hippocampus (Willis et al., 2021). Besides the developmental role, BDNF modulates neuronal function in adulthood (Nilsson et al., 2020). BDNF levels predict a vulnerability to injury, such as ischemic stroke, and can also predict clinical outcomes—higher BDNF levels reflect better outcomes (Stanne et al., 2016). As an additional example, first-episode psychosis patients display an acute rise in EGF levels in the blood (Haring et al., 2015). A similar rise has been witnessed in multiple sclerosis patients after symptom improvement (Tejera-Alhambra et al., 2015). The growth factor change may differentiate patient populations with better or worse clinical outcomes (Scalabrino, 2021). Such mechanisms may be a part of the natural compensatory mechanisms or mimic them. The resulting improvements have significantly favourable effects on inhibitory cells

and neurotransmission, as these cells carry the highest allostatic and synaptopathological load (Holm et al., 2009; Rijal et al., 2021).

Additionally, the alterations in inhibitory activity seem to implicate synaptic architecture (Porcher et al., 2018). Perhaps, evolution has formed robust mechanisms to handle developmental dysfunction, for example, by compensating or altering receptor subunit or their partner molecule, such as adhesion molecule dynamics, during development, therefore scavenging neural circuit function (Gatto and Broadie, 2010). A high redundancy of adhesion molecules could be one such fail-safe mechanism, replacing one adhesion molecule with the operation of others to ensure the survival of an organism, although in a somewhat handicapped state (Vanaveski et al., 2018). The cost of such compensation is further iterations away from the homeostatic norm and should inevitably result in an overburdened state, especially in a challenging environment (Lopatina et al., 2019). Some manifestations of endophenotype, such as those related to mood instability or cognitive dysfunction, seem to be widely shared among neuropsychiatric disorders. Perhaps, there is a common pre-programmed pattern of behavioural dysfunction or maladaptation—for example, involving a mesolimbic reward system (Wu et al., 2020), where the dopaminergic neurotransmitter system may gradually alienate from the homeostatic norm, leading to dysfunctional behaviours. While the behaviour becomes corrupted, the organism can survive and may continue producing offspring. Therefore, the cost on fitness is in evolutionary terms, acceptable. Such compensatory involvement may allow more dysfunctional circuitry to survive but not thrive. In such a state, outside intervention may be necessary to restore optimal functioning, if applicable. For example, the antidepressant fluoxetine rescues rodents from despair by inducing resilience in the mesolimbic reward system (Padilla et al., 2011). Stimulation of 5-HT2B receptors by fluoxetine in astrocytes leads to the transactivation of epidermal growth factor receptor, which in turn activates downstream signalling pathways like MAPK/ERK or PI3K/AKT (Verkhratsky et al., 2021). EGF-ErbB and NRG-ErbB pathways are potential targets for intervention at the early stages of development, before any building blocks of a disorder are added (Exposito-Alonso et al., 2020; Renshall et al., 2021). These pathways are also targets of intervention at late stages, such as mood disorders, but with diminishing returns (Shi and Bergson, 2020; Verkhratsky et al., 2021). BDNF expression overall has an anti-fragile effect on the brain with some improvements in symptoms of neuropsychiatric disorders, especially in those with an affective undertone (Rybakowski and Suwalska, 2010; Murínová et al., 2017; Liu et al., 2020). Increased expression of BDNF modulates expression of neural adhesion molecules and leads to a reshuffling of GABA and NMDA receptor subunit expression (Caldeira et al., 2007; Porcher et al., 2018; Levchuk et al., 2020). BDNF, or growth factors in general, seem needed to break out of gridlock and induce or re-induce plasticity on a circuit level. After growth factor signalling, cells change their expression profiles, perhaps introducing a developmental-like state open to refreshing circuitry (Guirado et al., 2014). We are just beginning to understand the GABAergic involvement in the mesolimbic

reward system; the complexity of the GABAergic interneurons' role in wakefulness and motivation is some of the core drivers behind brain function (Eban-Rothschild et al., 2020). GABAergic subunits have been associated with depressive and anxious mood traits in many mental disorders (Frajman et al., 2020; Marques et al., 2020). The fast-acting $GABA_A$ receptors are pentameric and are formed by various combinations of different α (α_1 to α_6), β (β_1 to β_3), γ (γ_1 to γ_3), δ, ε, π, θ, and ρ (ρ_1 to ρ_3) subunits (Sieghart and Sperk, 2002; Mortensen et al., 2012). The complexity of GABA receptor makeup grows parallel with adhesion molecules, which selectively connect the pre-and postsynaptic regions. Perhaps, the most significant effect of GABAergic transmission arises from the complex dynamical hierarchical inhibition of other neural cells, which can be achieved by fluent structural changes occurring at the molecular level and constant reshuffling and re-adjustment of circuitry and cell connectivity as needed (Feldmeyer et al., 2017). Success of these processes depends on various factors, such as stable and responsive energy metabolism and redundant and flexible synaptic architecture.

In conclusion, neural oscillations reflect a coordinated activity of neurons across the brain. This coordination fails only in a disease state due to underlying dysfunctions. ASD and SCZ display breakdowns of connectivity and functionality of local ensembles or higher-order structures. The source of these dysfunctions seems to be related to energy metabolism or synaptic pathologies. Perhaps susceptible genetics remains masked throughout development by different compensatory mechanisms. Once a threshold of insults challenges the already overburdened homeostasis, susceptible individuals may lack further compensatory potential, forcing the neural functioning into some inferior pre-programmed state, perhaps as an attempt to avoid an even more sinister fate (Castellani and Arking, 2020). In the ensuing maladaptation, we can see expression changes and reshuffling of synaptic structures, as if the brain tries to reinvent itself or at least parts of it. Interventions that support GABAergic inhibitory cell function and inhibitory neurotransmission seem to mitigate some of the adverse outcomes, notably in disorders with an affective component. A lack of hierarchical coordination by inhibitory neurotransmission may represent a fundamental dysfunction and target for intervention. The challenge here is how to model such a complex and ever-changing system.

1.2.1. Energetic predisposition in inhibitory neurotransmission

Mitochondria are abundant in neurons, particularly at synapses (Palay, 1956). A primary function of the synaptic mitochondria is local intermediate biosynthesis and energy production (Sheng et al., 2017). Mitochondrial distribution is dynamically regulated to match synaptic activity; more active synapses accumulate more mitochondria (Cserép et al., 2018). Mitochondria are further involved in sustaining calcium homeostasis, redox signalling, and synaptic vesicle recycling (Giorgi et al., 2012; Marland et al., 2016; Stefanatos and Sanz, 2018; Angelova and Abramov, 2018). Synapses are more sensitive to energetic abnormalities, as synaptic mitochondria can buffer fewer Ca^{2+} ions (Brown et al., 2006; Núñez

et al., 2007). A dysregulation in Ca^{2+} homeostasis can lead to asynchronous vesicle release, resulting in alterations of existing synaptic dynamics, which possibly lead to a synaptic degeneration observed in SCZ and other brain disorders (Schinder et al., 1996; Glantz et al., 2006; Sas et al., 2007; Vos et al., 2010; Guo., 2016). Mitochondrial dysfunction is a key player in the manifestation of depression and anxiety, reflecting a widespread role of energy production and regulation mechanism in the predisposition (Allen et al., 2018). Mitochondria are the primary intracellular source of reactive oxygen species (ROS) and the first to suffer from resulting oxidative stress (Kudin et al., 2004). Mitochondrial DNA is highly mutable, with an estimated mutation rate of ~5–15 times higher than the nuclear genome (Payne et al., 2013; Arbeithuber et al., 2020). Therefore, a cell's energy metabolism becomes highly dependent on the recycling of aberrant mitochondria. As neurons do not store significant reserves of high-energy metabolites, synaptic transmission becomes especially reliant on the regulatory interplay between synaptic activity and local energy production (Schönfeld and Reiser, 2013).

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1α or PGC1α) is a master regulator of mitochondrial biogenesis; it regulates the mitochondrial number, oxidative metabolism, calcium signalling, and cellular adaptations to stressful stimuli (Bianchi et al., 2006; Handschin and Spiegelman, 2006; Wenz, 2013; Gill et al., 2019). Metabolic sensors such as AMPK and sirtuins interact with PPARGC1α (Canto and Auwerx, 2009), and PPARGC1α, in turn, downstream the Peroxisome proliferator-activated receptor γ (PPARγ), as well as many other receptors and factors (Handschin and Spiegelman, 2006). The expression of PPARGC1α in the brain concords with highly active brain regions, such as the frontal cortex, striatum, and hippocampus (Cowell et al., 2007). These regions display more inhibitory cell types, including those positive for the calcium-binding protein—parvalbumin (Cowell et al., 2007; Lucas et al., 2014). PPARGC1α is required for normal PV^{+} interneuron function (Bartley et al., 2015). A downregulation of PPARGC1α leads to PV deficiency and dysfunctions of the GABAergic system—a primary inhibitory neurotransmitter system in the brain (Korpi and Sinkkonen, 2006; Dougherty et al., 2014; Chua and Chebib, 2017; McMeekin et al., 2016; 2018). *PPARGC1A* and dependent genes demonstrate a connection to SCZ (McMeekin et al., 2016). Notably, clozapine significantly upregulated *PPARGC1A* in adipocytes, indicating an association between PPARGC1α facilitated energy metabolism and antipsychotics (Kristóf et al., 2016). The PPARGC1A interactome is associated with mood disorders and cognitive performance (Abe et al., 2011; McGrory et al., 2018; D'Angelo et al., 2019). PPARGC1A is implicated in affective disorders, such as MDD and anxiety disorder, as well as neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's (Jamwal et al., 2021; Vanaveski et al., 2021).

1.3. Dysfunction of behavioural adaptation

People with severe mental illness are more likely to be behaviourally compromised. They are more likely to have metabolic problems such as hyperglycemia/diabetes or dyslipidemia, which may further escalate metabolic syndrome (MetS); they may have hypertension and display a lack of self-care and unhealthy habits, such as smoking and a sedentary lifestyle (De Hert et al., 2009; De Hert et al., 2011; Nesvåg et al., 2015). A diagnosis of MetS is prevalent in SCZ and mood disorders (Sun and Jang, 2020). The MetS is linked to poor lifestyle choices, drug side effects, impactful life events, family history, and seasonal patterns (Pan et al., 2012; Papanastasiou, 2013; Hung et al., 2014; Kesebir et al., 2018). Recent findings from SCZ research support metabolic outcomes before antipsychotic treatment and underline an important role of metabolism in SCZ pathology (Kriisa et al., 2017). Some metabolic alterations seem acute and are reversed by antipsychotic treatment, while others lead to long-term metabolic profile changes (Parksepp et al., 2020). The brain has zealously guarded inner metabolic homeostasis, so a deviation from the homeostatic norm may prove dysfunctional. Understanding a metabolic background of an organism may offer a venue to peek inside the inner workings of the brain and explain the behavioural outcomes.

Perhaps DISC1 characterises a difficulty of investigating polygenic complexity, being an accidental finding from a study of a Scottish pedigree with an unusually high occurrence rate of mental disorders (Blackwood et al., 2001). A discovered translocation in the *DISC1* demonstrates a significant linkage with clinical phenotypes such as SCZ, schizoaffective disorder, BPD, and recurrent MDD. A follow-up study of an extended pedigree identified significantly lower levels of glutamate in the dorsolateral prefrontal cortex (DLPFC) and lower cortical thickness in individuals with translocation (Doyle et al., 2015; Thomson et al., 2016). The DISC1 finding has gained further support from the truncated mouse model, displaying fewer cells in the outermost layer of the cortex, corresponding to the layers II–III in the adult human brain—a region enriched by a diversity of inhibitory neurons (Shen et al., 2008; Tremblay et al., 2016). The DISC1 interactome is broadly associated with the cytoskeletal organisation and biogenesis, mRNA/protein synthesis, cell cycle/division, intracellular transport, signal transduction processes, and synaptogenesis (Camargo et al., 2007). The interactome is further associated with the changes in the broader cascade of molecules, which correlate with psychosis and cognitive ability (Tomppo et al., 2012; Rampino et al., 2014; Teng et al., 2018). Other findings indicate hypometabolism of the glutamate-glutamine cycle in the DLPFC of MDD patients (Michael et al., 2003). Interestingly, DISC1 seems to regulate lactate metabolism in astrocytes and could significantly affect neural energy supply in inhibitory circuitry (Holley et al., 2013; Jouroukhin et al., 2018).

Our relative interest was fuelled by the notion that one of the model strains—129Sv, carries a 25 base pair frameshift deletion within exon 6 of the *Disc1* gene, resulting in a premature termination codon in exon 7 (Koike et al., 2006; Chubb et al., 2008). The resulting mutant strain displayed a gene-dosage-dependent effect

in a delayed non-match-to-place task, a task that taxes frontal cortical and fronto-hippocampal circuitry (Jones and Wilson, 2005; Koike et al., 2006; Eichenbaum, 2017). The spatial performance and flexibility studies using different variants of the Barnes maze supported cognitive deficits (Riedel et al., 2018). The impairments in the Barnes maze were related to the complexity of the task, indicative of an executive functioning deficit over memory impairments. Morris water maze studies further supported the executive deficit (Stefani and Moghaddam, 2002; Featherstone et al., 2008). These studies in mice could translate to a higher-order executive functioning deficit in humans and reflect the dysfunctional integrity or integration of the prefrontal cortex in neuropsychiatric disorders. Also, we employed a widely used reference strain, Bl6, to dissect a role of Disc1 truncation (Koike et al., 2006). Behavioural studies demonstrated differences between these two mouse strains of interest; notably, the Bl6 line is more active and venturous, whereas 129Sv is idler and displays a higher level of anxiety (Contet et al., 2001; Võikar et al., 2001; Abramov et al., 2008; Heinla et al., 2014). As such, 129Sv may model a patient population with mood lability or instability features.

Here, we employed the dopamine-enhancing drug amphetamine (AMPH), which precipitates psychotic episodes in healthy individuals indistinguishable from the acute psychotic episode observed in schizophrenic patients (Bell, 1965; Fluyau et al., 2019). We induced psychotic-like behaviour in rodent models by pharmacological administration of AMPH (Janowsky et al., 1973; Castner et al., 1999; Ham et al., 2017). Studies of AMPH-induced psychosis use one or more parameters to characterise the extent of pharmacological manipulation, horizontal locomotory activity being a common one (Young et al., 2007). Most studies evaluating the development of AMPH-induced motor sensitisation were performed in rats. Repeated AMPH administration in adult rats produced a robust sensitisation, disrupted latent inhibition, and decreased attentional vigilance (Murphy et al., 2001; Russig, 2002; Russig et al., 2003; Ham et al., 2017). Considering recent findings which indicated an association between metabolic abnormalities and SCZ/BPD/MDD, we were interested in the underlying metabolic predisposition of these strains (Zuccoli et al., 2017). Several metabolic studies demonstrated abnormalities in SCZ before and after the treatment with antipsychotics (Thomson et al., 2016; Kriisa et al., 2017). Notably, clozapine substantially affected metabolism by inducing weight gain in patients treated with antipsychotics (Hummer et al., 1995). Though considered rare, secondary psychosis can also be induced by metabolic disorders (Bonnot et al., 2015). Therefore, some proportion of the predisposition could be explained by the metabolic background of patients and can be modelled in these somewhat distinct mouse strains.

1.4. Dysfunction of synaptic architecture

Most SCZ patients manifest clinical symptoms in the second or third decade of life (Hill, 2016; Häfner, 2019). The SCZ literature, however, points to indistinctly observable subclinical signs of neuropathology since infancy or childhood. During this premorbid phase—before any sign of psychotic disorder, mild quantifiable deviations may appear. These abnormalities include delays in motor development, attentional dysfunction, deficits in receptive language, poor academic achievement, social isolation, and emotional detachment (Sørensen et al., 2010; Fusar-Poli et al., 2013; Slomiak et al., 2017). Such premorbid subclinical symptoms may present in other neurodevelopmental disorders, notably ASD (van Laarhoven et al., 2019). A fluctuating nature of these premorbid signs possibly reflects self-correcting measures (compensatory attempts) to ensure close to normal development (Clifton et al., 2019). A progression of symptoms from subclinical signs to full-blown disorder remains unclear and would immensely benefit from the discovery of early biomarkers, especially on a clinical level. Translational research indicated that many risk genes converge in closely interacting molecular networks; for example, disruptions in the *Disc1* gene result in altered expression of neural adhesion molecules Nrxn1 and Nrxn3 (Seshadri et al., 2010; Brown et al., 2011). Patient studies and knock-out/knock-down models of Neurexins displayed several phenotypes related to ASD and SCZ (Brown et al., 2011; Reichelt et al., 2012; Ji et al., 2015; Uchigashima et al., 2020). Neurexins contain a modular structure comprising one transmembrane domain, six laminin, one neurexin, one sex hormone-binding globulin domain, and three epidermal growth factor (EGF)—like domains in their extracellular regions (Südhof, 2008). Any of these modular domains may be a target for mutations, leading to the alteration of signal transduction and higher-order functions. Notably, the general disruption of Neurexins during development destabilises neural filopodia and reduces dendritic arbour complexity as neurons mature, inevitably resulting in behavioural aberrations in later stages of development (Chen et al., 2010). These changes reflect a developing disorder, indicating a critical role of adhesion molecules' in developing and maintaining neural networks.

The human genome encodes many adhesion molecules; however, our interest here is driven by a small family of less-studied genes—IgLONs. The IgLON family is composed of five neural adhesion molecules: OPCML (OBCAM; IgLON1; Schofield et al., 1989), NTM (IgLON2; Struyk et al., 1995), LSAMP (IgLON3; Horton and Levitt, 1988), NEGR1 (KILON; IgLON4; Funatsu et al., 1999), and IgLON5 (Grimwood et al., 2004; Sabater et al., 2014). IgLONs are relatively simpler than Neurexins and are characterised by a glycosylphosphatidylinositol (GPI) anchor and three immunoglobulin domains (Pimenta and Levitt, 2004). The three immunoglobulin domains are used to form homo- and heterophilic dimers on the plane of the membrane as part of a larger signalling complex (Reed et al., 2004; McNamee et al., 2011). All IgLON family members are expressed in neurons and oligodendrocytes, except for NTM, which is exclusively expressed in neurons (Sharma et al., 2015). Overall, the family is shown to participate in

myelino-, axono-, dendrito-, and synaptogenesis in different brain regions (Struyk et al., 1995; Mann et al., 1998; Chen et al., 2001; Gil et al., 2002; Li et al., 2006; Hashimoto et al., 2009; Sugimoto et al., 2010; Akeel et al., 2011; Yu et al., 2012; Sharma et al., 2015). An early onset of expression during embryogenesis and a continuous requirement in adulthood implies that IgLONs have essential roles throughout the life cycle and are of interest in different disease states (Schwarz et al., 2009). Indeed, LSAMP is associated with emotional regulation and social behaviour in a mouse model (Innos et al., 2011, 2012, 2013a, 2013b; Philips et al., 2015); a linkage has been reported for psychiatric disorders such as MDD and SCZ in humans (Behan et al., 2009; Koido et al., 2012, 2014; Karis et al., 2018). Although Ntm knock-out animals display emotional learning deficits, the overall phenotype is less pronounced (Mazitov et al., 2017). In humans, polymorphisms in the NTM gene are associated with intelligence and aggressiveness (Pan et al., 2011; Brevik et al., 2016). The genetic locus of *NTM* and *OBCAM* is associated with depression (Schol-Gelok et al., 2010); additionally, *OBCAM* is associated with SCZ (O'Donovan et al., 2008; Panichareon et al., 2012). Both genes' micro-rearrangements in the brain are also associated with ASD (Maruani et al., 2015). Negr1 deficiency in mice results in the enlargement of ventricles and shrinkage of the whole brain volume; paralleled by behavioural deviations related to psychiatric disorders (Singh et al., 2019). Polymorphisms in the *NEGR1* gene are associated with white matter integrity (Dennis et al., 2014), depression (Hyde et al., 2016; Howard et al., 2019), and obesity in several genome-wide association studies (Melén et al., 2010; Hotta et al., 2011; Elks et al., 2012; Poveda et al., 2014). IGLON5, the newest addition to the family, is implicated in neurodegeneration (Sabater et al., 2014; Leypoldt et al., 2015; Nissen and Blaabjerg, 2019). Seemingly, adhesion molecules connect a range of phenotypes from early and late life and are associated with developmental and degenerative disorders.

1.5. Concluding remarks

In conclusion, mental disorders are characterised by behavioural, emotional, and cognitive changes driven by genetic mutations in the brain. From a genetics perspective, mental disorders may appear sporadically through *de novo* mutations or, more likely, run in families, resulting from the inheritance of many common low-impact low-risk variants. The discovery of these common variants and how they add to susceptibility remains challenging. In this thesis, we investigated three models emphasising GABAergic neuroinhibition, metabolic profile, and synaptic architecture. In the PPARGC1α overexpression model, we investigated a connection between energy metabolism (PPARGC1α-PPARγ pathway) and GABAergic inhibitory neurotransmission. In the metabolomic study, we employed a comparative two-strain approach to model a predisposition of psychosis by acute and chronic AMPH administration. Later, we were interested in imitating metabolic profile changes previously seen in patient populations. Third, we characterised the expression of a neural adhesion molecule family in the mouse brain to assess

their biomarker potential. We consider all these experiments met moderate success, and the key conclusions of these experiments can add value to the overall pool of knowledge in deciphering the underpinnings of mental disorders. However, one must remember that these models represent a simplified picture of parallel processes in humans, though they offer faster, cheaper, and more ethical alternatives to human research.

2. AIMS OF THE STUDY

This study aimed to extend a general knowledge base for modelling mental disorders. The specific goals of the study were:

1. Characterise a transcriptional pattern of IgLONs (Bl6N and 129Sv) and try to connect these expression patterns with mental disorder endophenotypes

2. Characterise metabolic profiles of the two distinct mouse strains (Bl6N and 129Sv) in the AMPH challenge and assess the viability of mixed strain modelling

3. Characterise the PPARGC1α overexpression mouse model (Bl6J) and study the intervention potential of PPARGC1α-PPARγ pathway stimulation

3. MATERIALS AND METHODS

3.1. Animal studies (I–III)

Animal procedures in all the studies were performed following the European Communities Directive (86/609/EEC) based on the permits from local representative authorities. The Estonian National Board of Animal Experiments permitted chronologically the first two experiments (No. 29, April 28, 2014, and No. 87, May 4, 2016). The National Animal Experiment Board of Finland permitted the third experiment (ESAVI/10165/04.10.07/2016).

3.1.1. Animals for IgLON family expression analysis (I paper)

Male wild-type mice (C57BL/6 Bkl; ScanburAB, Sollentuna, Sweden, n = 3–6) were used to characterise the baseline expression of IgLONs. The three mutant groups (Lsamp$^{-/-}$, Ntm$^{-/-}$, Lsamp$^{-/-}$/Ntm$^{-/-}$) and one control group were used for the compensatory study (n = 6 in each group). The creation of Lsamp-deficient mice is described by Innos et al. (2011), and Ntm heterozygous mutant strain (032496-UCD B6; 129S5-Ntm^{tm1Lex}/Mmucd) was acquired from the Mutant Mouse Regional Resource Centre at UC Davis (Mazitov et al., 2017). The mutant groups were crossbred to gain double knock-out animals and were accordingly used for transcription profiling. Mice were housed 7–8 animals per cage (1264C Eurostandard type II cages; 268 × 215 × 141 mm; Tecniplast, Italy) based on allocation after weaning and maintained under a 12-h light/dark cycle, with lights on at 7:00 AM. Animals had ad libitum access to food and water. Cage enrichment was provided by bedding (aspen chips, 4 HP, Tapvei, Estonia) and nesting material (aspen wool, PM90L, Tapvei, Estonia), both being changed weekly. Animals were 3–6 months old at the time of tissue collection. Breeding and housing were performed in the Institute of Biomedicine and Translational Medicine, University of Tartu.

3.1.2. Animals for metabolic profiling (II paper)

Inbred male mice (C57BL/6NTac; Taconic Germantown, New York; n = 41 and 129S6/SvEvTac; Taconic Germantown, New York; n = 39) were used for the study. The experimental animals were housed 6–10 per cage under a 12 h light/dark cycle with lights on at 7:00 AM. The room temperature was kept at 21°C. Animals were housed in their respective home cages (1290D Eurostandard type III cages; 425 × 276 × 153 mm; Tecniplast, Italy) with bedding (aspen chips, 4 HP, Tapvei, Estonia) and nesting material (aspen wool, PM90L, Tapvei, Estonia); both were changed weekly. The animals had ad libitum access to Ssniff universal mouse and rat maintenance diet (cat# V1534; Ssniff, Germany) and reversed osmosis-purified water, except during the testing period. Behavioural testing, including habituation, started at 6–9 weeks and lasted 13 days. At the time of sample

collection, the animals were 8–11 weeks old. Breeding and housing were performed in the Laboratory Animal Centre of the Institute of Biomedicine and Translational Medicine, University of Tartu.

3.1.3. Animals for PPARGC1α overexpression study (III paper)

The creation of a PPARGC1α-enhanced strain is described by Mudò et al. (2012). In short, overexpression of PPARGC1α was achieved by the Thy1 promoter, resulting in overexpression of PPARGC1α in mature neurons. These mutants were further backcrossed over several generations with the C57Bl6/J strain. PPARGC1α transgenic animals and respective wild-type controls were used. The mice were housed in a cage system wherein each cage was individually ventilated (Mouse IVC Green Line; 391 × 199 × 160 mm; air inlet and outlet valves in the cage lid, on top of the cage; a rate of air change was set at 75 times per hour with the maximum airspeed of 0.05 m/s; half of the cage covered by a wire bar food hopper; Tecniplast, Italy). The cage enrichment was provided by bedding (aspen chips, 4 HP, Tapvei, Estonia), nesting material (equal amount of aspen strips, PM90L, Tapvei, Estonia and Sizzle Nest paper strands, Dates and Group, UK), and aspen brick (100 × 20 × 20 mm, Tapvei, Estonia), changed weekly. Food (Global Diet 2916C, pellet 12 mm, Envigo, IN, USA) and water (filtered and UV-irradiated) were available ad libitum. Room temperature was 22 ± 2 °C; relative humidity was 50 ± 15% and maintained under a 12-h light/dark cycle, with lights on from 6:00 AM to 6:00 PM. Animals were 169–170 days old at the beginning of the experiments, which lasted for 60 days. Breeding and housing were performed in the Laboratory Animal Centre of the Institute of Life Sciences, University of Helsinki.

3.2. Bioinformatics (I paper)

Bioinformatic analysis of alternative first exons and respective upstream regions (5'UTR) of rodent and human Opcml and Ntm transcripts was performed by detecting potential analogy with the known structure of the Lsamp gene (Pimenta and Levitt, 2004). Analogous gene structure was confirmed by the respective alignment of Opcml, Ntm, and Lsamp 1a and 1b transcripts with Clustal Omega Multiple sequence alignment service (Sievers et al., 2011). Alternative transcripts were mapped and confirmed by sequence analogy using NCBI Refseq and Non-Refseq databases (Altschul et al., 1990). MEGA5 software was used to align EST sequences to transcripts (Tamura et al., 2011). PredGPI web service was used to predict the location of GPI anchor binding sites (Pierleoni et al., 2008). All the alignments of either DNA or amino acid sequences were performed using the Clustal Omega Multiple sequence alignment (Sievers et al., 2011).

3.3. Behavioural testing (II paper)

3.3.1. Locomotor activity

Animals were randomly divided into three administration groups for behavioural testing (Figure 1). Locomotion of individual mice was measured in a lit room (400 ± 25 lx), in soundproof photoelectric motility boxes (448 × 448 × 450 mm) made of transparent plexiglass, and connected to a computer (TSE Technical & Scientific Equipment GmbH, Germany). After each animal, the floor of the boxes was cleaned with a 5% ethanol solution. Latin square design was used to randomise daily measurement cycles. Immediately after recording the locomotor activity, the animals were sacrificed one by one using cervical dislocation and decapitated; afterwards, the trunk blood was collected for metabolomic analysis.

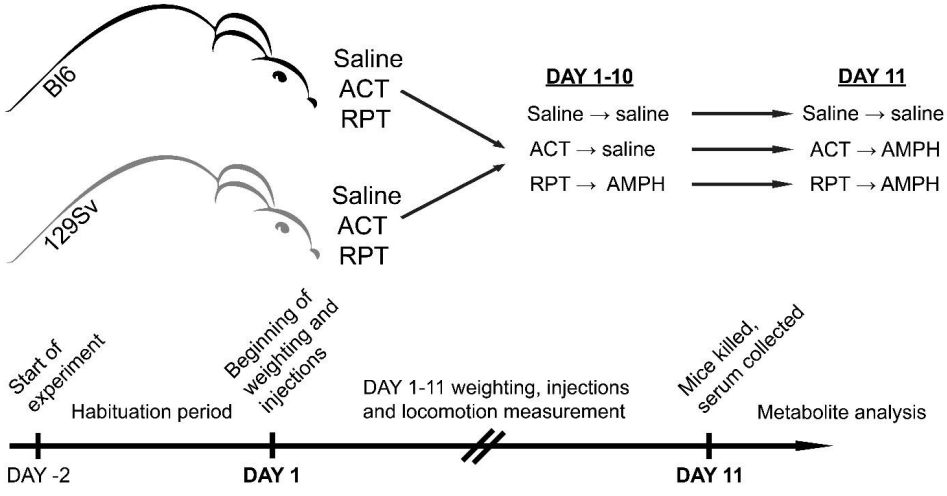


Figure 1. Representation of the experimental design for amphetamine challenge test. The first two days were allocated for adaptation to the testing environment, followed by actual experimental days 1–11 for locomotor activity measurements. The routine followed on days 1–10 was as follows: the animals were weighed; two groups of mice received an intraperitoneal injection of 0.9% saline in the volume of 10 ml/kg, whereas the third group received AMPH (d-amphetamine, 3 mg/kg IP; Sigma-Aldrich, Germany). AMPH dose was determined based on a previous study and dose validation (Innos et al., 2013b). After saline or AMPH, the animals were placed into single housing cages for 30 min for an incubation period for a drug to take action (1284L Eurostandard type II cages; 425 × 276 × 153 mm, Tecniplast, Italy). The 30-minute incubation was followed by a transfer of the animals into individual motility boxes for 30 min, where the activity of the mice was recorded; afterwards, the animals were returned to single cages to avoid any aggregation effect and increased aggressiveness due to a strong stimulating effect of AMPH (no more than 30 min). On day 11, one of the saline groups received a dose of saline, and the other group was administered AMPH (3 mg/kg). The saline group was used as a control for the effects of acute AMPH administration. The repeated AMPH group received AMPH (3 mg/kg).

3.4. Behavioural testing (III paper)

Altogether 15 wild-type females (Wt F), 9 PPARGC1α transgenic females (Tg F), 9 wild-type males (Wt M), and 11 transgenic male (Tg M) mice were used for behavioural experiments. Mice were video-traced by Noldus EthoVision XT 10 system (Noldus Information Technology, Wageningen, The Netherlands) where applicable. Noldus EthoVision XT 13 system software was used for data extraction with a Lowess's track smoothing option as default. A distance travelled by the subjects, the time spent in pre-defined zones, as well as defined behaviours (vertical counts or rearings, grooming, head-dips) were recorded. Latin square design was used to randomise the measurements.

3.4.1. Elevated plus-maze

The maze consisted of two open (300 × 50 mm) and two enclosed arms (300 × 50 mm, inner diameter), connected by a central platform (50 × 50 mm), uplifted 400 mm above the floor. The floor of each arm was light grey, and the closed arms had slightly transparent (150 mm high) side- and end walls made of plexiglass. Illumination level in open arms was ~150 lx. At the start of the experiment, a mouse was placed in the centre of the maze facing towards one of the enclosed arms and released for measurement. The mouse was then observed for 5 min. The latency to the first open arm entry, the number of open-and-closed arm entries (four paw criteria), and the time spent in different maze zones were measured. The number of head dips, rearings, and faecal boli was counted manually after the trial from a video recording.

3.4.2. Open field and light-dark box activity

The mice were released at the corner of the novel open-field arena (300 × 300 mm, Med Associates, St. Albans, VT), and their horizontal and vertical activity was recorded for 30-min. Illumination in the open field was ~150 lx. A peripheral zone was defined as a 60 mm wide corridor along the wall. A light-dark box test was conducted in the same arena using infrared light sensors detecting horizontal and vertical activity. A dark insert (non-transparent for visible light) was used to divide the arena into two halves, and an opening in the wall (a door with a width of 55 mm and a height of 70 mm) allowed free movement from one compartment to another. Illumination in the centre of the light compartment was ~550 lx. The animals were placed in the dark compartment and allowed to explore the arena for 15 min.

3.4.3. Spontaneous alternation in T-maze

The T-maze was made of grey PVC. Each arm measured 300 × 100 mm; a removable central partition extended from the centre of the black goal wall of the T to 70 mm into the start arm. This modification prevented the animals from seeing or smelling the non-chosen arm during the sample run, thus minimising interfering stimuli. The entrance to each goal arm was fitted with a guillotine door. Each trial consisted of an information-gathering sample run, immediately followed by a choice run. For the sample run, a mouse was placed in the start arm, facing away from the choice point with the central partition in place; the door of the start arm was closed, and the doors to the goal arms were opened. After opening the door on the start arm, the mouse could choose a goal arm and be confined there for 10 s by lowering the respective guillotine door. Then, the central partition was removed, the mouse was replaced in the start arm (door closed), and the doors to both goal arms were opened again, followed by the opening of the start door. Alternation was defined as entering the opposite arm to that entered during the sample trial (whole body, including tail). Three trials were run daily with an inter-trial interval of at least 1 hour on two consecutive days (for 6 trials altogether).

3.4.4. Barnes maze

The diameter of the elevated Barnes maze platform is 100 cm; the maze has 20 holes (5 cm diameter) equally distributed around the perimeter, with a goal box attached under one of the holes. The maze is divided into 20 equal sectors with inner and outer areas. The inner area is defined as 15 cm from the edge of the maze (diameter 70 cm), and the outer region is composed of sectors with holes, one of which is defined as a goal zone. The animals were habituated to the arena and the goal box before the experiment for at least 2 min to learn to enter the goal box voluntarily. Training (acquisition) was carried out in 3 trials per day until escape into the goal box or max duration of 180 s, with an intermission of at least 1 hour, with an aversive overhead light. Before the actual trial, the mouse was placed in the non-transparent cylinder in the centre of the arena. After 15 s, the cylinder was removed, and the animal was set free to explore the arena. Once the mouse entered the goal box, it was allowed to stay there for 10–15 s and then was removed from the goal box and placed back in the cage. If the animal did not find the box in the 180 s, it was guided there by hand. On day 4 (10^{th} measurement) and day 6 (16^{th} measurement), a probe trial was performed (90 s period in the arena without a goal box) to test a recall of the goal box. Trials 11–15 were for reversal testing, during which the escape box was switched directly to the opposite side of the maze.

3.5. Molecular experiments (I paper)

3.5.1. Tissue collection

A trained specialist dissected a mouse brain according to the coordinates obtained from the mouse brain atlas (Franklin and Paxinos, 1997). The mouse brain was divided into 16 areas to achieve optimal brain-wide coverage. The tissue samples were individually dissected, frozen in liquid nitrogen, and stored in the –80 °C freezer until further analysis.

3.5.2. Two-step qRT-PCR (qPCR)

IgLON transcript levels were determined by a two-step RT-qPCR (qPCR). Total RNA was extracted from each tissue sample using a Trizol reagent (Invitrogen) per the manufacturer's protocol. Per the protocol, the first-strand cDNA was synthesised using Random Hexamer (Applied Biosystems) and SuperScriptTM III Reverse Transcriptase (Invitrogen). Quantitative TaqMan Assay with FAM-BHQ-probe was designed to detect Lsamp 1a/1b, Opcml 1a/1b, Ntm 1a/1b, Negr1, and Iglon5 transcripts. In the case of twin transcripts, the universal reverse primer was combined with an alternative forward oligo specific for either the 1a or 1b transcript (Figure 2).

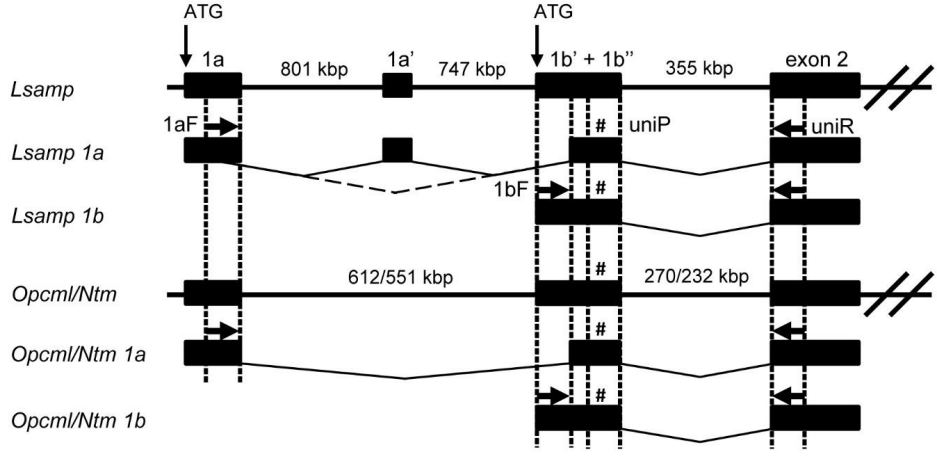


Figure 2. Twin promoter structure of *OPCML*, *NTM* and *LSAMP*. Genomic structure of the 5′ part of 1a and 1b promoter-derived transcripts. The 5′ part of the 1b transcript is assembled by adding 1b' + 1b" + exon 2, followed by the downstream exons in both rodents and humans. The 5′ part of the 1a transcript is typically assembled by adding 1a + 1b" + exon 2, followed by the downstream exons. An exception is the *Lsamp* 1a transcript in rodents, where one extra exon (1a') is included: 1a +1a' +1b" + exon 2. Horizontal arrows denoted as 1aF and 1bF indicate transcript-specific forward primers on 1a and 1b first exon, respectively. The horizontal arrow denoted as uniR indicates universal reverse primer on exon two, and # denoted as uniP indicates a custom probe on 1b".

Custom TaqMan Probe was bound to the universal 1b' exon. Synaptophysin mRNA levels were determined using the pre-designed Taqman Gene Expression Assay (Applied Biosystems): Mm00436850_m1 (Heinla et al., 2015). TaqMan Universal PCR Master Mix was used as a reaction buffer according to the manufacturer's protocol. Each reaction mix was divided into 10 µl quadruplicates. ABI Prism 7900HT Sequence Detection System with ABI Prism 7900 SDS 2.4.2 software (Applied Biosystems) was used for qPCR detection. All qPCR data are presented on a linear scale, as $2^{-\Delta CT}$, where ΔCT is the cycle threshold (CT) difference between the gene of interest and housekeeping gene *Hprt1* (Livak and Schmittgen, 2001).

3.5.3. Protein extraction and Western blotting

Frozen tissues were sonicated in ice-cold RIPA buffer (ThermoFisher Scientific) supplemented with protease inhibitor (Life Technologies). Protein lysates were centrifuged for 10 min at 12 000 g at 4 °C. The supernatant was collected, and protein concentration was determined by the BCA method (Pierce BCA Protein Assay Kit, ThermoFisher Scientific). NuPAGE Electrophoresis System (Life Technologies) components and equipment were used according to the manufacturer's instructions. For western blotting, the membranes were blocked in 3% dry milk on a rocker for 60 min at RT. Next, the membranes were incubated with mouse anti-Negr1 (1:200) (sc-393293, Santa Cruz), mouse anti-Ntm (1:200) (sc-390941, Santa Cruz), or rabbit anti-GAPDH (1:10 000) (247002, Synaptic Systems) primary antibodies for 60 min at RT, and after that overnight at 4 °C under gentle agitation. All primary antibodies were diluted in 3% dry milk with 0.1% Tween-20. After the primary antibody incubation, the membranes were washed six times in Milli-Q water and further incubated with corresponding secondary antibodies for 1 h at RT under agitation. Secondary goat anti-mouse antibody (A21057, Invitrogen) and goat anti-rabbit antibody (35569, Jackson ImmunoResearch) were diluted in PBS-0.1% Tween-20 to obtain 1:15 000 and 1:40 000 concentration, respectively. After incubation with the secondary antibodies, the membranes were washed six times in Milli-Q water, followed by a 20-min wash with PBS-0.1% Tween-20 with shaking. Re-Blot Plus Strong Solution (1x) (2504, Millipore) was used to strip and re-use the membrane. Antibody detection was performed using the LI-COR Odyssey CLx system (LI-COR Biotechnologies). Images were converted to greyscale, and the quantification was performed using Image Studio Lite v 3.1.4 (LI-COR Biotechnologies). Relative protein expression levels for NEGR1 and NTM were obtained after normalisation to GAPDH.

3.6. Molecular experiments (II paper)

3.6.1. Serum collection and analysis

1,5 ml Eppendorf tubes were pre-processed with 20 µl of EDTA (ethylene-diamine-tetra-acetic acid) and used for the animal blood collection. The tubes with blood samples were tilted back and forth and kept at room temperature for approximately 30 minutes, followed by centrifugation at 4 °C at 2000 g for 10 minutes. Plasma was transferred into new tubes and stored at −80 °C until their use (Tuck et al., 2009). The endogenous metabolites from plasma were analysed with the AbsoluteIDQ™ p180 Kit (Biocrates Life Sciences AG, Innsbruck, Austria). The levels of metabolites were determined using a flow injection analysis tandem mass spectrometry (FIA-MS/MS) and a liquid chromatography (LC-MS/MS) technique on a QTRAP 4500 mass-spectrometer (Sciex, USA) based on the manufacturer's protocol. Identification and quantification of the metabolites were performed using multiple reaction monitoring (MRM) along with internal standards. Calculations of the metabolite concentrations were automatically performed by MetIDQ™ software (Biocrates Life Sciences AG, Innsbruck, Austria). Data quality check was based on the level of detection as well as the level of quantification.

3.7. Molecular experiments (III paper)

3.7.1. Tissue collection

The mouse brain dissection was performed according to the coordinates obtained from the mouse brain atlas (Franklin and Paxinos, 1997). The tissue samples were individually dissected, frozen in liquid nitrogen and stored in the −80°C freezer until further analysis.

3.7.2. Two-step qRT-PCR

Total RNA was extracted using the RNeasy lipid tissue kit (Qiagen), followed by cDNA synthesis using Superscript VILO cDNA synthesis kit (Invitrogen). qPCR amplification was performed using the LightCycler 480 II instrument (Roche Diagnostics). Reactions were run in 96-well plate format in a final volume of 10 µl in triplicates. The PCR reaction mixture contained 2 µl cDNA and 100µM forward (F) and reverse primers (R) in 1X SYBR Green Master Mix (Roche). The reaction was carried out at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s, 60 °C for 20 s and 72 °C for 10 s. Expression levels were calculated by the $2^{-\Delta CT}$ method using the levels of GAPDH, the reference gene (Livak and Schmittgen, 2001).

3.8. Statistical analyses

In all the analyses, $p < 0.05$ was considered statistically significant. Shapiro–Wilk test was applied for the normality assumption of data. In general, behavioural and body weight outcomes corresponded to normality assumptions. Values on graphs are shown as mean ± SEM or mean ± 95% CI. Statistical tests were carried out using the Statistica software (StatSoft), and figures were created with GraphPad Prism (La Jolla) or Adobe Illustrator software (Adobe) or Pandas package (Python).

3.8.1. Statistical analyses (I paper)

One-way ANOVA or Student's t-test was used to analyse IgLON gene and protein expression levels (parallel in two mutant subgroups: Group I included Wt, $Lsamp^{-/-}$, $Lsamp^{-/-}/Ntm^{-/-}$, and Group II included Wt, $Ntm^{-/-}$, $Lsamp^{-/-}/Ntm^{-/-}$). In Western blot data analysis, the Student's t-test was used to detect statistically significant differences between the study groups. All qPCR data are presented on a linear scale, as $2^{-\Delta CT}$ (Livak and Schmittgen, 2001), where ΔCT is the difference in cycle threshold (CT) between the gene of interest and the housekeeping gene, *Hprt1*. *Hprt1* levels were optimised in our previous studies (Vanaveski et al., 2017) and proved to be one of the most stable housekeeping genes across different organs and tissue types in other studies (Svingen et al., 2015).

3.8.2. Statistical analyses (II paper)

The body weight changes were analysed by repeated-measures ANOVA [strain × test day (day 1 vs day 11)]. Horizontal locomotion was analysed by two-way ANOVA [strain × administration (saline, acute AMPH, repeated AMPH)] or by repeated-measures ANOVA [subgroup × test day (day 1 vs day 11)], followed by (unequal N) Tukey HSD post hoc test wherever applicable. When only a part of metabolite data was normally distributed, the Kruskal–Wallis analysis (multiple comparisons of mean ranks for all groups) was performed to analyse the effects of administration on metabolite levels, followed by Kruskal–Dunn's multiple comparisons, wherever applicable. Mann–Whitney U-test was applied to compare the raw data of two independent samples (strong and weak responders). A general linear model (GLM) multivariate analysis with a backward elimination procedure was performed to examine the associations between the distance travelled, metabolites, and their ratios in the 129Sv mice responding differently to repeated AMPH. To normalise the distribution, we performed a logarithmic transformation ($\log_{10}$) of the values of dependent characteristics before analysis. A partial eta2 value of ≥ 0.26 was defined as a significant effect (Cohen, 1992).

3.8.3. Statistical analyses (III paper)

The behavioural data were analysed by two-way ANOVA or repeated measures two-way ANOVA, followed by Tukey's unequal N HSD posthoc test, wherever applicable. The student's t-test was used for imaging data; the student's t-test or ANOVA, followed by the Dunnett posthoc test, was used for qPCR and immunoblotting data. Data expression values and immunoblots are given as means ± SEM of the averages in independent experiments. Unpaired Student's t-test was used for imaging and electrophysiology data, and the Student's t-test or ANOVA, followed by Dunnett's post hoc test, for qPCR and immunoblotting data.

4. RESULTS AND DISCUSSION

4.1. Discussion (I paper)

In the current scientific study, we investigated five genes of the IgLON family. First, we performed in silico analysis revealing eight transcripts. Next, we designed a qPCR experiment to quantify the gene expression of *IgLONs* in the Wt mouse brain. Once we determined the baseline expression levels, we were further interested in exploring any compensatory effects in the knock-out animals. We used Ntm, Lsamp and their double knock-out for the compensatory study.

4.1.1. Structural characteristics of IgLONs

Ntm, *Opcml*, and *Lsamp* displayed similar genomic structures in mice and humans, characterised by two alternative promoter regions, 1a and 1b, whereas *Negr1* and *Iglon5* suggested the existence of a single promoter. The alternative 5′ regions of 1a and 1b transcripts encode for alternative N-terminal signal peptides (Vanaveski et al., 2017). However, the following processed polypeptides contain identical N-termini, indicating that the complex alternative splicing serves as a regulatory process (Pimenta and Levitt, 2004). Signal peptides are removed during processing, usually to diversify the proteins' structure by post-translational modifications or to time their delivery to the cell surface (Huang et al., 2010; Kubick et al., 2018). *IgLONs* also shared a GPI anchor binding site and three pairs of cysteine residues, one pair for each of the three immunoglobulin domains (Vanaveski et al., 2017).

Based on the type and the number of domains, IgLONs are closely related to Nectins and Nectin-like SynCAMs (Walmod et al., 2007). Nectins demonstrate rod-like shapes, where the first two immunoglobulin domains, which are the furthest from the cell surface, interact in *cis* and *trans* in the *puncta adherentia* junction of a synapse (Honda et al., 2006). *Iglons* share the highest intra-family conservation in the first two immunoglobulin domains (Vanaveski et al., 2017). We can therefore expect *Iglons* to share a similar mode of interaction, where the I and II immunoglobulin domains are used for establishing *cis* and following *trans* interaction (Narita et al., 2011). Once the IgLON dimer has extended from the cell surface, based on affinity preferences, it may interact in *trans* (Reed et al., 2004). Analogously, the III immunoglobulin domain is reserved for extra-family interactions, such as the FGFR family (Turner et al., 2012; Ranaivoson et al., 2019).

4.1.2. Expression of IgLON transcripts

IgLONs displayed characteristic expression patterns in neural tissues. The twin transcripts of *Opcml*, *Ntm*, and *Lsamp* revealed 1a transcript dominance over 1b in normal conditions in adult animals (Figure 3). Later likely reflects a process where different promoter regions converge the signal from multiple transcription factors or numerous signalling pathways (Iijima et al., 2016). One of the twin

transcripts possibly performs a housekeeping role in the adult brain, and the other is used for dynamic expression to achieve neuroplasticity (Zabidi et al., 2015; Jagomäe et al., 2021). Anatomically, the pattern of IgLON expression demonstrates a sustained descending expression from frontal cortical regions towards the subcortical structures of the brain. The gene expression pattern in adulthood reflected the pathways formed during development (Jagomäe et al., 2021). The existing literature supports IgLON´ participation in shaping corticothalamic, pontocerebellar, and different limbic-related pathways (Keller et al., 1989; Pimenta et al., 1995; Struyk et al., 1995; Mann et al., 1998; Singh et al., 2019). The study of the interaction between FGFR2 and NEGR1 would further support this notion (Szczurkowska et al., 2018) as Fgfr2 is required to develop the medial prefrontal cortex and its connections with limbic circuits (Stevens et al., 2010).

Importance of IgLON function is supported by behavioural experiments with different knock-out lines, which show dysfunction in the social, emotional and fear-related encoding (Innos et al., 2012; Bregin et al., 2019; Singh et al., 2019). The widespread expression of IgLONs in the fronto-cerebellar pathway fits well with premorbid signs, such as delayed motor development, whereas high temporal expression is connected to social functioning deficits (Sørensen et al., 2010; Fusar-Poli et al., 2013; Slomiak et al., 2017; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2020). The delayed motor development in childhood seems to be followed by executive functioning deficits in later stages, dysfunctions which can be back-tracked to the fronto-cerebellar pathway (Diamond et al., 2003; Ridler et al., 2006). In addition to participating in neural tract development, IgLONs show a role in developing a stable mood phenotype, reflecting a possible gene dosage-dependent effect, where lower expression of Lsamp leads to a more stable mood. This notion was supported by lower rates of anxiety in EPM and Morris water maze as well as less aggression in male-to-male social interactions in Lsamp knock-out mice (Innos et al., 2011; Innos et al., 2012). The dampening of anxiety increased an exploratory drive and resulted in Lsamp mutant animals finding buried food rewards faster. From an evolutionary perspective, adequately regulated anxiety and exploratory behaviour would dictate a prey animal's survival. Lsamp gene expression levels are dynamically regulated in adult mice in response to a predator odour, resulting in a positive correlation between Lsamp expression and increased anxiety response (Kõks et al., 2004). Therefore, the dampened response in Lsamp-deficient animals may lead to enhanced exploratory activity in a wrong environmental context, such as in an environment occupied by a predator, resulting in lower fitness. This dynamic response, perhaps, goes sour in neurodevelopmental disorders and results in overexpression of IgLONs in the wrong context, such as chronic LSAMP overexpression in the DLPFC of people with schizophrenia (Behan et al., 2009).

The effect of IgLONs is not limited to the amygdala and fear response; instead, IgLONs seem to be widely expressed and associated with widespread alterations in GABAergic, dopaminergic and serotonergic systems (Innos et al., 2012; Bregin et al., 2019; Bregin et al., 2020). These alterations, perhaps, reflect abnormal migration as IgLONs have a notable role in developing the neocortex and subcortical

structures (Jagomäe et al., 2021). Changes in migration might affect neural progenitors, such as future inhibitory, dopaminergic and serotonergic cells. IgLONs are also shown to participate in myelino-, axono-, dendrito- and synaptogenesis in different brain regions; therefore, their dysfunction may be implicated in neuronal progenitor survival and proliferation, neural outgrowth guidance, synaptogenesis, pruning and post-mitotic survival. High expression of IgLONs, notably 1a transcripts in the frontal cortex, seems to support their role in highest-order cognitive functions. Therefore, their dysfunction in frontal cytoarchitecture may contribute to endophenotypes of many neurodevelopmental disorders (Schubert et al., 2015). Lsamp knock-out animals are hypersensitive to $GABA_A$ modulators and display an altered ratio of $GABA_A$ subunits α1 and α2 in favour of the latter one (Innos et al., 2011). As the absence of a functional Gabra2 seems to affect the development of the midbrain, the upregulation of *Gabra2* in Lsamp mutants is compensatory, reflecting GABAergic and dopaminergic dysfunction (Purves-Tyson et al., 2021). Also, there is a notably decreased sensitivity to AMPH and increased sensitivity to cocaine and morphine (Innos et al., 2012). The results from the place preference task and lower expression of DAT in the mesencephalon further support the dopaminergic dysfunction. Distinct effects of dopaminergic agonists would implicate the dysfunction of the dopaminergic system in the midbrain, dysfunction of dopaminergic afferents and their targets in Lsamp mutants (Jedynak et al., 2015). The serotonergic system also displays alterations, notably higher serotonin turnover, supported by higher expression of MaoA in raphe nuclei (Bregin et al., 2020). Escitalopram reverses 5-HT turnover; however, it cannot normalise behavioural parameters. A complementary expression of the serotonin transporter (encoded by the Slc6a4 gene) and Lsamp show a high expression activity in the raphe. The expression in both pre- and postsynaptic terminals would indicate a effect on serotonergic system integrity (Bregin et al., 2020). The GABAergic, dopaminergic and serotonergic alterations may again be related to the abnormal development, as IgLONs are expressed in the developing neocortex and midbrain (Jagomäe et al., 2021). Other family members, although less studied, show endophenotypes related to a broad spectrum of psychiatric disorders (Mazitov et al., 2017; Brunetti et al., 2019; Singh et al., 2018; Singh et al., 2019; Noh et al., 2019; Karis et al., 2018). These notions would link IgLONs with major neurotransmitter systems and reflect their widespread role in mood, social behaviour and cognitive functioning. However, how IgLON family interactions result and contribute to polygenic disease susceptibility remains to be studied (Wojtowicz et al., 2020).

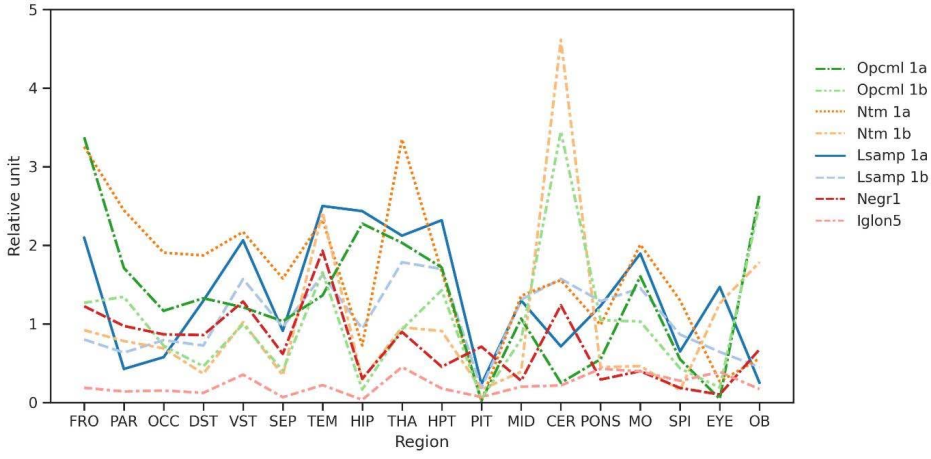


Figure 3. Relative transcript expression of IgLONs in mouse brain. The expression is shown in 16 brain regions, eye and spinal cord: the areas of the cerebral cortex–frontal (FRO), parietal (PAR), occipital (OCC), and temporal cortex (TEM; includes amygdala); the basal forebrain structures–dorsal striatum (DST), ventral striatum (VST), brain septum (SEP), hippocampus (HIP); the structures of the interbrain–thalamus (THA) and hypothalamus (HPT); midbrain (MID; including colliculi); the structures of hindbrain–pons (PONS), cerebellum (CER) and medulla (MO). The expression levels are shown as $2^{-\Delta CT}$ in relation to the *Hprt1* levels. The exact values ± SEM for all qPCR data in the brain is presented in Table 1.

Table 1. A relative transcript expression of IgLONs as compared to the *Hprt1* housekeeping gene in different areas of the brain and spinal cord (mean $2^{-\Delta CT} \pm$ SEM).

		Lsamp				**Neurotrimin**				**Opcml**				**Kilon**		**Iglon5**	
		1A		**1B**		**1A**		**1B**		**1A**		**1B**					
No	**Tissue**	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM	Aver-age	SEM
1	Frontal cortex	**2.096**	0.806	**0.801**	0.295	**3.252**	0.873	**0.920**	0.333	**3.373**	0.691	**1.268**	0.398	**1.224**	0.447	**0.187**	0.087
2	Parietal cortex	**0.426**	0.139	**0.634**	0.193	**2.444**	0.062	**0.781**	0.204	**1.710**	0.200	**1.343**	0.310	**0.973**	0.097	**0.140**	0.085
3	Occipital cortex	**0.576**	0.192	**0.792**	0.117	**1.905**	0.150	**0.688**	0.352	**1.165**	0.688	**0.722**	0.476	**0.866**	0.382	**0.152**	0.082
4	Caudate putamen	**1.294**	0.755	**0.724**	0.397	**1.870**	0.500	**0.366**	0.067	**1.325**	0.377	**0.460**	0.280	**0.857**	0.485	**0.122**	0.058
5	Ventral striatum	**2.062**	0.479	**1.569**	0.219	**2.169**	0.475	**1.022**	0.371	**1.211**	0.184	**0.996**	0.113	**1.284**	0.574	**0.353**	0.053
6	Septum	**0.911**	0.238	**0.959**	0.182	**1.577**	0.334	**0.344**	0.051	**1.033**	0.182	**0.406**	0.125	**0.617**	0.225	**0.067**	0.016
7	Temporal cortex and amygdala	**2.498**	0.349	**1.621**	0.380	**2.325**	0.347	**2.419**	0.456	**1.361**	0.293	**1.657**	0.333	**1.929**	0.400	**0.221**	0.006
8	Hippocampus	**2.433**	0.382	**0.938**	0.187	**0.724**	0.289	**0.290**	0.125	**2.274**	0.507	**0.164**	0.077	**0.303**	0.125	**0.034**	0.044
9	Thalamus	**2.121**	0.883	**1.783**	0.291	**3.347**	1.482	**0.956**	0.292	**2.030**	0.937	**0.930**	0.223	**0.897**	0.553	**0.450**	0.137
10	Hypothalamus	**2.317**	0.331	**1.697**	0.096	**1.663**	0.228	**0.908**	0.107	**1.717**	0.167	**1.428**	0.257	**0.454**	0.179	**0.178**	0.026
11	Pituitary gland	**0.232**	0.161	**0.183**	0.04	**0.025**	0.022	**0.166**	0.128	**0.019**	0.007	**0.048**	0.024	**0.71**	0.229	**0.069**	0.04
12	Midbrain and colliculi	**1.297**	0.592	**1.308**	0.622	**1.357**	0.800	**0.391**	0.237	**1.067**	0.532	**0.802**	0.352	**0.276**	0.152	**0.201**	0.063
13	Cerebellum	**0.713**	0.211	**1.571**	0.116	**1.556**	0.872	**4.611**	1.893	**0.250**	0.226	**3.448**	1.090	**1.236**	0.101	**0.216**	0.114
14	Pons	**1.229**	0.494	**1.289**	0.614	**0.986**	0.497	**0.448**	0.116	**0.551**	0.335	**1.048**	0.543	**0.292**	0.093	**0.429**	0.144
15	Medulla	**1.893**	0.959	**1.452**	0.591	**2.008**	0.582	**0.463**	0.209	**1.604**	0.608	**1.029**	0.345	**0.398**	0.062	**0.395**	0.182
16	Spinal cord	**0.648**	0.058	**0.864**	0.142	**1.298**	0.137	**0.156**	0.057	**0.549**	0.115	**0.434**	0.077	**0.184**	0.017	**0.275**	0.031
17	Eye	**1.468**	0.388	**0.643**	0.116	**0.266**	0.059	**1.26**	0.303	**0.046**	0.011	**0.189**	0.077	**0.101**	0.034	**0.389**	0.119
18	Olfactory bulb	**0.250**	0.147	**0.449**	0.217	**0.559**	0.313	**1.783**	0.922	**2.644**	0.649	**2.522**	0.077	**0.675**	0.170	**0.170**	0.150

4.1.3. Compensatory expression of IgLONs

Our compensatory study showed that the other family members cannot substitute *IgLON*s. However, an increased synaptophysin expression in the hippocampus could be related to an extra-family compensatory attempt to substitute Ntm deficiency by increasing synaptogenic activity (Figure 4). Possibly, deficient Ntm expression and resulting deficiency of homophilic interactions between neurons can be substituted by other synaptic proteins; however, a lack of formation of circuits in cooperation with other IgLONs during the development will still result in behavioural deficits. In a Lsamp deficient strain, we demonstrated a statistically significant decline in Ntm 1a transcript and Negr1 protein expression in the frontal cortex. These changes were brain region-specific. Possibly, these genes could be used as markers to characterise the disease phenotype and tissue-specific alterations in the brain in neurodevelopmental disorders (Leblond et al., 2021). We expect the III immunoglobulin domain to have an essential role in tissue-specific interactions in cooperation with downstream signalling partners, analogously to Nectin1 *cis*-interaction with various isoforms of FGFR (Bojesen et al., 2012) and Nectin4 *cis*-Interactions with ErbB2 tyrosine kinase receptor (Kedashiro et al., 2019). Negr1 is already shown to be associated with Fgfr2; however, the interactions of other family members and their extra-family remain unknown.

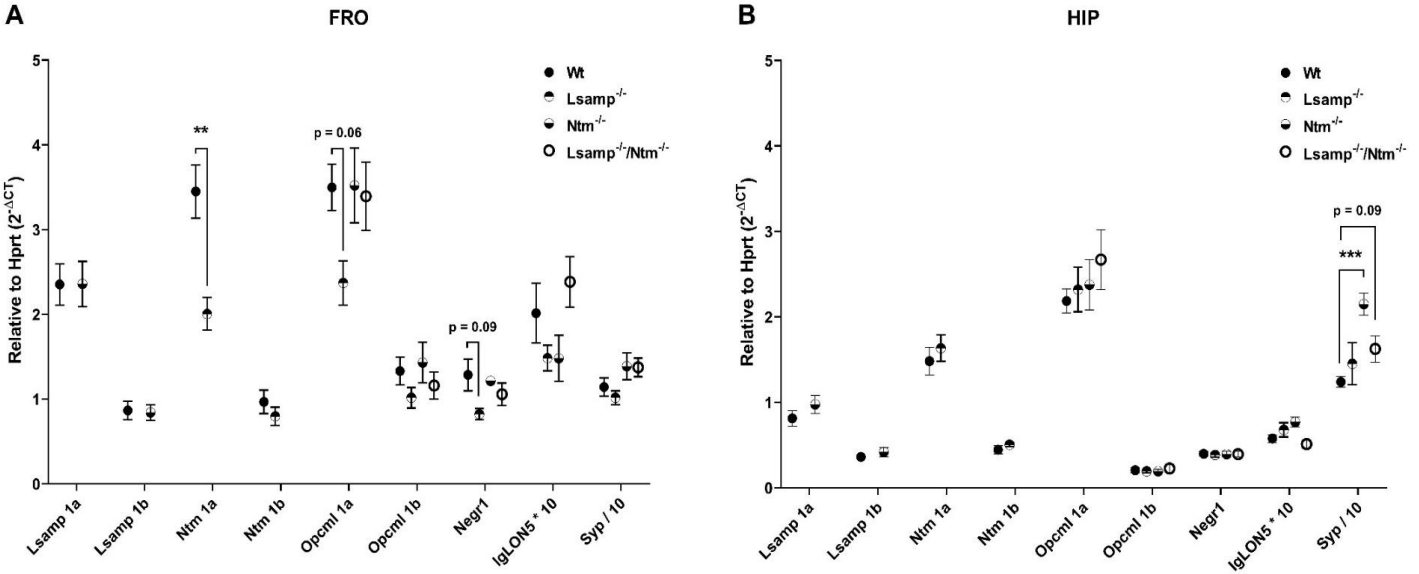


Figure 4. Relative transcript expression of IgLONs; The expression levels are presented as $2^{-\Delta CT} \pm$ SEM and in comparison to Hprt1 levels for (A) frontal cortex (FRO) and (B) hippocampus (HIP) based on promoter activity at the age of 4–5 months of the animals. Visual corrections are made for IgLON5 and Syp by multiplying or dividing by a factor of 10, respectively. One-way ANOVA was used for every isoform in parallel in two mutant subgroups: Group I: Wt (wild-type), Lsamp$^{-/-}$, Lsamp$^{-/-}$/Ntm$^{-/-}$, and Group II: Wt, Ntm$^{-/-}$, Lsamp$^{-/-}$/Ntm$^{-/-}$. Tukey's HSD test further emphasized intra-group differences. (A) The expression alterations did not survive posthoc analysis for *Opcml* 1a (Tukey HSD p = 0.06) and *Negr1* (Tukey HSD p = 0.092). The average expression level of Ntm 1a transcript was significantly reduced in Lsamp$^{-/-}$ compared to Wt [$F_{(2, 10)} = 2.66$, t-test p = 0.003] in the frontal cortex.

(B) Expression changes were detected for Iglon5 and Syp; for the Iglon5 transcript in the hippocampus, a statistically significant difference was observed in Group I [$F_{(2, 15)} = 6.8$, one-way ANOVA p = 0.008]. Further intra-group analysis revealed a significantly higher expression level in the Lsamp$^{-/-}$ compared to Wt (Tukey HSD p = 0.045) and Ntm$^{-/-}$. The expression levels of Syp in the hippocampus were significantly different in Group II [$F_{(2, 15)} = 13.99$, one-way ANOVA p = 0.0004]. Further, intra-group analysis showed that the expression was significantly higher in the Ntm$^{-/-}$ as compared to Wt (Tukey HSD p = 0.0004), Lsamp$^{-/-}$/Ntm$^{-/-}$ (Tukey HSD p = 0.022), and Lsamp$^{-/-}$ [$F_{(2, 10)} = 3.59$, t-test p = 0.031]. n = 6 in all groups; **p < 0.01; ***p < 0.001.

4.1.4. Conclusion

Recent findings revealing a connection between specific IgLON transcripts and suicide, drug use, and mental disorders would indicate that these molecules play a relevant role in forming neuropsychiatric disease susceptibility (Karis et al., 2018). The outcomes of the current work indicate a widespread expression of IgLONs in the brain and their coherence with some major brain pathways implicated in neurodevelopmental disorders (Jagomäe et al., 2021). The data from the deletion mutant, especially in the case of Lsamp, would indicate alterations in GABAergic, dopaminergic, and serotonergic systems. These findings are supported by behavioural, pharmacological, and expression-related data (Innos et al., 2012; Bregin et al., 2019; Bregin et al., 2020). Investigation in schizophrenia patients has further supported the role of these genes in disease susceptibility; however, the complex expression pattering and unknown interaction partners leave numerous questions unanswered. We can expect the IgLONs to offer a biomarker potential or even indicate new molecular pathways for treatment; however, this notion can only be confirmed by having more models and data about these molecules and their interactions. Differential promoter activity may also offer a potential for intervention by selectively inducing IgLON expression in the region of interest. Meanwhile, the IgLON mutant strains provide enough validity to model and study neurodevelopmental disorders and, perhaps, affective disorders.

4.2. Discussion (II paper)

In the current scientific study, we investigated the effect of AMPH-induced psychosis-like state on metabolic profile using mice model. The metabolomic research was conducted using the blood plasma of mice. The two mouse strains, 129Sv and Bl6, used in the experiment were divided into three groups: saline-treated, acutely AMPH-treated and chronically AMPH-treated. Locomotor activity was measured for 11 days after the blood collection. Considering the background of these strains, some of the main findings are discussed as follows.

4.2.1. Induced changes in body weight and behaviour

During experimental handling, our model strains 129Sv and Bl6 responded differently to a stressful challenge. The 129Sv strain's response to the daily manipulations was characterised by body weight loss independent of drug treatment (Figure 5). In our previous study, 129Sv displayed an enhanced weight gain in the home cage control group (Narvik et al., 2018). Exposing the same strain to environmental enrichment resulted in body weight decline and desensitisation of dopaminergic response (Heinla et al., 2014). As dopaminergic dysfunction is thought to be involved in stress response, these findings indicate that behavioural manipulations were more stressful for 129Sv (Mizoguchi et al., 2000). Both strains revealed no significant differences in basal motor activity (Koike et al., 2006). However,

during the experimental conditions, the increase of locomotor activity was significantly higher in the acutely treated Bl6, probably related to stronger AMPH-induced striatal DA efflux (Chen et al., 2001). Elevation of locomotor activity in response to repeated AMPH was, on average, more pronounced in 129Sv (Figure 5). 129Sv also displayed an increased variation in the activity of the repeated AMPH group, resulting in a bimodal distribution. In this bimodal distribution, the animals whose response did not differ from the acute AMPH group were considered weak responders, and the animals with up to 5-fold augmentation were considered strong responders.

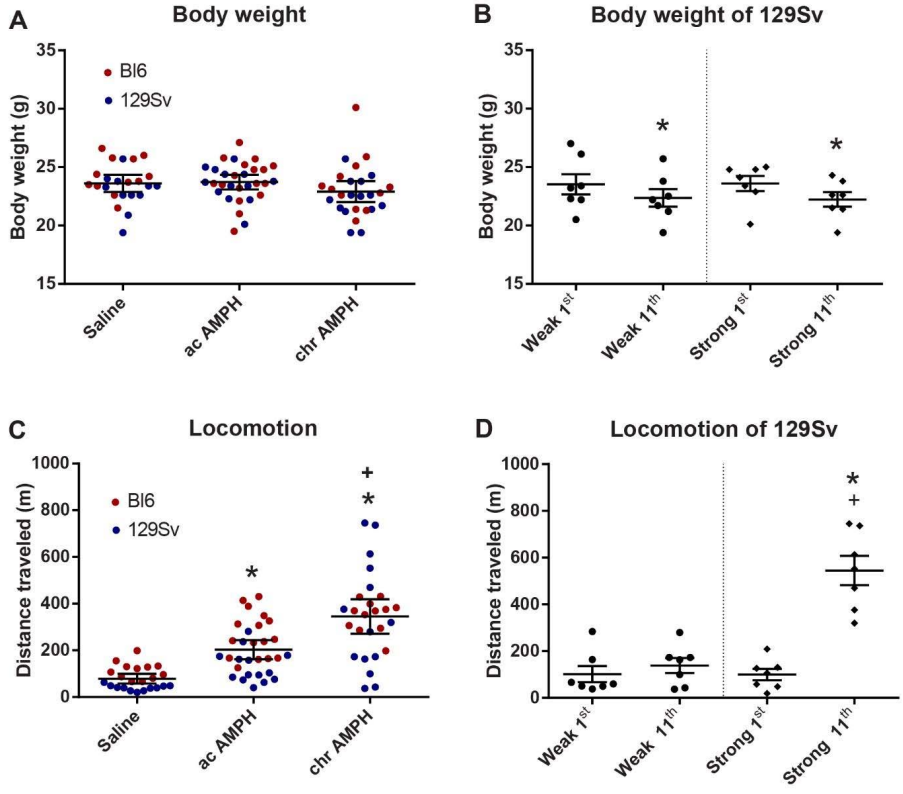


Figure 5. Locomotion and body weight changes. Bodyweight **(A–B)** and distance travelled **(C–D)** for pooled and weak/strong responders (mean values ± SEM). **(A, C)** Both strains' data are pooled and indicated by blue dots for 129Sv and red dots for Bl6. **(B)** Only 129Sv displayed a statistically significant change in their body weight. The main effect of body weight change is denoted by *. **(C)** Both strains displayed a statistically significant increase in horizontal activity in response to AMPH treatment. Also, Bl6 showed a statistically significant change in the acute treatment already. The main effect of locomotion change is denoted by *. **(D)** A notable activity increase in response to chronic AMPH treatment was seen in the 129Sv strong responder group. The results were analysed using one-way ANOVA, followed by an unequal N Tukey HSD test. *$p < 0.05$, $^{+}p < 0.05$.

4.2.2. Induced changes in energy metabolism

The current study established several significant metabolite changes that reflect energy metabolism after acute AMPH treatment. Later involves the elevation of BCAA—isoleucine and leucine levels in Bl6 (Figure 6). The alteration of isoleucine and leucine accompanied a progressive shift in the ratio of BCAA and AAA. However, the same ratio did not achieve statistical significance in 129Sv, possibly because the increased BCAA consumption served as an energy source during the acute treatment. The ratio of acylcarnitines C3 and C5 with carnitine shifted in favour of short-chain acylcarnitines in 129Sv, supporting BCAA breakdown (Figure 6). BCAAs were used as an additional energy source in both lines to replenish the energy needed due to the treatment-related metabolic load (Nie et al., 2018). Later was because of the overburdening of hexose metabolism, reflected by a progressive decline in the level of hexoses (including glucose). Human studies demonstrate that BCAAs and related metabolites are associated with insulin resistance and diabetes and can predict diabetes development and intervention outcomes (Newgard, 2012). Therefore, isoleucine and leucine play a crucial role in metabolic homeostasis, and their elevation and breakdown reflect a compensatory response.

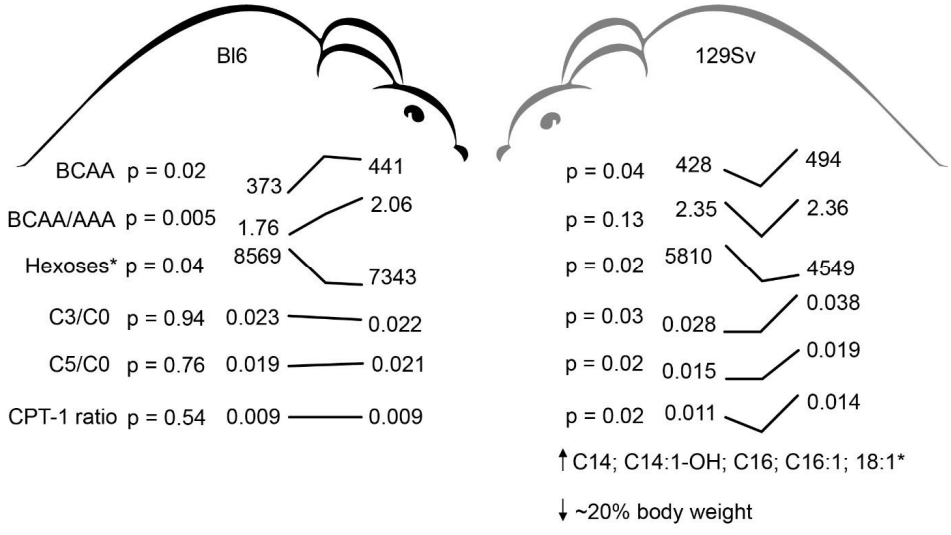


Figure 6. Energetically relevant metabolite changes in the mouse strains, Bl6 and 129Sv. The line visually presents median values in the three treatment groups—saline-treated, acutely AMPH-treated and chronically AMPH treated. D-amphetamine-induced statistically significant metabolite changes (μmoles, median) and their ratios in both strains (Kruskal–Wallis test, $p < 0.05$).

Further accumulation of mid and long-chain acylcarnitines in 129Sv would indicate an increased mitochondrial β-oxidation. The elevated ratio between long-chain acylcarnitines and carnitine (CPT-1 ratio) further reflects an increase of β-oxidation (Longo et al., 2016). 129Sv is characterized by a general state of metabolic inflexibility and mitochondrial inefficiency that leads to an accumulation of metabolic intermediates of fatty acid oxidation, such as some medium-chain and long-chain acylcarnitines. Long-chain and medium-chain acylcarnitines are associated with an increased risk of all-cause mortality or hospitalization; notably, C16, C18:1, and C18:2 acylcarnitines were significantly higher in the patients with end-stage heart failure (Ahmad et al., 2016). C14 supplementation is associated with lipid accumulation by inhibiting the AMPK/ACC/CPT1 signalling pathway, modulating a downregulation of acetyl CoA carboxylase and carnitine palmitoyl transferase 1 pathway (Zheng et al., 2021). The AMPK/ACC/CPT1 pathway is sensitive to clozapine treatment (Kim et al., 2012). These results suggest that Bl6 can sustain hexose metabolism longer, whereas 129Sv is energetically more compromised.

In our attempt to explain the bimodal response in 129Sv, we divided the strain into weak and strong responders. The strong responders to AMPH displayed elevated levels of long-chain acylcarnitines (C12, C14, C14:1-OH, C16:1) and the reduced levels of hexoses compared to the weak responders (Table 2). This difference in the bimodal response could be related to a reduced availability of inhibitory transmitter glycine and an increased availability of tyrosine as a precursor molecule of catecholamines in the strong responders (Vanaveski et al., 2018). A rapid change in the ratio of BCAA and AAA in the Bl6 strain may cause behavioural inhibition (Blomstrand, 2006). The BCAAs displace aromatic amino acids at the large neutral amino acid transporter, a rate-limiting transporter, at the blood-brain barrier (Smith et al., 1987). BCAAs induce protein synthesis, therefore, also deplete plasma tryptophan. In conclusion, altering cerebral precursors of monoamines, including dopamine, can be further differentiated into weak and strong responders (Fernstrom, 2005; Neuhaus et al., 2009).

A strong negative correlation between C18:1 and hexoses was found (Vanaveski et al., 2018), demonstrating that the animals with the lowest hexoses displayed the highest levels of C18:1. C18:1 is shown as the pharmacologically active compound to block the activity of glycine type 2 transporter (Carland et al., 2013) and therefore is responsible for accumulating glycine in the synaptic cleft (Jiménez et al., 2015). Glycine plays a role as an inhibitory as well as an excitatory neurotransmitter in the brain (Hernandes and Troncone, 2009). It achieves the inhibitory effect by binding to glycine receptors and co-modulates GABAergic neuroinhibiton by shaping mIPSC dynamics (Aubrey and Supplisson, 2018). Glycine achieves neurostimulation by binding to the D-serine/glycine site on the NMDA receptor so glutamate can activate the receptor (Johnson and Ascher, 1987; Clements and Westbrook, 1991). These metabolic changes connect compromised energy expenditure to altered inhibitory and excitatory neurotransmission.

Table 2. Changes in the weak and the strong responders. Distance travelled (m), metabolites (μmoles), and their ratios (median and range) in 129Sv responding differently to d-AMPH categorized as the weak and the strong responders (Mann–Whitney U-test, $p < 0.05$).

	Weak ($N = 7$)	Strong ($N = 7$)	Z-value	p-value	Effect size (η^2)
Distance traveled on day 11	163 37–279	552 320–746	–3.07	0.002	0.67
C12	0.10 0.000–0.13	0.12 0.096–0.16	–2.04	0.04	0.30
C14:1	0.058 0.040–0.069	0.069 0.059–0.089	–2.11	0.04	0.32
C14:1-OH	0.013 0.000–0.018	0.016 0.013–0.025	–1.98	0.05	0.28
C16:1	0.085 0.067–0.11	0.10 0.083–0.14	–2.04	0.04	0.30
PC aa C36:3	50.9 29.1–58.2	42.6 27.4–47.9	2.04	0.04	0.30
Hexoses	5,551 2,764–5,937	3,792 3,284–4,787	2.04	0.04	0.30
C4/C5	2.82 1.88–3.32	2.25 1.84–2.55	2.17	0.03	0.34
Glycine/Glutamine	0.55 0.45–0.61	0.45 0.37–0.49	2.43	0.02	0.42

Effect size estimates are indicated by η^2, where partial eta^2 value ≥ 0.26 was defined as a large effect.

4.2.3. Induced changes in biogenic amines

We detected a reduction in the levels of biogenic amines (including ADMA, αAAA, and kynurenine) in the Bl6 repeated AMPH group (Figure 7). Elevated levels of ADMA inhibit NO synthesis and lead to impaired endothelial function (Sibal et al., 2010). An interplay of citrulline and ADMA displays a critical regulatory effect, where citrulline protects endothelium from ADMA-induced impairment (Xuan et al., 2015). The beneficial effect of citrulline may be attributed to the preservation of NO production, activation of the NO/cGMP signalling pathway, and suppression of superoxide anion overproduction (Xuan et al., 2015). αAAA is a component of the lysine metabolism pathway and a marker of oxidative stress (Yuan et al., 2011; Zeitoun-Ghandour et al., 2011). A recent metabolic study of diabetes patients' plasma samples suggested that αAAA may modulate glucose homeostasis and diabetes risk (Wang et al., 2013). Studies on rodents also showed that αAAA modulates kynurenic acid (KYNA) levels in the brain. KYNA is a neuroactive metabolite that interacts with NMDA, AMPA/kainate, and alpha 7 nicotinic receptors (Sekine et al., 2015). In vivo, free-moving

rats exposed to αAAA through microdialysis in the hippocampus showed significantly decreased KYNA levels (Chang et al., 1997; Poh et al., 2019). Brain levels of KYNA are elevated in the post-mortem brains of patients with SCZ (Schwarcz et al., 2012). In physiological conditions, the kynurenine pathway produces KYNA, picolinic acid, or essential pyridine nucleotide—NAD+ (Lim et al., 2017). The KYNA and picolinic acid are neuroprotective, whereas NAD+ is a crucial co-factor in mitochondrial energy production (Chen et al., 2010; Massudi et al., 2012; Tóth et al., 2021). However, the kynurenine pathway under inflammatory conditions shifts to overexpressing QUIN and other neurotoxic and/or pro-inflammatory molecules (Pérez-De La Cruz et al., 2007; Braidy et al., 2009). Accumulation of QUIN can lead to neuronal dysfunction and/or death (Pérez-De La Cruz et al., 2012; Lim et al., 2015).

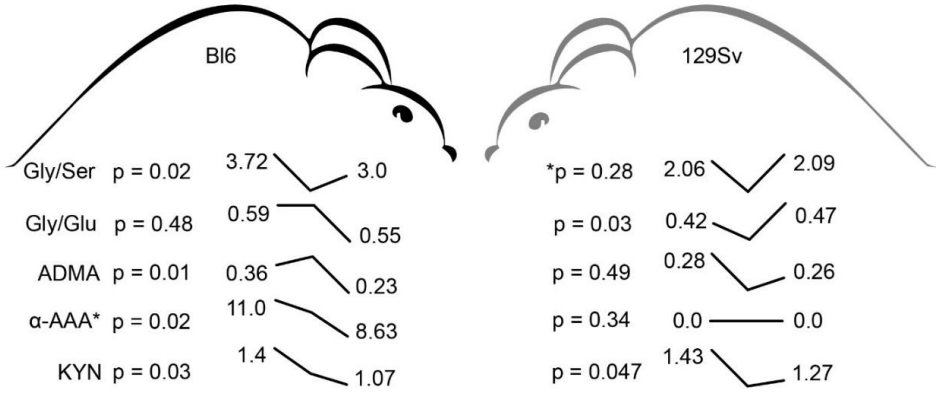


Figure 7. Regulatory metabolite changes in the mouse strains B16 and 129Sv. The line visually presents the median values of the three treatment groups—saline-treated, acutely AMPH-treated and chronically AMPH treated. D-amphetamine-induced statistically significant differences of metabolites (μmoles, median; Kruskal–Wallis test, $p < 0.05$).

4.2.4. Conclusion

In our experiment, distinct metabolic profiles appeared for 129Sv and Bl6 after repeated AMPH administration. Contrary to the elevation of BCAAs, kynurenine, citrulline, and ADMA levels were reduced by repeated AMPH treatment, showing alterations in NMDA, NO-mediated, and energy production-related mechanisms. In Bl6 mice, only moderate sensitisation for AMPH was observed, whereas 129Sv mice could be divided into two subgroups. The weak subgroup displayed no progressive sensitisation to AMPH, resembling a depression-like state, whereas the strong subgroup responded with a robust sensitisation, resembling a psychotic-like state. Depressive and psychotic symptoms were seen in patients with psychosis (Sönmez et al., 2016). Therefore, we can speculate that the distinct behaviour of 129Sv mice in stressful situations may, to a certain extent, reflect the characteristics of prodrome and, once challenged by AMPH, emulate the onset of psychosis. Our model demonstrated a susceptibility of Disc1 mutants to psychotic disorders.

4.3. Discussion (III paper)

4.3.1. Weight changes in PPARGC1α transgenic mice model

PPARGC1α transgenic (Tg) mice gained more weight as compared to the wild-type (Wt) controls (Figure 8; Consitt et al., 2010). The weight gain could be related to GABAergic changes in the mesolimbic dopamine reward system, altering food intake (Rui et al., 2013). Previous studies have indicated a vulnerability of the mesolimbic dopaminergic system in local overexpression models (Ciron et al., 2012). The same circuit is also responsible for susceptibility to alcoholism and anxiety (Enoch et al., 2008). The altered food intake would explain weight changes and predisposition to obesity (Gastaldi et al., 2007; Zorzano et al., 2010). Abnormal body weight gain was also noted in PPARGC1α knock-out animals (Leone et al., 2005). Thiazolidinediones (pioglitazone and rosiglitazone), the known agonists of PPARγ, were used clinically as insulin sensitisers in type 2 diabetes, and their use also concorded with weight gain in patients (Soccio et al., 2014). Therefore, a balanced expression of PPARGC1α seems necessary for fine-tuning adaptation to counter physiological stressors, and the inability to do so results in physiological and behavioural abnormalities (Lin et al., 2004; Wu et al., 2011).

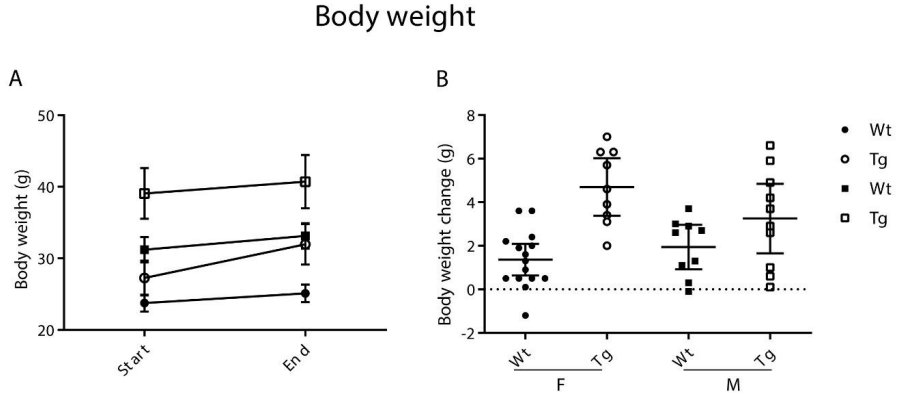
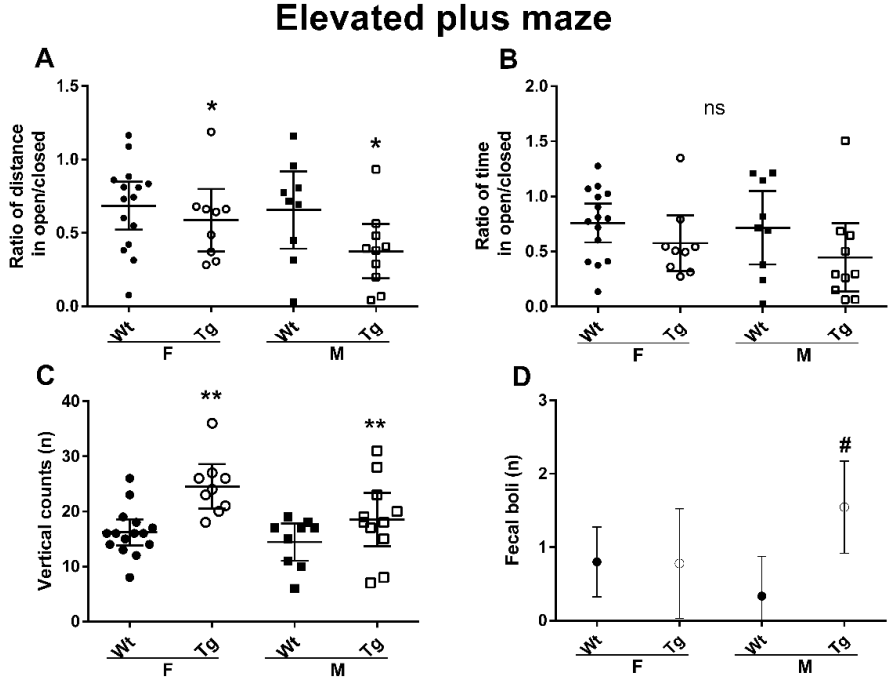


Figure 8. Comparison of body weight change before and after behavioural experiments in PPARGC1α Tg mice model. (A) PPARGC1α Tg female (M_{start} = 27.26 vs M_{end} = 31.96 g) and male (M_{start} = 38.23 vs M_{end} = 41.48 g) mice indicated a trend to gain more weight as compared to Wt female (M_{start} = 23.75 vs M_{end} = 25.11 g) and male (M_{start} = 31.20 vs 33.14 g) mice. The weight change during 6 weeks demonstrated a statistically significant Gt ($F_{(1, 40)}$ = 44.22, $p < 0.0001$), sex ($F_{(1, 40)}$ = 86.45, $p < 0.0001$) and time ($F_{(1, 40)}$ = 24.93, $p < 0.0001$) effect. Post-hoc analysis revealed a weight gain in all groups during the testing period ($p < 0.001$). The weight gain was highest among the female ($p < 0.001$) and transgenic ($p = 0.001$) animals. Though the interaction effect of time x sex x genotype was not statistically significant ($F_{(1, 40)}$ = 3.57, $p = 0.066$), PPARGC1α Tg females (4.7 g, 17.4%) and male mice (3.25 g, 8.6%) indicated a trend to gain more weight as compared to Wt female (1.36 g, 5.8%) and male mice (1.94 g, 6.3%). The results were analysed using two-way repeated-measures ANOVA, followed by Tukey Unequal N HSD.

4.3.2. PPARGC1α mutants display anxiety-like behaviour

The notable weight gain was supplemented by anxiety-like behaviour independent of sex in elevated plus-maze (EPM) and light-dark box (LDB). In the EPM test, PPARGC1α Tg mice preferred closed areas in the distance but not in the time-related dimension (Figures 9A and B). The number of vertical counts was increased in the Tg mouse group (Figure 9C). Also, Tg male mice had a higher defecation rate (Figure 9D). Although the classical parameters indicated less support for anxiety, it might be related to the light intensity of the EPM. Interestingly, Wt and Tg animals demonstrated no activity difference in the open field (Vanaveski et al., 2021). Again, the light intensity may offer some explanation, and perhaps the body weight differences may shadow some anxiety phenotype. In the Light-dark box (LDB) test, there was a strong preference for a dark area in the Tg groups (Figures 9E and F). Again, Tg mice made more vertical counts; however, these occurred mainly in the dark area (9G). The increased vertical activity could signify agitation or stress (Boulle et al., 2014). Notably, the increase in anxiogenic behaviour was linked to changes in the GABAergic system. Also, $GABA_A$ receptors containing the α2 subunit were implicated in anxiety disorders and required for the anxiolytic effects of GABAergic drugs (Löw et al., 2000; Engin et al., 2012). The behaviour of PPARGC1α Tg mice indicated mild anxiety in LDB, weak anxiety in EPM, and lack of anxiety in OF (open field).



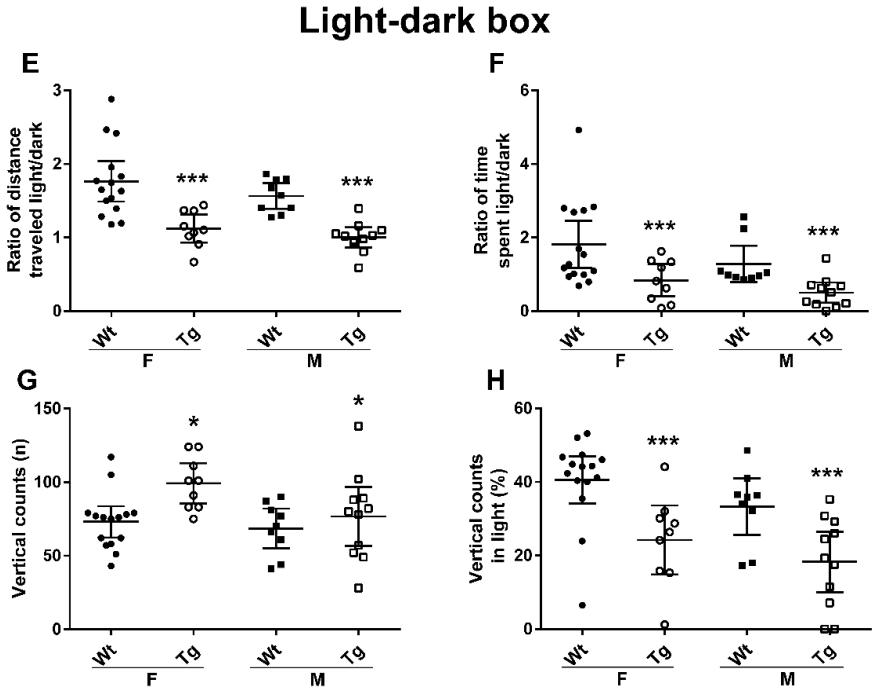


Figure 9. Increased anxiety-like behaviour in PPARGC1α transgenic mice. 24 wild-type (Wt) and 20 PPARGC1α transgenic (Tg) mice were examined using behavioural tests. Female (F) and male (M) mice were analysed separately using four different groups: Wt F (n = 15), Wt M (n = 9), Tg F (n = 9) and Tg M (n = 11). The data are displayed as mean ± 95% CI. *p < 0.05, **p < 0.01, ***p < 0.0001 for Tg vs. Wt mice. Most of the findings are reported by comparing the Tg vs Wt group (non-sex-specific findings). The main effects are shown in Figures A, C, and E–H. (A–D) Elevated plus-maze (EPM) was conducted to assess anxiety behaviour for 5 min as a test period. Statistical analyses were performed using two-way ANOVA, followed by Tukey's unequal N HSD posthoc test. (A) The ratio of distance travelled in open vs closed areas was reduced in the PPARGC1α Tg mice. $F_{(1, 40)} = 4.24$, $p = 0.046$. (B) The time spent was not significantly different $F_{(1, 40)} = 3.74$, $p = 0.06$. (C) The number of vertical counts was higher in Tg mice. $F_{(1, 40)} = 14.04$, $p = 0.0006$. (D) The number of faecal boli was increased in PPARGC1α Tg males. Gt × Sex $F_{(1, 40)} = 5.23$, $p = 0.028$. (E–H) Light–dark box (LDB) test was carried out for 10-min. (E) The ratio of the total distance travelled. $F_{(1, 40)} = 32.46$, $p < 0.00001$. (F) The ratio of the time spent in light vs dark areas was lower in PPARGC1α Tg mice. $F_{(1, 40)} = 12.26$, $p = 0.0012$. (G) PPARGC1α Tg mice made more vertical counts than Wt $F_{(1, 40)} = 8.76$, $p = 0.005$. (H) The percentage of vertical counts made in the dark area $F_{(1, 40)} = 19.07$ $p = 0.00009$.

4.3.3. PPARGC1α mutants exhibit impaired decision-making

4.3.3.1. Delayed decision-making as revealed in T-maze test

The alternation in T-maze is a natural behaviour for rodents (Deacon and Rawlins, 2006). In the T-maze test, the mean alteration rate of six trials varied between 83–86%, indicating a high spatial memory performance in all test groups. However, a closer look at decision latency revealed that it took significantly longer for PPARGC1α Tg animals to complete a decision-making process during the first decision and alternation (Figure 10A). Increased anxiety or a lack of motivation is likely to suppress the decision-making region in the frontal cortex (Zeeb and Winstanley, 2013; Park et al., 2016). The effect of anxiety and a lack of stimulation on a food reward might have suppressed a novelty-seeking behaviour, such as a progressive lack of motivation over the three trials (Costa et al., 2018). A lack of novelty-seeking predicts depression (Stedenfeld et al., 2011). The α2 subunit is primarily expressed in the hippocampus, amygdala, and frontal cortical areas, and expression alterations might have led to delayed decision-making (Hörtnagl et al., 2013). In addition to anxiety, the α2 subunit is also connected to depression (Vollenweider et al., 2011). While assessing depressiveness in a mouse model was challenging, anhedonia displayed in depressed patients and avolition displayed in schizophrenia patients were indicated in the current mouse model (Foussias and Remington, 2010; De Fruyt et al., 2020).

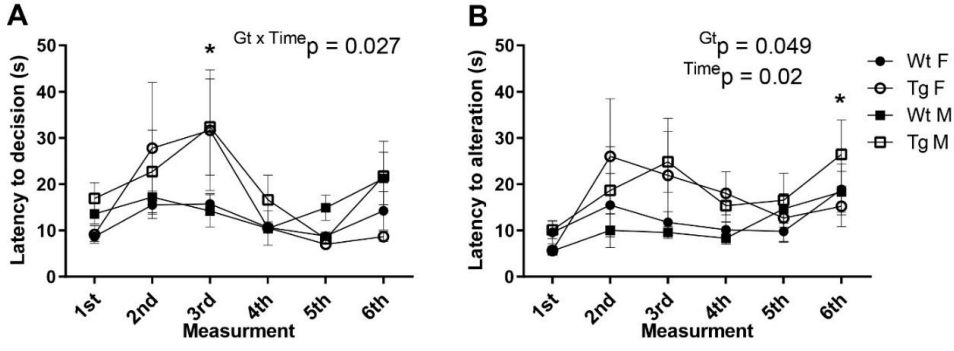


Figure 10. Executive functioning and spatial cognition in T-maze. The T-maze test was carried out for two days, 3 trials per day and at least 1-hour gap between the two trials. **(A)** Latency to decision revealed an overall longer time for decision-making by PPARGC1α Tg, notably on the third trial of the first day. **(B)** Latency to alternation also showed a longer alteration time, notably on the third trial of the second day (overall during the sixth trial). *$p < 0.05$**.**

4.3.3.2. Impaired spatial performance in Barnes maze

The Barnes maze was used to study spatial learning and memory performance across 16 trials for five consecutive days (1–9th trial for acquisition, 10th and 16th for probe trial, and 11–15th for reversal learning). To study the relearning paradigm, the goal box was changed to the opposite side of the arena on the 11th day. In the acquisition phase, the distance travelled on the platform ($F_{(1, 40)}$ = 14.44, p = 0.00048; Figure 11A) and the time spent revealed Gt ($F_{(1, 40)}$ = 9.16, p = 0.004, not shown) effect. The distance travelled (p = 0.002) and the time spent (p = 0.03) on the arena were significantly lower for PPARGC1α Tg groups. Effective learning occurred in all the groups during the experiment ($F_{(13, 520)}$ = 4.28, p < 0.00001; Figure 11AB). Latency to enter the target demonstrated the main Gt ($F_{(1, 40)}$ = 7.11, p = 0.011) and the Time ($F_{(13, 520)}$ = 5.16, p < 0.00001) effect. To further explain the extended time spent by Wt on the arena, we created a re-exploration parameter (duration on the arena–first entry latency to the target zone). The re-exploration time revealed a Gt ($F_{(13, 377)}$ = 1.83, p < 0.007) effect (Figure 11C). Wt animals explored the arena more after discovering the target zone (p = 0.021). Also, the average distance from the target demonstrated an interaction effect of Gt x Sex ($F_{(13, 520)}$ = 8.15, p < 0.0068). Wt male mice preferred to be closer to the goal box (p = 0.007), reflecting their awareness of the safe area (Figure 11D). Visual analysis of the time spent on the arena in the Barnes maze revealed that Wt F, Tg F, and Tg M preferred wall-hugging or serial search strategy during acquisition (Figure 11E). Tg M had the greatest difficulty finding a safe box, as indicated by the random time spent in different zones. Wt F, Tg F, and Tg M continued to use the wall-hugging strategy in the relearning phase. Wt males, however, spent a proportionally higher percentage of time in the target zone, even after the safe box was switched to a new location, demonstrating a pattern of moving between the old and new locations and indicating a use of spatial strategy. During reversal learning, Tg mice, especially males, had difficulty finding the target zone and again relied on a wall-hugging or a serial search strategy. While the female mice preferred the wall-hugging strategy in both stages, the males demonstrated a sharp contrast; Wt males used spatial, and Tg males used the wall-hugging strategy, indicating a reduced performance among PPARGC1α Tg male mice. A higher percentage of failed instances supports the outcome (Wt M = 1.59%, Tg M = 8.44%, Wt F = 2.86%, Tg F = 0.79%). A probe trial analysis revealed a similar overall pattern of wall-hugging mixed with inner arena cross-visits in all the groups.

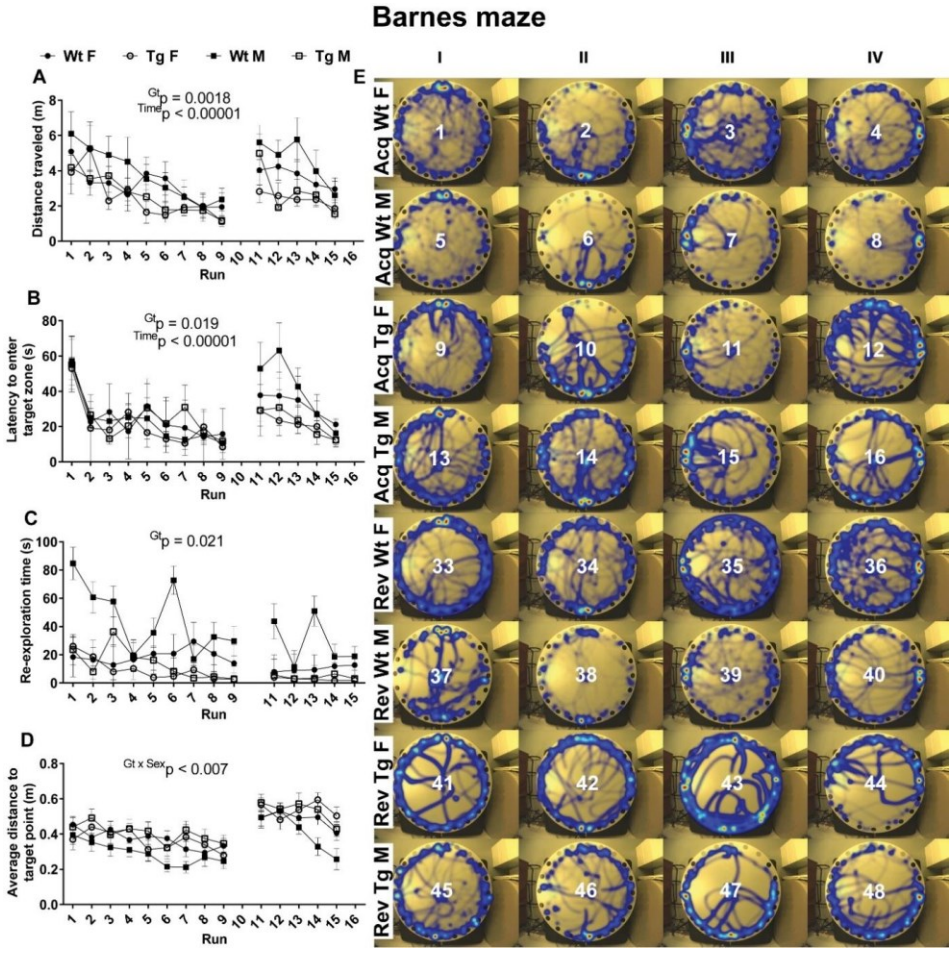


Figure 11. Spatial learning and spatial working memory assessment in the Barnes maze experiment. The behavioural data is presented for 16 trials during five consecutive days; the trials 1–9 for acquisition, the trials 11–15 for reversal learning with a target zone directly opposite to that of the acquisition, and the trials 10 and 16 for probing acquisition and reversal learning, respectively. **(A)** The PPARGC1α Tg mice travelled significantly less ($p = 0.0018$, main Gt effect) and spent less time on the arena (main Gt effect, $p = 0.03$; not shown). On average, all the groups improved their performance during the experiment ($p < 0.00001$, main Time effect). **(B)** The latency to enter the target zone showed the Gt effect ($p = 0.019$). Tg mice were quicker to enter the safe box in the target zone. Entry latency also showed the main Time effect ($p < 0.00001$), indicating a performance improvement in all the groups. **(C)** Re-exploration time (duration on the arena–latency to first entry into the target zone) revealed Gt ($p = 0.021$) effect; Wt mice preferred to continue exploring after identifying the target zone. **(D)** The average distance from the target hole showed the interaction effect of Gt x Sex ($p = 0.007$); Wt male mice kept a lower average distance from the safe box. **(E)** Heatmap visualisation by time spent on the arena revealed different search strategies between the groups (comparison of the four target zones I–IV during acquisition and reversal learning). During the acquisition (Acq), Wt mice, especially the males, preferred a spatial search strategy to enter the target zone (5–8), whereas Tg mice, especially the males, had difficulty in finding the target zone

using a spatial strategy, and therefore relied more on a wall-hugging or serial search strategy (13–16). During the reversal learning (Rev), Wt mice preferred to spend time in the previous target zone and the new target zone, directly opposite to the previous target zone(37–40), whereas other groups relied on the wall-hugging strategy (33–36, 41–44, 45–48). All the female mice preferred the wall-hugging strategy in both stages (1–4, 9–12, 33–36, 41–44); the male mice, however, showed contrasting outcomes; the Wt males used spatial, and Tg males used the wall-hugging strategy, indicating a reduced performance in PPARGC1α Tg male group. A higher percentage of the failed instances further supported the notion of a reduced spatial memory performance to find a safe box altogether during the testing period of 180 seconds in the PPARGC1α Tg male group (failure rate: Wt M = 1.59%, Tg M = 8.44%, Wt F = 2.86%, Tg F = 0.79%). Statistical analyses were done using repeated-measures two-way ANOVA, followed by Tukey's unequal N HSD post hoc test. The data is displayed as mean ± SEM. Abbreviations: Acq–acquisition, Rev–reversal learning.

4.3.4. Increased expression of GABRA2 in the frontal cortex and hippocampus

Anxiogenic behaviour is strongly associated with $GABA_A$ α2 receptor subunit changes. GABARA2 is highly expressed in the frontal cortex, hippocampus and striatum (Vollenweider et al., 2011). These regions also concord with the expression of PPARGC1α (Cowell et al., 2007). qPCR analyses in our study revealed that the expression of GABARA2 was increased in the hippocampus of the PPARGC1α Tg mice. In the frontal cortex, the gene expression variation between individual animals was rather considerable, and the trend did not reach any statistical significance in the PPARGC1α Tg group ($p = 0.058$, $n = 7$; Figure 11A). However, the protein expressions from both areas confirmed α2 subunit increase (Figure 11B). In contrast, the level of a more widely expressed subunit, $GABA_A$ receptor subunit α1, was not altered (Figure 11C). A closer study of hippocampal regions revealed that $GABA_A$ α2 was expressed by neurons, as exemplified by immunopositive cells in the dentate gyrus, CA1 and CA3 subregions of the hippocampus (Vanaveski et al., 2021). Double Staining of $GABA_A$ α2 and gephyrin in the CA1 region of the hippocampus supported an increased clustering of $GABA_A$ receptors in postsynaptic neurons of Tg mice. Analysis of the gephyrin channel more specifically showed a significant increase in the percentage of gephyrin signals colocalised with $GABA_A$ α2 in the stratum radiatum (SR) layer of PPARGC1α Tg mice, perhaps reflecting the upregulated potential of inhibitory neurotransmission (Wt: 16.09 ± 2.973 vs Tg: 29.62 ± 4.367, $p = 0.03$; Vanaveski et al., 2021). GABAergic cells residing predominantly along the border of the SR and stratum lacunosum moleculare (SLM) of the CA1 region are depolarised and excited by serotonin acting through 5-HT2AR (Wyskiel and Andrade, 2016). Parallel in humans, serotonergic innervation is dominated by 5-HT2AR, although brain region-specific patterns apply (Sugden et al., 2009). A basket cell in this region strongly influences hippocampal function and is enriched by the α2 subunit (Booker and Vida, 2018; Malik et al., 2022; Speigel and Hemmings Jr, 2022).

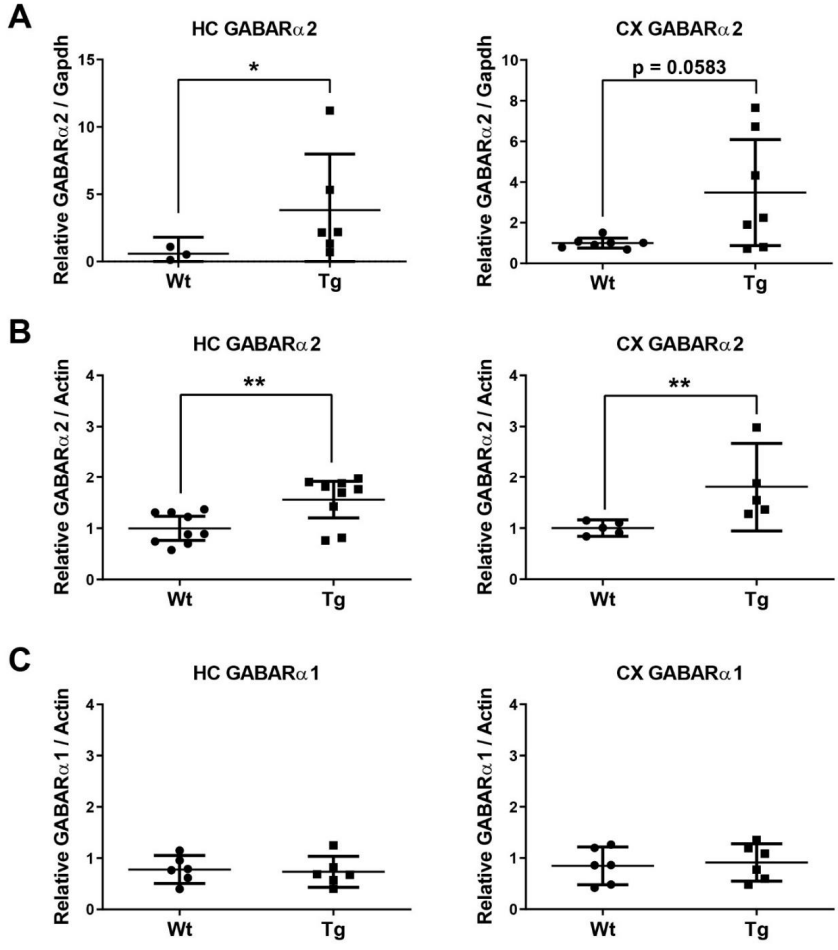


Figure 12. GABA-A receptor α2 subunit expression increases in PPARGC1α transgenic mice. (A) Quantitative PCR was performed using cDNA from the hippocampus (HC) and frontal cortex (CX) of 4-month-old wild-type (Wt) and PPARGC1α transgenic mice (Tg). Quantifications were done using Gapdh expression as control and were analysed by the Student's t-test. The values are presented as means ± SEM, n = 7. Left, HC; GABARa2 mRNA levels were increased in the hippocampus of Tg mice compared to Wt animals. *p < 0.05. Right, CX. In the frontal cortex, the difference was not significant between the groups. p = 0.058. (B) Immunoblottings using lysates from the hippocampus and frontal cortex of 3-month-old Wt and PPARGC1α Tg mice were done using anti-GABAR a2 and anti-b-actin antibodies as control. GABAR a2 is shown at 52 kDa (upper lanes) and b-actin at 42 kDa (lower lanes). Quantification of GABARa2 levels was done using b-actin as control and was analysed by the Student's t-test. The values are in means ± SEM. n = 9 for HC, n = 6 for CX. **p < 0.01 for Tg vs Wt. (C) Representative immunoblots showed GABARa2 at 52 kDa and b-actin as control at 42 kDa. (D) Immunoblottings were done using anti-GABAR a1 antibody and anti-b-actin antibody as control. Left, HC; Right, CX. GABAR a1 levels were quantified using b-actin as a control and were analysed using the Student's t-test. The values are given as means ± SEM. n = 7 for HC, n = 6 for CX. There was no significant difference between the groups. (E) Representative immunoblots showed $GABA_A$ α1 at 52 kDa (upper lane) and b-actin as control at 42 kDa (lower lanes).

4.3.5. Altered GABAergic neurotransmission in the hippocampus

GABAergic transmission changes were mapped by measuring individual cells in hippocampal slices by the patch-clamp method. GABAergic synaptic events were recorded from CA1 pyramidal neurons revealing that the frequency of mIPSCs (Wt: 3.24 ± 0.48 Hz; PPARGC1α Tg: 6.27 ± 0.94 Hz, t = 2.7, df = 13, p = 0.02; Figure 13A left) and sIPSCs (Wt: 5.55 ± 0.98 Hz; Tg: 9.28 ± 1.03 Hz; t = 2.6, df = 14, p = 0.02; Figure 13B left) was higher in the Tg group. The amplitude of mIPSCs (Wt: 20.31 ± 1.97 pA; Tg: 25.62 ± 1.98 pA; t = 1.9, df = 13, p = 0.08; Figure 13A right) and sIPSCs (Wt: 21.31 ± 2.41 pA; Tg: 31.80 ± 4.98 pA; t = 1.9, df = 14, p = 0.08; Figure 13B right) followed a similar trend, but the differences did not reach any statistical significance. These findings demonstrate an enhanced GABAergic neurotransmission in the PPARGC1α Tg mice, reflecting an increased release probability and an enhanced number of GABAergic synapses in the hippocampal neurons. These changes could shift the E/I balance and result in at least partial desynchronisation of local microcircuitry (Connor et al., 2017).

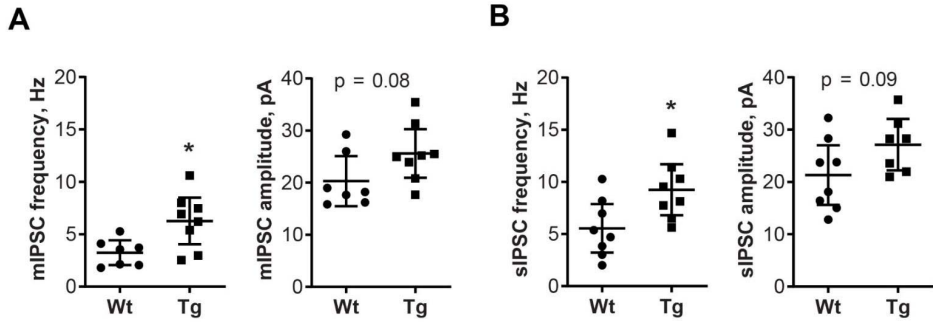


Figure 13. GABA transmission increase in PPARGC1α Tg mice. Electrophysiology was done in hippocampus CA1 neurons using parasagittal sections of 4 Wt and 4 PPARGC1α Tg mice aged 2 months. The records and averaged traces of electrophysiological events are shown. (A) Representative traces of miniature inhibitory postsynaptic currents (mIPSCs) in CA1 pyramidal neurons were higher in PPARGC1α Tg mice. (B) The frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) was higher in PPARGC1α Tg mice than in Wt. Quantification was done using the unpaired Student's t-test. The values are individual measurements per cell shown as mean ± SEM, n = 7–8 (Wt), n = 8 (Tg). *p < 0.05 for Tg vs Wt.

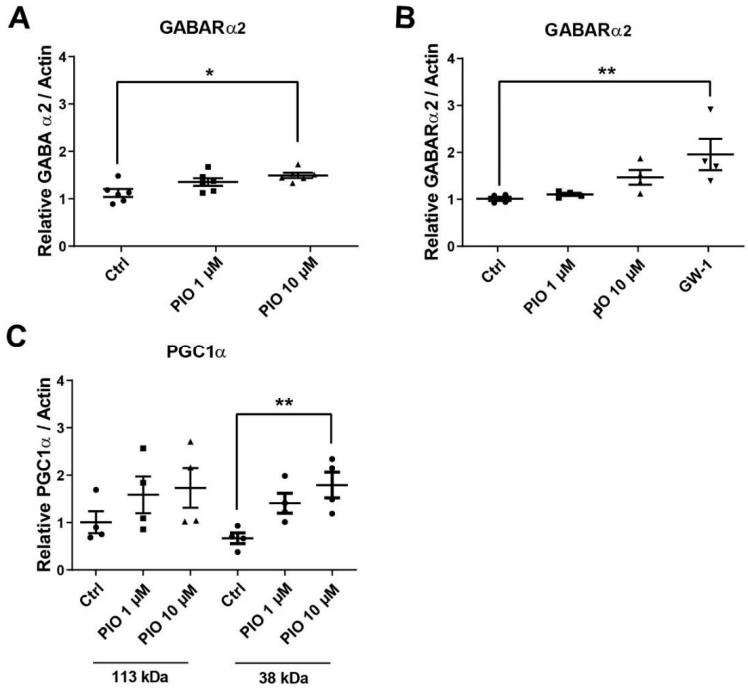


Figure 14. Pioglitazone increases $GABA_A$ receptor α2 and PPARGC1α in primary neurons. (A) Primary neurons were procured from the embryonic E17 rat brain cortex and cultured for 5 days. The cells were then stimulated with 1 or 10 μM pioglitazone (PIO) for 24 h, followed by immunoblotting using anti-GABARa2 or anti-PPARGC1α antibodies and anti-b-actin antibodies as a control. The Student's t-test did quantifications and analysis and ANOVA followed by Dunnett's post hoc test. (B) Neurons were stimulated with 1 or 10 mM PIO or 2 mM PPARg agonist N-(2-benzoyl phenyl)-O-[2-(methyl-2-pyridinyl amino) ethyl]-L-tyrosine hydrate (GW-1) for 2 days followed by immunoblotting. Quantifications were done using b-actin as a control. The analysis was performed by the Student's t-test and ANOVA followed by Dunnett's post hoc test. The values are given in means ± SEM, n = 4. **$p < 0.01$ for GW-1 treatment vs controls. (C) Please note that the two isoforms of PPARGC1α in the neurons are shown here as 113 and 38 kDa bands, of which the latter was significantly increased by 10 mM PIO. The values are presented as means ± SEM, n = 4. *$p < 0.05$ for 10 mM PIO vs controls.

4.3.6. Pioglitazone elevates GABRA2 in cultured neurons

PPARGC1α acts with other nuclear transcription factors, such as PPARγ. Further investigation of the PPARGC1α-PPARγ pathway can shed light on GABARα2 subunit expression changes. The drug pioglitazone, an agonist of PPARγ, was used to induce GABARα2 subunit change in primary cortical neurons of the embryonic rat brain. 10 μM pioglitazone significantly increased the GABARα2 subunit level in the neurons (Figure 14A). The treatment with the PPARγ agonist GW1929 also elevated GABARα2 in the neurons, demonstrating the involvement of PPARγ receptors (Figure 14B). Pioglitazone further specifically elevated the 38 kDa neuronal isoform of PPARGC1α in the neurons (Martínez-Redondo et al., 2015; Figure 14C). Altogether these results show that GABARα2 subunit expression in cortical neurons resulted from PPARGC1α-PPARγ pathway stimulation. However, one must consider the involvement of a complex network of factors up and downstream of PPARGC1A while interpreting these results.

4.3.7. Conclusion

The dysfunction of energy metabolism is frequently associated with mood disorders. Here, we demonstrated a connection between $GABA_A$ α2 subunit alteration and the PPARGC1A-PPARγ pathway. Both up-regulation and down-regulation of PPARGC1A are likely to result in dysfunctional outcomes. The PPARGC1α overexpression led to a dysfunctional phenotype with anxiolytic and depressive-like behaviour. The PPARGC1A interactome was associated with mood disorders and cognitive performance supporting our findings (Abe et al., 2011; McGrory et al., 2018; D'Angelo et al., 2019). In a likely scenario, the upregulation of mitochondrial dynamics led to an altered synaptic activity compensated by the reshuffling of GABAergic subunits. The reshuffling might have led to maladaptive serotonergic innervation and resulted in a depressive phenotype. The weight gain and motivational issues could implicate a mesolimbic reward system. The model offers a new venue for exploring mood-related disorders derived from energetic lability. Drugs like lithium improve mood disorder symptoms by enhancing mitochondrial dynamics. Therefore, other drugs, such as pioglitazone, could offer a similar improvement in mood-related symptoms by introducing stability in energy metabolism. We demonstrated the potential of repurposing drugs, such as pioglitazone, in mood-related disorders, which will likely enhance GABAergic inhibitory neurotransmission through the reshuffling of the α2 subunit. A resulting increase in inhibitory tone altered the inhibitory balance between different subtypes of inhibitory cells and might have had a global impact on forming the phenotype (Smucny et al., 2022).

4.4. Potential of animal models

The human genome encodes approximately 765 adhesion molecules, of which 2/3 are expressed in the brain. IgLONs comprise ~1% of all adhesion molecules expressed in the brain. Functionally, IgLONs are likely to form homo- and heterodimers. Diglons have developmental and maintenance roles in association with their partner molecules. Interestingly, the intra-family conservation hint at their specific role in a narrow context; however, their multimodal participation in different functions and complex expression patterns indicate some role of these molecules at the brain level. Both are probably true; IgLON adhesion molecules are needed to stabilise the brain's GABAergic, glutamatergic, and serotonergic circuitry. However, their alteration or deletion has a faint effect on overall phenotypes, at least in a mouse model, reflecting their redundancy. Human studies reflect a more critical role of IgLONs, perhaps because of a more diverse nature of the human brain. These molecules also participate in diversifying neural circuitry on a granular level. There is some sign that the diversity of neurons increases information denseness and lowers neural firing intensity, perhaps leading to a more capable brain (Padmanabhan and Urban, 2010; Rigotti et al., 2013). On the modelling front, understanding a complex nature of these molecules and their interactions could explain the complexity of the brain and give rise to incremental phenotypes or spectrums in different traits and disorders. The challenge with modelling the impact of such genes is their small effect size and, therefore, the need for large sample sizes, especially for characterising incremental differences between models. Moreover, all ~500 adhesion molecules in CNS must be explored for a complete picture.

Recent clinical research connects DISC1 mutations to various neuropsychiatric disorders (Thomson et al., 2016). Studies in rodents demonstrate that misassembling full-length DISC1 protein alters DA homeostasis, leading to apparent behavioural deficits (Trossbach et al., 2016). Indeed, a naturally occurring mutation of Disc1 in the 129Sv strain strongly affects DA homeostasis and adaptation in a stressful environment (Clapcote and Roder, 2006; Dahoun et al., 2017; Narvik et al., 2018). Disc1 impairment is also associated with parvalbumin-positive interneuron dysfunction (Delevich et al., 2020). These neurons display a high energetic demand and may be metabolically compromised in the event of nutritional deficiency resulting in abrupt behavioural changes. We demonstrated a potential of metabolic modelling by concentrating on metabolic and behavioural profiles. A genetic dimension can be added to this model by comparing transgenic animals as we did with 129Sv. Such a comparative multi-strain approach may enable a detection of general or subpopulation-specific markers. As described here, the 129Sv reflected a general predisposition to psychosis in a vulnerable population. The 129Sv even reflected a bimodal response in the first-episode psychosis. Although not the most precise approach, these models offer a rapid understanding that can be further modelled in specific genetic backgrounds. For example, ASD could be modelled using autism-like social behaviour and metabolic profiles with AAA, NAD+, arginine and glutamate pathway alterations

(Rangel and Gil, 2019). Once alterations in human subjects are known, they can be induced in rodents, allowing them to be used as models for different interventional outcomes. In this way, genetic complexity can be simplified to a certain extent. Metabolomics is currently the most promising approach for robust biomarker discovery.

We concentrated on energetic alterations in mature neurons in one of our models, the PPARGC1α upregulation model. The overexpression of PPARGC1α might not have been well tolerated in our model, resulting in an altered E/I balance. The increase in inhibitory tone is an example of this. Although we could not differentiate the alterations between local or global circuits, we could connect our results to specific brain regions. The decision-making deficit is associated with the frontal cortex, whereas the spatial deficit is related to the hippocampus. Both showed the overexpression of $GABA_A$ subunit α2 in our model. The α2-containing $GABA_A$ receptor upregulation was expected to promote resiliency; however, the opposite was seen (Benham et al., 2021). In our model, PPARGC1α Tg animals displayed anxiety-like behaviour in EPM and LDB as well as progressive avolition in TM, as their exploratory drive was suppressed and worsened in consecutive trials. Note that a lack of $GABA_A$ receptors containing subunit α2 led to an anxiogenic-depressive phenotype with similar indications of avolition (Vollenweider et al., 2011). A lack of food reward might not have changed the results in TM, but carrying out runs with and without food reward could allow for a more specific dissection of the delay in decision-making. For example, the mesolimbic dopamine reward system is highly vulnerable, notably in overexpression models, and the $GABA_A$ subunit α2 is known to be highly expressed in limbic regions (Fritschy and Möhler, 1995). Other options are also possible; for example, serotonin 5-HT2A receptors have a notable role in memory and cognition (Zhang and Stackman Jr, 2015). The intersection of increased GABAergic tone and serotonergic signalling can be expected in our model. The somewhat distorted anxiety phenotype would most likely indicate a role of other $GABA_A$ subunits. For example, the alteration of the α5 subunit is more likely to explain changes in locomotion and working memory (Jacob, 2019). As $GABA_A$ subunits have differential expression patterns in the brain, different subunit alterations lead to mosaicism of the phenotype, perhaps as was seen in our experiment. These different regions convey the dysfunction to other neurotransmitter systems. From a perspective of modelling mental disorders, PPARGC1α Tg animals are likely to reflect a mood instability or lability in affective disorders.

The models described in the current thesis offer an excellent pharmacological testing system; however, more region-specific methods would be needed to map neural changes.

CONCLUDING REMARKS

In our journey to link susceptibility genes to neuropsychiatric endophenotypes, we explored three models emphasising the GABAergic system. One of our fundamental interests was energy metabolism, primarily in the PPARGC1α overexpression and secondly in the metabolic predisposition model. Our interest can be explained by the notion that synapses lack significant energy reserves, forcing synaptic firing in high concordance with energy production. Therefore, disturbances in mitochondrial dynamics will lead to an altered synaptic firing and excitatory/inhibitory balance, inevitably cascading to a higher-order mental dysfunction.

Energy metabolism is tightly controlled by regulatory factors such as PPARGC1α, a master regulator of mitochondrial biogenesis, which adapts cells to stressful stimuli. Our interest was to characterise the effect of PPARGC1α upregulation in a rodent model. The behavioural analyses performed on the PPARGC1α overexpression model revealed an altered functioning and increased anxiety-like behaviour. Deeper exploration revealed an alteration of $GABA_A$ receptor subunit α2 expression in PPARGC1α mutant brains, reflecting a compensatory reshuffle of synaptic components as an attempt to adapt to new circuit dynamics. The alteration in circuit dynamics was supported by electrophysiological recordings, demonstrating a change in the frequency of spontaneous and miniature inhibitory postsynaptic currents in hippocampal neurons. These findings support the homeostatic interplay between mitochondrial energy production and GABAergic inhibitory neurotransmission in sensitive brain areas, such as the hippocampus and frontal cortex. Pharmacological manipulations with pioglitazone, a PPARγ agonist, in cell model confirmed our findings. Pioglitazone may also offer a new path for clinical intervention in mood disorders. Our results connect the PPARγ-PPARGC1α pathway to GABARA2 expression and GABAergic neurotransmission. The outcome of these molecular alterations was an anxiogenic and depressive phenotype, perhaps reflecting a more general mood lability model.

Our second fundamental interest was the neurodevelopmental risk gene DISC1. DISC1 demonstrated a significant linkage with clinical phenotypes such as schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. Among many other functions, DISC1 regulates mitochondrial trafficking to the synaptic environment. In the DISC1 mutant mouse model, we explored the effect of gene truncation on behavioural and metabolic outcomes. Disc1 mutants demonstrated a consistent decrease in parvalbumin immunoreactivity in the frontal cortex. Previous observations indicated the 129Sv strain to display an increased anxiety-like behaviour and disturbances in higher-order executive functioning. We can hypothesise that 129Sv and PPARGC1α models can lead to a similar disturbance of synaptic energy metabolism and result in some predefined pattern of maladaptation. In both models, the primary pathological vulnerability lies in inhibitory neurotransmission related to parvalbumin-positive interneurons, which are fast-firing and highly energy-dependent.

Considering recent metabolic findings in psychosis patients, we tried to model the underlying metabolic state in a standard and predisposed mouse model. The sensitisation by amphetamine in the metabolic predisposition model was paralleled by increased energy consumption and a decline in circulating hexoses. A progressive increase of β-oxidation in the 129Sv strain reflected the augmented energy production demand. Also, our interest was renewed by the bimodal response in the 129Sv chronic treatment group, displaying the weak and the strong responders. Interestingly, the weak responders in the 129Sv chronic group exhibited an inhibited or depressed behaviour, whereas the strong demonstrated a psychotic phenotype. Human studies indicate a similar bimodal response in the first-episode psychosis with depressive and psychotic phenotypes. We hypothesised that the increased energy demand of 129Sv animals would force them to pre-emptive adaptation to fatty acid utilisation; the animals, which show a successful adaptation, will display a psychotic phenotype, while animals that cannot adapt display a depressive phenotype. The depressive phenotype is a default response to unmet challenges. Once the energy metabolism is overburdened, rapid induction of brain-wide depression could be induced to ensure the consciousness and survival of an organism. Besides the energetic predisposition, the 129Sv was also intolerant to oxidative stress, as indicated by strong oxidative potential and the down-regulation of anti-oxidative metabolites. The strong oxidative potential may lead to co-morbidities, such as cardiac dysfunction and metabolic syndrome, widely seen in schizophrenia and mood disorder patients. In translational terms, 129Sv can better reflect the predisposed population. One can propose using Bl6 as a representative strain for a healthy control population and 129Sv as a representation of the predisposed population. Therefore, 129Sv can serve as a model to investigate metabolic, negative, positive, and cognitive symptoms of different disorders. The outcome of this two-strain implementation offers an enhanced venue to explore predisposition in complex mental disorders.

The last in our fundamental interests was neural adhesion molecules; these molecules lay a foundation of neural networks during brain development and maintain the once-formed circuits in adulthood. IgLONs achieve these functions by selectively applying twin promoters and three immunoglobulin domains. The twin promoters maintain once-formed structures during the brain development and a sustained neuroplasticity in adulthood. On the other hand, the immunoglobulin domains of adhesion molecules exchange information between the interaction partners. The three-domain structure leaves these molecules open to relay the information between cells. The information flows through the first immunoglobulin domain between cells and the third domain to cis extra-family interaction partners. The immunoglobulin domains are highly conserved as mutations of these regions will result in alterations of information exchange between partner molecules and cells. Once such anomalies occur, these can further lead to a circuit level and higher-order disruptions of mental activity. Therefore, the importance of the domain is, perhaps, best characterised by the high conservation of these genes throughout evolution. Deviations in laying the early neural pathways might

be some of the first dysfunctions seen in the premorbid phase of neurodevelopmental disorders. However, the redundancy of adhesion molecules hints at the existence of fail-safes. IgLON expression pattern in specific brain areas indicates their potential role in forming executive and sensory-motor as well as emotional and memory-related circuits. Notably, the cumulative expression in the cerebellum, somatosensory and motor cortex would fit early manifestations of motor symptoms in neurodevelopmental disorders. IgLON expression in the brain regions responsible for emotional and social encoding and the behavioural alterations in transgenic models would fit with progressive social deficits in autism spectrum disorder and schizophrenia. One of the regions of significantly high IgLON expression is the frontal cortex; more importantly, IgLON expression changes in the cortex are connected with many mental disorders in humans. IgLONs offer a potential of being early biomarkers for quantifying the dysfunctions during disease manifestation and progression due to their high ongoing expression in brain regions of interest. Promoter-specific manipulation may offer ways to correct some neural dysfunction in neurodevelopmental disorders. In addition, the IgLON deficient strains offer a validity for studying complex polygenic mental disorders.

There are many ways to model dysfunctions inherent to mental disorders. In general, small changes in the genetic level may result in a ripple effect, leading to higher-and-higher order dysfunctions. These ripples are further empowered or diminished by other genetic and environmental factors. In the current thesis, we explored some alterations attributed to the connection between energy metabolism and inhibitory neurotransmission. Based on clinical findings, we also attempted to mimic the metabolic background of psychosis in model strains. Last, we explored adhesion molecules and their potential as biomarkers.

CONCLUSIONS

1. IgLONs displayed high expression levels and complex expression patterns in the mouse brain. The highest expression of *IgLONs* was seen in the anterior parts of the cerebral cortex as well as in the cerebellum. The expression pattern was specific and indicated the developmental pathways during brain formation. The genetically modified mouse strains demonstrated no simple substitution by other family members, highlighting complex inner family dynamics and their potential interactions with outside partners. The Lsamp deficiency influenced the expression of other IgLON family members. The presented results are in good accordance with previous behavioural and pharmacological studies, indicating a prominent role of IgLONs in regulating brain functions.

2. The sensitisation with amphetamine, an indirect dopamine agonist, burdened energy metabolism and was further responsible for accumulating oxidative stress. In both experimental strains, Bl6 and 129Sv, the levels of hexoses were diminished; however, the Bl6 strain revealed a more advantageous metabolic profile. 129Sv showed a general state of metabolic inflexibility accumulating metabolic intermediates of β-oxidation, such as C14, C16, C18:1, and C18:2 acylcarnitines, paralleled by loss of anti-oxidative biogenic amines, such as ADMA, αAAA, and kynurenine. Furthermore, the 129Sv strain showed symptoms mimicking the bimodal response, psychotic and depressive, as seen in first-episode psychosis patients. Therefore, the genetic background of the 129Sv strain offers a potential to model psychosis in predisposed populations.

3. PPARGC1α overexpressing mutants displayed anxiogenic-depressive behavioural phenotype. Later was accompanied by the upregulation of the $GABA_A$ receptor subunit α2 in the frontal cortex and hippocampus and further paralleled by increased inhibitory tone, as reflected by mIPSCs and sIPSCs frequency changes. In the cell culture model, PPARγ agonist pioglitazone induced similar upregulation of $GABA_A$ receptor subunit α2 through the PPARγ-PPARGC1α pathway. The model underlines a linkage of energy metabolism with mood lability phenotype.

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SUMMARY IN ESTONIAN

Neuropsühhiaatriliste häirete loommudelite kvantitatiivne uurimine: metaboolsed, käitumuslikud ja geneetilised profiilid

Vaimsete häirete esinemine põhjustab märkimisväärseid kõrvalekaldeid inimese mõtlemises, emotsioonides ja käitumises. Vaimsed häired on oma olemuselt mitmekesised, nii erineva geneetilise kui ka keskkonnast tingitud soodumusega. Eelnimetatud mitmekesisuse tõttu on neid häireid raske diagnoosida, omavahel eristada ja ravida. Vaimsete häirete keeruline iseloom raskendab ka nende haiguste uurimist ja uute ravimeetodite välja töötamist. Üks suurimaid uurimistöid pidurdav asjaolu on tõhusate haigusmudelite nappus. Haigusmudelite nappust aitaks leevendada vaimse häirega seotud tunnuse kogumite translatoorne uurimine. Täpsemalt on vaja jagada inimese haiguse fenotüüp hoomatavateks ja mõõdetavateks osadeks ehk endofenotüüpideks. Seejärel saab taasluua patsiendi endofenotüüpe mudelloomades ja transleerida ravivõimalusi mudelloomadest patsiendile. Mudelloomade rakendamine kiirendab märkimisväärselt teadustööd ja ravimeetodite väljatöötamist. Oluline on mõista, et teaduspõhine sekkumine haiguse kulgu võimaldab pidurdada haiguse süvenemist ja seeläbi vähenda sotsiaalmajanduslike kulusid kui ka inimkannatusi.

Käesolevas töös on rakendatud kolme erinevat loommudelit uurimaks nende translatoorset potentsiaali. Esmalt vaatlesime neuraalsete adhesioonimolekulide rolli vaimsete häirete kujunemises. Järgnevalt metaboolse profiili rolli esmase psühhoosi mudelis. Kolmandaks energiametabolismi regulatsiooni rolli meeleoluhäiretes.

Esimene uurimissuund kätkeb endas neuraalseid adhesioonimolekule, mis osalevad nii närvivõrkude arengus kui ka hiljem nende närvivõrkude hoolduses. Just neuraalsete adhesioonimolekulide ekspressiooni muutused võivad olla ühed varajasemad markerid, mis peegeldavad vaimse häire kujunemist. Põhinedes IgLONite ekspressioonimustrile näib neil olevat roll täidesaatvate, sensomotoorsete, emotsioonide ja mäluga seotud närvivõrkude moodustamisel. Ka mudelloomade käitumuslik analüüs kinnitab kõrvalekaldeid. Ühtlasi kattub ekspressioonimuster vaimsete häiretega seotud ajuregioonidega. Eriti huvipakkuv on IgLONite domineeriv ekspressioonitase eesmises ajusagaras; regioonis, mis defineerib inimese täidesaatvad võimed.

IgLONid saavutavad oma funktsionaalse mitmekesisuse kaksikpromootori ja kolme immunoglobuliini domeeni selektiivse rakendamisega. Kaksikpromootor tagab ekspressiooni paindlikkuse, võimaldades erinevaid transkriptsioonifaktorite miljöösid. Erinevad miljööd rakenduvad närvivõrkude moodustumisel arengu käigus ja neuroplastilisuse tagamisel täiskasvanueas. Kolmest immunoglobuliini domeenist koosnev struktuur tagab omakorda teabe edastamise rakkude vahel ja samuti raku pinnal. IgLONite immunoglobuliini domeenid on tugevasti konserveerunud, peegeldades nende molekulide olulist rolli kesknärvisüsteemis. Näiteks

on teada Negr1 interaktsioonipartner FGFR2, mis osaleb eesaju ja limbiliste ajustruktuuride arengus. IgLONite keeruka ekspressiooni-, interaktsiooni- ja regulatsioonimustri uurimine aitab meil mõista vaimsete häirete polügeneetilist tausta.

Teine uurimissuund on arengulised riskigeenid, sealhulgas DISC1, mis on näidanud olulist seost erinevate kliiniliste häiretega nagu skisofreenia, skisoafektiivne häire, bipolaarne häire ja depressioon. Disc1 mutantid näitavad parvalbumiini immunoreaktiivsuse järjekindlat vähenemist eesmises ajukoores, peegeldades seeläbi 129Sv hiireliinile omaseid häireid täidesaatvates funktsioonides ja suurenenud ärevuskäitumist. DISC1 reguleerib paljude muude funktsioonide hulgas mitokondrite transporti neuroni kehast sünapsisse.

Võttes arvesse hiljutisi metaboolseid leide esmase psühhoosi patsientidel, käsitlesime metaboolset seisundit normaalses ja eelsoodumusega hiireliinis. Mõlemale, nii eelsoodumuse kui ka eelsoodumuseta, hiireliinile administreeriti psühhoaktiivset ainet–amfetamiini. Sensitiseerumine amfetamiini suhtes põhjustas katseloomadel olulise liikumisaktiivsuse tõusu ja seeläbi energiametabolismi intensiivistumise, millele viitas ringlevate heksooside vähenemine mõlema hiireliini veres. Ka β-oksüdatsiooni järkjärguline suurenemine 129Sv liinis peegeldas täiendavat energiametabolismi profiili muutust ja suurenenud nõudlust energia järele. 129Sv liinil kujunes kroonilise manipulatsiooni tulemusel välja bimodaalne vastus, mida käsitlesime nõrga ja tugeva vastuse rühmana. 129Sv liini nõrga vastuserühma esinejad näitasid pidurdunud või depressiivset käitumismalli, samas kui tugeva rühma esindajad demostreerisid psühhoosile viitavat liikumisaktiivsuse tõusu. Katseloomadel, kes olid võimelised kohanduma rasvhapete metabolismile, esines psühhootiline fenotüüp, samas kui loomadel, kes ei olnud metaboolselt võimelised kohanema, esines depressiivne fenotüüp. Lisaks eelmainitud energeetilisele eelsoodumusele näib 129Sv liin olevat haavatav ka oksüdatiivse stressi suhtes. Viimasele viitab antioksüdatiivsete metaboliitide oluline vähenemine 129Sv liinis. Erinevad inhibitoorsed interneuronid on eriti tundlikud energiametabolismi labiilsuse suhtes. Nende neuronite tüsistused ehk peegeldavadki 129Sv isendite haavatavust ja seetõttu ka liini potentsiaali vaimuhäirete mõistmisel.

Kolmas uurimissuund on seotud just energiametabolismi regulatsiooniga. Mitmed vaimsed häired, näiteks meeleoluhäired, seostuvad energiametabolismi muutustega. Energiametabolismi muutus molekulaarsel tasandil häirib paratamatult kõrgemat järku ajutegevust. Mitokondrite patoloogilised muutused ja sellest lähtuv energiametabolismi labiilsus põhjustab muutusi nii sünaptilises aktiivsuses kui ka eksitatoorse/inhibitatoorse närviülekande tasakaalus. Meie huvi energiametabolismi vastu seletab asjaolu, et sünapsitel puuduvad olulised energiavarud, mistõttu sünaptiline aktiivsus leiab aset ranges kooskõlas lokaalse energia tootmisega. Vaimuhaiguste uuringuis kerkib pidevalt esile just GABAergilise süsteemi haavatavus ajus. GABAergiline pidurdav närviülekanne tagab läbi hierarhilise närvivõrkude koordinatsiooni tähendusliku ajutegevuse. Inhibitoorse süsteemi nõrkus on suur energianõudlus, mis on tingitud intensiivsest rakkudevahelisest kommunikatsioonist. Energiametabolism on rangelt reguleeritud erinevate faktorite, sealhulgas PPARGC1α ehk mitokondriaalse biogeneesi

põhiregulaatori poolt. PPARGC1α kohandab koos teiste oluliste faktoritega raku energiametabolismi kooskõlas erinevate stressoritega.

Uurimustöö käsitleb energiametabolismi häirumisest tingitud pidurdava neurotransmissiooni seost meeleoluhäiretega ja võimaldab mõista, kuidas närvivõrgud kohanduvad energiametabolismi aktiivsusega. PPARGC1α üleekspressiooni mudelis muutub teabe edastamise dünaamika närvirakkude vahel põhjustades seeläbi käitumishäireid. PPARGC1α transgeensed isendid näitasidki ärevamat ja depressiivsemat käitumismalli kui nende metsiktüüpi kaaslased. Täpsemalt esines tõstetud pluss-puuris ja musta-valge kastis ärevuskäitumine. T-hargnevas labürindis esines progresseeruv motivatsiooni ja uudishimu vähenemine–anhedoonia. Lisaks esines Barnesi labürindis ruumilise orienteerumise häire. Edasine molekulaarbioloogiline uurimine näitas $GABA_A$ retseptori alaühiku α2 ekspressiooni muutust PPARGC1α transgeensete loomade ajus. Otsustamisvõime puudulikkuse saab siinjuures siduda eesmise ajukoore ja ruumilised toimingud hipokampuse tegevusega häirumisega. Mõlemad ajuregioonid näitavad meie mudelis $GABA_A$ alaühiku α2 üleekspressiooni. Selline muutus peegeldab sünaptiliste komponentide kompenseerivat ümberkorraldust, peegeldades püüdu kohaneda uue närvivõrgu dünaamikaga. Ka elektrofüsioloogilised mõõtmised toetasid muudatusi närvivõrgu dünaamikas, seda hipokampuse neuronite spontaanse ja miniatuurse inhibeeriva postsünaptilise voolu muutuse tasandil. Farmakoloogiline manipulatsioon neuronite rakukultuuris näitas PPARγ agonisti, pioglitasooni, võimet indutseerida $GABA_A$ retseptori alaühiku α2 ekspressiooni üleekspressioon. Pioglitasoon on kliiniliselt rakendatav II tüüpi diabeedi ravim, kuid võib omada käesoleva uuringu põhjal potentsiaali meeleoluhäirete ravis. Kokkuvõttes seovad meie tulemused PPARGC1α-PPARγ raja meeleolu labiilsuse fenotüübiga.

Käesolevas töös käsitletud mudelid võimaldavad biomarkerite avastamist ja pakuvad potentsiaalseid teid kliiniliseks sekkumiseks. Uurimistöö tulemused rõhutavad eriti GABAergilise neurotransmissiooni haavatavust.

1. IgLONite laialdane avaldumine ja avaldumise muster viitab nende olulisele rollile aju arengus ja hilisemas hoolduses. IgLONite ekspressioonimuster jäljendab aju arengu käigus moodustunud juhteteid. Kõrgeim IgLONite geeniekspressioon esineb frontaalkoores ja väikeajus. Seal avaldub ka IgLonite peamine osalus vaimsete häirete kujunemises. Ka mutantliinide analüüs viitab nende molekulide asendamatusele. Meie tulemused koos varasemate käitumuslike ja farmakoloogiliste uuringutega peegeldavad IgLONite olulist rolli aju talitluses.

2. Maladaptiivseid metaboolseid profiile on seostatud psüühikahäirete ja nendega kaasnevate komorbiidsustega. Amfetamiini poolt indutseeritud psühhoosi mudelis võimendus energiametabolism ja oksüdatiivne stress. Kahe hiireliini võrdlemine tõi esile erinevused nende hiireliinide käitumuslikus sensitiseerumises. Amfetamiini akuutne manustamine oli efektsem Bl6 hiirtel. Samas oli

Bl6 krooniline sensitiseerumine tagasihoidlik, kuid 129Sv hiirtel toimus oluline psühhoosikäitumise võimendumine. 129Sv hiireliin näitas üles üldist metaboolset paindumatust, akumuleerides β-oksüdatsiooni metaboolseid vaheühendeid, samal ajal aga kaotades antioksüdatiivseid biogeenseid amiine. 129Sv hiireliini geneetiline taust pakub potentsiaali, et modelleerida psühhootilist fenotüüpi eelsoodumusega inimpopulatsioonides.

3. PPARGC1α üleekspressiooniga mutantidel esineb ärev-depressiivne fenotüüp. Käitumuslikud muutused esinevad paralleelselt sünaptiliste komponentide ümberkorralduse ja muutunud elektrofüsioloogilise dünaamikaga. Aset leidis $GABA_A$ retseptori alaühiku α2 üleekspressioon, miniatuurse kui ka spontaanse inhibeeriva postsünaptilise potentsiaali voolu tasandil, mis kokkuvõtlikult peegeldab pidurdava fooni tõusu vähemalt eesajus ja hipokampuses. Meie tulemused näitavad tihedat seost mitokondriaalse energia tootmise ja GABAergilise pidurdava närviülekande vahel. Rakukultuuri eksperimentides kutsus pioglitasoon PPARγ-PPARGC1α raja kaudu esile $GABA_A$ retseptori alaühiku α2 samalaadse üleekspressiooni kui loommudelis. PPARGC1α üleekspressiooni mudel pakub võimalusi energeetilise labiilsuse modelleerimiseks meeleoluhäiretes.

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ORIGINAL PUBLICATIONS

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Education

2014–…	Doctorate in Neuroscience, University of Tartu, Estonia
2012–14	University of Tartu, Gene Technology (MSc), "Expression of LSAMP gene in the human brain."
2009–12	University of Tartu, Gene Technology (BSc), "Quantitative analysis of Lsamp promoters–1a and 1b"

Professional work experience

2018–19	Researcher, Quretec OY and University of Helsinki (SZ_TEST), Finland
2017–18	Junior scientist, BSMI, University of Tartu (PER ASPERA), Estonia
2016–18	Project labourer (IUT20-41), BSMI, University of Tartu, Estonia
2013–16	Project labourer (PUT129), BSMI, University of Tartu, Estonia

Professional supervisions

2018	Katt A, University of Tartu, Gene Technology (BSc), "ErbB family receptors and their ligand expression in mouse hippocampus."
2018	Kukkela K, University of Tartu, Gene Technology (BSc), "Expression of Egf family of ligands and ErbB family of receptors in mouse midbrain."
2016	Tamme A, University of Tartu, Gene Technology (MSc), "Egf gene expression in the model of amphetamine-induced psychosis."
2015	Narvik J, University of Tartu, Gene Technology (MSc), "IgLON family gene expression and compensatory mechanisms."

Professional training

3–5.07.2017	ECNP workshop Heidelberg "How to Make Preclinical Research Robust" (travel award)
28.08–02.09.2016	Rodent Models 2016 in Estonia "Behavioural phenotyping of rodent disease models–potential and pitfalls."
24.08–3.09.2015	Laboratory Animal Science I (certificate for animal handling)

Presentations and awards

12–14.06.2019	3rd Nordic Neuroscience Meeting 2019, Helsinki (poster presentation)

19–20.10.2017	The 2nd International Conference in Pharmacology, Riga (poster presentation)
2–5.09.2017	30th ECNP Congress, Paris (poster presentation, seminar award)
4–6.05.2017	European Neuroscience Conference by Doctoral Students meeting, Benidorm
2–6.07.2016	10th FENS Forum of Neuroscience, Copenhagen (poster presentation, travel award)
29–1.07.2016	European Neuroscience Conference by Doctoral Students meeting, Helsingor (oral presentation)
1–4.04.2014	Human evolution in the genomic era: Origins, populations and phenotypes (poster presentation)

Professional organizing

2016, 2018, 2019 – Estonian Doctoral students' science days, organiser

Publications

Vanaveski, T., Molchanova, S., Pham, D. D., Schäfer, A., Pajanoja, C., Narvik, J., Srinivasan, V., Urb, M., Koivisto, M., Vasar, E., Timmusk, T., Minkeviciene, R., Eriksson, O., Lalowski, M., Taira, T., Korhonen, L., Voikar, V., & Lindholm, D. (2021). Pgc-1α signaling increases GABA(A) receptor subunit α2 expression, gabaergic neurotransmission and anxiety-like behavior in mice. Frontiers in Molecular Neuroscience, 14, 588230. https://doi.org/10.3389/fnmol.2021.588230

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Professionaalne juhendamine

2018	Katt A, Tartu Ülikool, Geenitehnoloogia (BSc), "ErbB perekonna retseptorite ja neile seonduvate ligandide ekspressioon hiire hipokampuses"
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2016	Tamme A, Tartu Ülikool, Geenitehnoloogia (MSc), "EGF geeni ekspressioon amfetamiini manustamisel indutseeritud psühhoosi mudelis"
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Professionaalne enesetäiendus

3–5.07.2017	ECNP töötuba Heidelbergis "How to Make Preclinical Research Robust" (reisipreemia)
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Esitlused ja auhinnad

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19–20.10.2017	The 2nd International Conference in Pharmacology, Riia (posterettekanne)

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4–6.05.2017	European Neuroscience Conference by Doctoral Students meeting, Benidorm
2–6.07.2016	10th FENS Forum of Neuroscience, Copenhagen (poster-ettekanne, reisipreemia)
29–1.07.2016	European Neuroscience Conference by Doctoral Students meeting, Helsingor (suuline ettekanne)
1–4.04.2014	Human evolution in the genomic era: Origins, populations and phenotypes (posterettekanne)

Professionaalne korraldus

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Publikatsioonid

Vanaveski, T., Molchanova, S., Pham, D. D., Schäfer, A., Pajanoja, C., Narvik, J., Srinivasan, V., Urb, M., Koivisto, M., Vasar, E., Timmusk, T., Minke-viciene, R., Eriksson, O., Lalowski, M., Taira, T., Korhonen, L., Voikar, V., & Lindholm, D. (2021). Pgc-1α signaling increases GABA(A) receptor sub-unit α2 expression, gabaergic neurotransmission and anxiety-like behavior in mice. Frontiers in Molecular Neuroscience, 14, 588230. https://doi.org/10.3389/fnmol.2021.588230

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Philips, M.-A., Lilleväli, K., Heinla, I., Luuk, H., Hundahl, C. A., Kongi, K., **Vanaveski, T**., Tekko, T., Innos, J., & Vasar, E. (2015). Lsamp is implicated in the regulation of emotional and social behavior by use of alternative promoters in the brain. Brain Structure and Function, 220(3), 1381–1393. https://doi.org/10.1007/s00429-014-0732-x

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