

Title: The role of angiotensin II receptors in negative information processing from milliseconds to weeks

Previous epidemiology studies have shown that traumatic events had a reduced negative impact in people who are on antihypertensive drugs acting on the renin-angiotensin system¹. Recently, in an experimental medicine study, we demonstrated that even a single dose of losartan, an angiotensin II receptor antagonist, attenuates negative information processing without having undesirable “cognitive side-effects” such as disruptions in positive information processing, cognitive inflexibility or slower response times². Equally importantly, we showed that losartan did not disrupt positive information processing.

The current DPhil project will seek to investigate the modulatory role of losartan on negative information processing across time spans from milliseconds to weeks. This interdisciplinary project will endeavor to expand on our preliminary findings to investigate how losartan modulates negative information processing in environments in which the information content of negative events (e.g. painful electric stimuli and/or losing money) will be systematically manipulated (a full factorial experimental design). Using an experimental medicine approach (along with new methodologies that we are planning to use, such as computational modelling³ and pupillometry), we will aim to develop a holistic account of how exactly angiotensin II receptor antagonists modulate negative information processing, a known causal element of depressive symptoms. Furthermore, by relying on daily affective ratings up to 4 weeks pre-and-post losartan administration, and analysing this longitudinal data, we will shed light on how angiotensin system works on attenuating emotional response to negative experiences.

If successful, our findings will help identify whether the renin-angiotensin system may be a viable candidate for future drug development, and will have implications for the treatment of resistant major depressive disorder and PTSD⁴.

If you're interested in this project please contact Dr. Erdem Pulcu Erdem.pulcu@psych.ox.ac.uk and/or Dr. Andrea Reinecke andrea.reinecke@psych.ox.ac.uk

References

- 1 Khoury, N. M. *et al.* The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. *Journal of Clinical Psychiatry* **73**, 849 (2012).
- 2 Pulcu, E. *et al.* The Effects of the Angiotensin II Receptor Antagonist Losartan on Appetitive Versus Aversive Learning: A Randomized Controlled Trial. *Biological psychiatry* (2019).
- 3 Pulcu, E. A nonlinear relationship between prediction errors and learning rates in human reinforcement learning. *bioRxiv*, 751222 (2019).
- 4 Shkreli, L. *et al.* Angiotensin involvement in trauma processing—exploring candidate neurocognitive mechanisms of preventing post-traumatic stress symptoms. *Neuropsychopharmacology* **45**, 507-514 (2020).