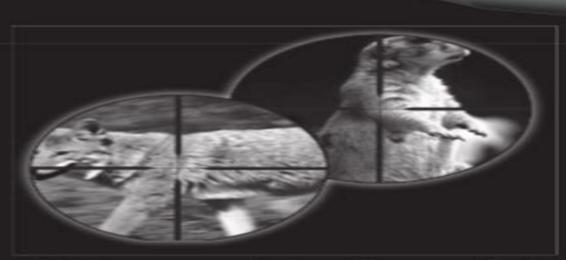


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Compulsive Alcohol Self-Administration in Rats Sanne Toivainen Eloff, 2025-03-12 Alcohol addiction hereafter equated to alcohol dependence according to the WHO ICD 10 classification or moderate to severe alcohol use disorder AUD according to the DSM classification of the American Psychiatric Association is a complex psychiatric illness with an approximate global lifetime prevelance of AUD of 14 1 % and 3 4 % for men and women respectively Only a subset of alcohol users develop addiction suggesting that research to discover novel treatments should consider individual differences in susceptibility for clinically relevant behaviors Continued use of alcohol despite negative consequences commonly referred to as compulsive use is a hallmark of the transition from recreational to addictive use of alcohol Research in animal models has begun to identify mechanisms behind compulsive alcohol taking but the neural basis of individual differences in this behavior remains poorly understood The main aim of this thesis is to investigate the neural mechanisms of individual susceptibility to compulsive alcohol use a key feature of alcohol addiction and the potential role of sex as a biological variable In paper I we characterized susceptibility to developing compulsive alcohol self administration in rats We identified an ensemble of neurons in the central nucleus of the amygdala CeA that promoted compulsive self administration We identified these neurons as PKC neurons one of two major subpopulations in the central nucleus Lastly we investigated the causal role of PKC itself in compulsive self administration by knocking down its expression and found that this reduced compulsive self administration In paper II we studied the role of the GABAB receptor agonist baclofen in compulsive alcohol self administration and on activity of neurons in the centrolateral amygdala CeL This study provides a mechanistic rationale for developing improved alcohol addiction medications that target GABAB receptors and PKC neurons in the CeL In paper III we characterized sex differences in animal models of alcohol addiction including compulsive alcohol self administration We found that female rats consumed equal amount of alcohol as males in unpunished conditions but that they were more resistant to aversive consequences when alcohol rewards were paired with either footshock or quinine adulteration We investigated potential predictors of compulsive self administration in both sexes and found that for male rats compulsivity was predicted by motivation to obtain alcohol whereas for females compulsivity was promoted by stress pain factors Lastly in

paper IV we characterize a novel tool for studying the role of PKC neurons a transgenic rat line that expresses Cre recombinase under the control of the PKC promoter allowing selective access to and control of PKC neurons Collectively these studies highlight PKC expressing neurons in the CeA as critical players in punishment resistant alcohol self administration pointing to a new avenue for developing targeted treatments The findings also emphasize the need for sex specific approaches in both preclinical models and clinical interventions *English Mechanic and World of Science*, 1899

The New Outlook for the Blind, 1975

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