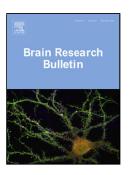
## Accepted Manuscript

Title: Behavioural inflexibility in a comorbid rat model of striatal ischemic injury and mutant hAPP overexpression

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PII:	S0166-4328(17)30488-6
DOI:	http://dx.doi.org/doi:10.1016/j.bbr.2017.07.006
Reference:	BBR 10978
To appear in:	Behavioural Brain Research
Received date:	20-3-2017
Revised date:	22-6-2017
Accepted date:	6-7-2017

Please cite this article as: Levit Alexander, Regis Aaron M, Garabon Jessica R, Oh Seung-Hun, Desai Sagar, Rajakumar Nagalingam, Hachinski Vladimir, Agca Yuksel, Agca Cansu, Whitehead Shawn N, Allman Brian L.Behavioural inflexibility in a comorbid rat model of striatal ischemic injury and mutant hAPP overexpression.*Behavioural Brain Research* http://dx.doi.org/10.1016/j.bbr.2017.07.006

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## ACCEPTED MANUSCRIPT

## Behavioural inflexibility in a comorbid rat model of striatal ischemic injury and mutant hAPP overexpression

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## Abstract (Max 250 words)

Alzheimer disease (AD) and stroke coexist and interact; yet how they interact is not sufficiently understood. Both AD and basal ganglia stroke can impair behavioural flexibility, which can be reliably modeled in rats using an established operant based set-shifting test. Transgenic Fischer 344-APP21 rats (TgF344) overexpress pathogenic human amyloid precursor protein (hAPP) but do not spontaneously develop overt pathology, hence TgF344 rats can be used to model the effect of vascular injury in the prodromal stages of Alzheimer disease. We demonstrate that the injection of endothelin-1 (ET1) into the dorsal striatum of TgF344 rats (Tg-ET1) produced an exacerbation of behavioural inflexibility with a behavioural phenotype that was distinct from saline-injected wildtype & TgF344 rats as well as ET1-injected wildtype rats (Wt-ET1). In addition to profiling the types of errors made, interpolative modeling using logistic exposure-response regression provided an informative analysis of the timing and efficiency of behavioural flexibility. During set-shifting, Tg-ET1 committed fewer perseverative errors than Wt-ET1. However, Tg-ET1 committed significantly more regressive errors and had a less efficient

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