

PROJECT FINAL REPORT - attachments

Grant Agreement number: 602805

Project acronym: AGGRESSOTYPE

Project title: Aggression subtyping for improved insight and treatment innovation in psychiatric disorders

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3.1. Summary of the main results/foreground of Aggressotype

Multi-level multi-species aggression data matrix



		Nos1	Lphn3	Rbfox1	Tph2	Balb/cj
Molecules / Cells		Cortisol levels are unaltered; significant reduction in brain DOPAC levels, DA and 5-HT turnover, and MAO activity in <i>nos1</i> mutants. Higher <i>mao</i> expression in mutants.	Impaired dopaminergic neuron development in <i>lphn3.1</i> morphants. No differences in basal levels of DA or 5-HT in the brain.	RNASeq will be performed at basal conditions and after behavioural tests.	<i>tph2</i> -mutant zebrafish have not been investigated within this consortium.	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in zebrafish.
		Increased DA levels in the striatum and PFC; reduced NA levels in PFC, amygdala, and raphe. Increased MAO expression in FC, reduced in amygdala and raphe in KO.	<i>Sitc6a3</i> expression dysregulated in PFC in <i>Lphn3</i> -KO.	Increased <i>Rbfox1</i> expression in ACC, nucleus accumbens, amygdala, septum, and striatum Balb/cj mice after acute or escalated aggression.	RNA sequencing in the amygdala of <i>Tph2</i> -deficient mice revealed a large number of differentially regulated genes belonging to mRNA processing, Notch, and IL-6 signaling pathways.	AR upregulation and Crh downregulation in ACC in the Balb/cj; no change in AR or Crh mRNA expression in amygdala and insula; <i>Rbfox1</i> upregulation in ACC, nucleus accumbens, septum, and striatum in Balb/cj mice after acute and escalated aggression. Whole genome and bisulphite sequencing in BALB/cj compared to BALB/cByJ mice show genetic variation in a) <i>Acor1c</i> , b) <i>Gm13030</i> , c) <i>Nrip5-ps</i> , d) <i>Mecon</i> , e) <i>Shank2</i> , f) <i>Aspr1a</i> and g) <i>Rbfox1</i> and differentially methylated positions in DNA in (i) <i>Cdk8</i> , (ii) <i>Tmem267</i> , (iii) <i>Jarid2</i> , (iv) <i>Trio</i> and (v) <i>Gm26917</i> .
		The risk allele (short, S) of NOS1-ex1f VNTR was associated with increased NOS1 expression in human post-mortem amygdala but not fore- or hindbrain.	The molecular consequences of variations in the LPHN3 gene have not yet been investigated in humans.	The molecular consequences of variations in the RBFOX1 gene have not yet been investigated in humans.	The molecular consequences of variations in the TPH2 gene have not yet been investigated in humans.	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in humans.
Circuits		Changes in 5-HT signalling from raphe nucleus in <i>nos1</i> mutant zebrafish.	<i>Lphn3.1</i> expressed in DA neurons of posterior tuberculum. Possible homology to A11 DA neurons in mouse.	Whole brain imaging will be done in <i>rbfox1</i> mutants in Barcelona in 2019.	<i>tph2</i> -mutant zebrafish have not been investigated within this consortium.	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in zebrafish.
		Brain imaging has not been performed in <i>Nos1</i> -KO animals.	Brain imaging has not been done in <i>Lphn3</i> -KO mice.	MRI in <i>Rbfox1</i> KO mice in Nijmegen to be performed in 2019 (Q1).	Decrease in FA in MCC and DMS seen in homozygous <i>Tph2</i> KO mice. No change in FA noted in ACC and nucleus accumbens. Aggressive homozygous <i>Tph2</i> KO associated with a decrease in Glx in the ACC and a decrease in N-acetyl-aspartate and phosphoethanolamine in the dorsomedial striatum.	Decreased FA in ACC and DMS; decreased ACC choline, GABA and taurine in 1H-MRS; decreased glutathione in 1H-MRS total brain volume increased in BALB/cj relative to cByJ.
		Healthy subjects with NOS1 ex1f-VNTR LL genotype show increased dlPFC activity during nogo trials and the predicted activation in the IFC during successful inhibition in the stop-signal task, while no significant activation was found in the SS group.	LPHN3 variants in human subjects have not been investigated in brain imaging studies within this consortium.	Risk allele carriers (CC, C/T) showed an increased response of the dorsal anterior cingulate cortex (ACC) during emotion processing, and a reduced response of the left inferior/middle frontal gyrus during inhibitory control compared to T/T carriers.	TPH2 variants in human subjects have not been investigated in brain imaging studies within this consortium.	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in humans.
Behaviour		Reduced aggression, increased anxiety-like behaviour in <i>nos1</i> -mutants	Hyperactivity in 6-day-old <i>lphn3.1</i> morphant larvae; hyperactivity and increased anxiety in adult mutants. Reduction of aggression.	Social interaction, aggressive behaviour will be studied in the <i>rbfox1</i> mutant fish in 2019 (Barcelona).	<i>tph2</i> -mutant zebrafish have not been investigated within this consortium.	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in zebrafish.
		Reduced aggression, hyperactivity, impaired fear conditioning, deficits in social behaviour, compulsive-like behaviour in 5-CSRTT in <i>Nos1</i> -KO.	Reduced aggression, hyperactivity, altered gait, poor object memory, impaired spatial memory, increased sociability but decreased social memory, increased impulsivity in CPT in <i>Lphn3</i> -KO.	Reduced aggression and social behaviour, hyperactivity, impaired sensorimotor gating and cued fear learning, mild inflexibility in visual discrimination task, increased impulsivity in <i>Rbfox1</i> -KO. Anxiety and activity-related measures are similar in control and overexpression mice.	Increased aggression, increased antisocial bite placement, reduced anxiety, no changes in social behaviour or 5CSRTT, mild hyperactivity in homozygous <i>Tph2</i> -KO.	Increased aggression, antisocial bite placement, inattention (5CSRTT omissions), increased anxiety, reduced fear conditioning, reduced social interaction, normal reversal learning associated with reward, impaired punishment learning in Balb/cj vs Balb/cByJ. BALB/cj aggressive, inattentive (CPT) phenotype rescued by methylphenidate.
		Increased aggression in males with the risk genotype of NOS1-ex1f VNTR (SS-allele), especially after stressful life experiences.	LPHN3 variants have been implicated in ADHD.	RBFOX1 has been associated with aggressive traits in humans.	Lower aggression and low anxiety in males homozygous for the TPH2 -703G/T (rs4570625).	BALB/cj vs BALB/cByJ mouse model does not have an equivalent in humans.

Figure1: Aggressotype Data matrix showing the main scientific output of WP1, WP2, WP3, WP4, WP6 and WP10

4.2 Main Dissemination activities of Aggressotype



Figure2: Aggressotype project movie can be found on the project website: <https://www.aggressotype.eu/>



Figure 3: Aggressotype scientists have started a blog called “MiND the gap”. It is the joint scientific blog of several multicenter projects on developmental psychiatry, funded by the European Union: MiND, which is an Integrated Training Network (ITN) meant to educate a new breed of neuroscientists. MiND studies clinical, cellular and molecular underpinnings of ADHD and autism. Aggressotype, which focuses on the neurobiology of different forms of aggression. To do so, we employ large genetic datasets, cell and animal models, and clinical studies.

CoCA (Comorbid conditions of ADHD) investigates the genetic and epidemiological basis of ADHD and its comorbid disorders (mood and anxiety disorders, substance use, obesity). Also we conduct a clinical study using chronobiological interventions, exercise, and mHealth technology.

Furthermore, this blog is bolstered by the German Center of Developmental Psychiatry, located in Frankfurt am Main as collaboration between the Departments of Psychiatry, Child and Adolescent Psychiatry (both in Mainz and Frankfurt), the Departments of Clinical Psychology in Mainz and Frankfurt, the Department of Medical Psychology in Frankfurt and the IDEA center in Frankfurt.

Finally, the IMpACT study group (which works on the genetics of adult ADHD) contributes to this blog along with the ECNP Network on ADHD across the Lifespan. These projects combine a number of excellent scientists from all over Europe and also the US (please see the individual projects for a detailed list), which here will blog and comment on the latest findings in ADHD, ASD and aggression research. Also related topics will be touched upon, especially mood disorders. In doing so, we hope to create a timely and comprehensive knowledge database on developmental psychiatry that keeps you updated on the hottest research in this exciting field!



Figure4: Together with ADHD Europe a short movie has been made. ‘Shine a Light – understanding ADHD (<https://www.youtube.com/watch?v=XmS7jUhb74A>). The movie was released during the ADHD Awareness Month 2018 and was created by Laura Ghirardi, Nicoletta Adamo, Arjan de Brower, and a number of early career researchers from the MiND consortium; it was filmed and edited by the company "4QFilms". The project was supported by generous funds from the EU-Funded projects MiND, Aggressotype, CoCA and Eat2BeNICE.

Aggressotype project logo



Annex B: List of Aggressotype partners with contact names

Partner Nr.	Beneficiary	First Name	Last Name	Email
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