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P.2.13 High reproducibility across sites in a preclinical study through a coordinated behavioural and pharmacological protocol

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In preclinical research, the rate of non-reproducible findings is estimated to be 50-80% in the United States alone. The inability to replicate scientific findings points toward systematic inefficiencies in the way studies are planned, executed, analyzed, and reported. Moreover, the associated cost to irreproducible results includes great monetary losses, as well a negative impact in the drug development pipeline [1]. There are suggestions that by identifying the variables that affect data quality and the level of robustness of findings, an improvement in reproducibility of preclinical studies could be achieved [2,3,4]. Therefore, by means of the European Autism Interventions - A Multicenter Study for Developing New Medications (EU-AIMS) project part of the Innovative Medicines Initiative (IMI) we were able to test the impact that standardization across sites has in view of reproducing an experimental protocol for behavioral evaluation and drug testing using the genetically modified Shank2 KO model across 3 sites. And so, to improve data reproducibility, several factors of the study design were aligned carefully between the three sites involved while some other factors were not, increasing the robustness of the study.

Given the previous phenotypic description of ASD-like behavior [5] rats were placed in a novel environment to evaluate the phenotype in a control condition and under the effect of a pharmacological intervention with the mGluR1 antagonist JNJ162596857, analyzed by a three-way ANOVA. Additionally, a comparison between 2 scoring methods (i.e. automated versus hand-scored behavior) was performed using the same videos and then compared through a four-way ANOVA.

Consistent hyperactive and repetitive behavioral phenotype of Shank2 KO and WT was found across all three sites: Shank2 KO rats show significantly increased walking ($F(1,65) = 94.95$, $p<0.001$) rearing ($F(1,65) = 35.9$, $p<0.001$) and circling behavior ($F(1,65) = 22.69$, $p<0.001$) relative to the WT rats. Moreover, we found a consistent dose-dependent attenuation of motor activity and circling behavior following treatment in both genotypes across study sites: walking $F(3,195) = 125.3$, $p<0.001$, rearing $F(3,195) = 192.6$, $p<0.001$ and rotations $F(3,195) = 12.19$, $p<0.001$. Lastly, at all sites the automated scoring values for walking, rearing, and rotations were higher than the hand-scored ones ($F(1,65) = 112.1$ $P<0.001$, $F(1,65) = 47.8$ $P<0.001$, and $F(1,65) = 52.9$ $P<0.001$, respectively) for both genotypes. However, irrespective of the scoring method, the hyperactive and repetitive circling phenotype of the KOs was reliably detected at all three sites, as well as its dose-dependent suppression by JNJ16259685 treatment.

Following standardization across sites, it was shown that reproducibility of behavioral pharmacological data in rodents can be established. Thorough discussions between the centers prior to and subsequent interactively writing of the study protocol seemed to contribute to the robustness of the study outcome. The selection of the factors that were aligned shown to have an impact on the reproducibility rate, so more attention should be paid to the standardization of protocol between and within laboratories. Furthermore, the consistent mismatch for the different scoring methods across sites revealed the impact of phenotype definition for interpretation of the genotypic and pharmacological findings.

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P.2.14 Characterisation of a new model of frontotemporal dementia for neuroprotective studies with cannabinoids

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Frontotemporal dementia (FTD) is a heterogeneous group of progressive neurodegenerative disorders of early onset which involve a degeneration of the frontal and temporal lobes responsible of the modulation of cognition, personality, social behavior and language [1]. Around 65% of the cases are characterized for the presence of aggregates of