

## Summary

While myriads of studies indicate that chronic or acute alcohol intoxication impairs cognitive performance, whether and how this substance also modulates experience-dependent neuroplasticity remains largely unresolved. Our project addresses this question based on the hypothesis that interactions between alcohol and neuroplasticity might actually account for the deficits in impulse control associated with acute alcohol intoxication.

Humans show a striking capacity to learn and adapt to new tasks with practice. This ability is not only necessary to successfully achieve goal-directed behaviors in ever changing environments but also to maintain a high level of neurocognitive efficiency. Completing new tasks initially requires an important executive scaffolding to maintain instructions in working memory, monitor performance, etc.; this scaffolding not only slows down task completion but is also demanding and energetically costly because it engages largely distributed prefrontal networks. Task automatization, a learning process enabling to dramatically reduce the neurocognitive resources devoted to new tasks while maintaining a high level of performance, allows to rapidly reduce the demand for executive control. Automatizing behavior with practice depends on the brain's capacity to modify its functional organization, and mainly results in a decrease of frontal executive task scaffolding and a sharpening of task-related brain activity.

Based on evidence for the effect of acute alcohol intake on the inhibitory/excitatory balance, and on the role of this neurotransmission balance in experience dependent plasticity, we hypothesize that acute alcohol intake will disrupt task automatization processes. Importantly, we posit that this disruption might partly account for the deleterious psychosocial effects of alcohol intoxication: Since the capacity for executive control is limited, the constant and high executive loading resulting from a systematic lack of automatization leads to a rapid decrease in the capacity to control other aspects of behavior, which might in turn result in impulsivity or aggressiveness.

To test this hypothesis, we plan to use as a model the effect of practice on inhibitory control (IC), a key executive function referring to our ability to suppress unwanted cognitive or motor processes. Compelling evidence supports the deleterious effects of alcohol intake on IC, ensuring clear interactions between alcohol and the functional network underlying IC. Moreover, over the past decade we have established a model of behavioral and neurophysiological IC plasticity allowing us to generate testable predictions on the effects of alcohol on the neurocognitive plastic mechanism of IC. Finally, IC is a paradigmatic example of the effect of task automatization on brain functional organization.

Training-induced improvements in IC are indeed typically associated with the two automatization process described above: a shift of IC from top-down frontal to bottom-up parietal forms of inhibition (i.e. a decrease in executive scaffolding), together with a sharpening of functional responses in task-related ventrolateral prefrontal activity. Critically, since these two functional reorganization patterns likely depend on GABAergic transmission, we hypothesize that acute alcohol intake will disrupt practice-related automatization of IC.

We plan to test this hypothesis using a double-blinded randomized placebo-controlled intervention trial combined with neuroimaging: Healthy participants will practice an IC task after the intake of alcohol vs placebo. Behavioral and electrical neuroimaging analyses of the EEG recorded during the training will allow identifying the interaction between alcohol and the plastic modifications induced by task practice.

We predict that as compared to the placebo group, we predict that the alcohol group will show less automatization as indexed by flatter learning curve, and limited automatization-related functional reorganizations with practice.

The proposed investigation on the effect of acute alcohol intake on experience-dependent task automatization addresses a largely unexplored, thought critical, consequence of alcohol on cognition, which has the potential to identify new mechanistic accounts for the deleterious effects of this substance on executive dysfunctions and impulse control failure. Our project is solid because it: i) is hypothesis-driven and confirmatory; ii) complies with the gold-standard methodology for randomized controlled trials (double-blinded, placebo controlled); iii) combines sophisticated behavioral and functional neuroimaging measures.