**Delay aversion in rats and marmosets:**
**of impulsivity and risk-proneness in adolescence and in A.D.H.D.**

*Walter Adriani (1), Arianna Manciocco (1,2), Augusto Vitale (1), Giovanni Laviola(1)*

*(1) Section of Behavioural Neuroscience Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Roma, Italy*
*(2) Molecular Design Department, CNR, Rome, Italy*

While impulsive behaviour is characterized by inability to tolerate a delay of gratification, the risk-proneness has been defined as a suboptimal attraction to reward uncertainty. These concepts are useful to model preclinically the symptoms of major neuro-psychiatric disorders, characterized by reduced self-control. In lab rats, we performed two experiments dealing with Serotonin "7" receptor, 5-HT(7), and with Dopamine transporter, DAT. We hypothesized that both proteins could play a key role in ADHD-relevant behavioral symptoms.

*Experiment 1* - Methylphenidate (MPH) administration in adolescent rats was used to produce a long-lasting increment of adult 5-HT(7) expression (mainly in the *nucleus accumbens* i.e. in the ventral striatum). This neural system is functionally related to impulsive behavior, since the administration of a selective 5-HT(7) antagonist, SB-269970, fully counteracted the MPH-reduced impulsive behavior and enhanced impulsivity when administered alone in naive rats. Conversely, the mixed 5HT(1a/7) agonist, 8-OH-DPAT, reduced impulsive behaviour in naive adolescent rats and in SB269970-produced impulsive adults.

*Experiment 2* - We inoculated lentiviral vectors for intra-accumbal modulation of DAT gene expression in four groups of rats: control, constitutive silencing (SIL), regulatable enhancement (DAT+), or both (DAT+SIL). While anxiety was elevated in SIL rats, the DAT+SIL and DAT+ rats (to a lesser extent) displayed a strong preference for large/uncertain over small/certain rewards, which disappeared upon switch-off over DAT-enhancer, consistently reappearing afterwards.

These behavioral-pharmacology and in-vivo genetic experiments do demonstrate clearly in rats that altered DAT function in forebrain is associated with an ADHD-like profile of enhanced gambling-proneness. Agonist modulation over 5-HT(7) might be proposed also for ADHD therapy.

*Callithrix jacchus,* a NW monkey, was tested with a delay-discounting choice task. We identified overlapping subpopulations within independent factors. For the factor termed "strategy", subjects were classified as "flexible" or "non- flexible" based on a progressive decrease (or not) in their preference for Large/Delayed reward with increasing delay. As for "efficiency", subjects were

classified as “progressive” or “regressive” in their capacity (or not) to maximize the pellet gain, as delay increased.

Upon small (< 9s) delays, “non-flexible” subjects showed greater motor impulsivity than “flexible” individuals, which however never developed a clear preference for the Small/Immediate reward, demonstrating lack of impulsivity in this species. With regard to larger (> 9s) delays, “progressive” subjects showed a higher decrease in their preference for Large/Delayed reward than “regressive” subjects, which however did not indicate impulsivity due to the task’s economic features. In conclusion, a profile of initially low motor impulsivity predicts elevated flexibility of choices, also allowing better payoff in terms of pellet gain.