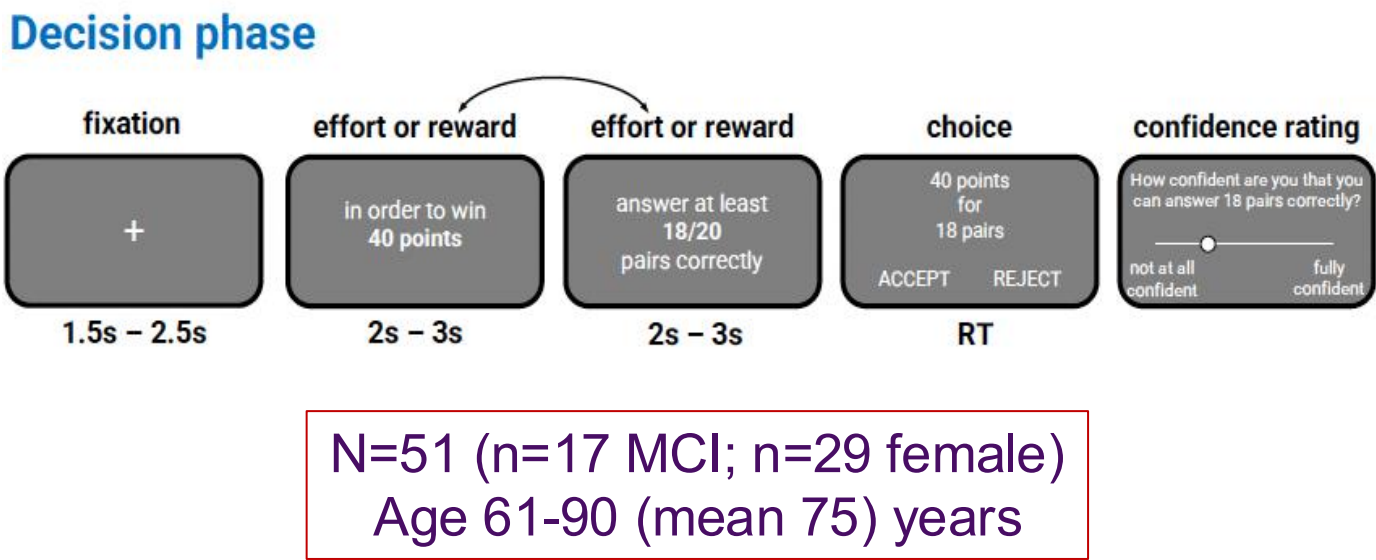
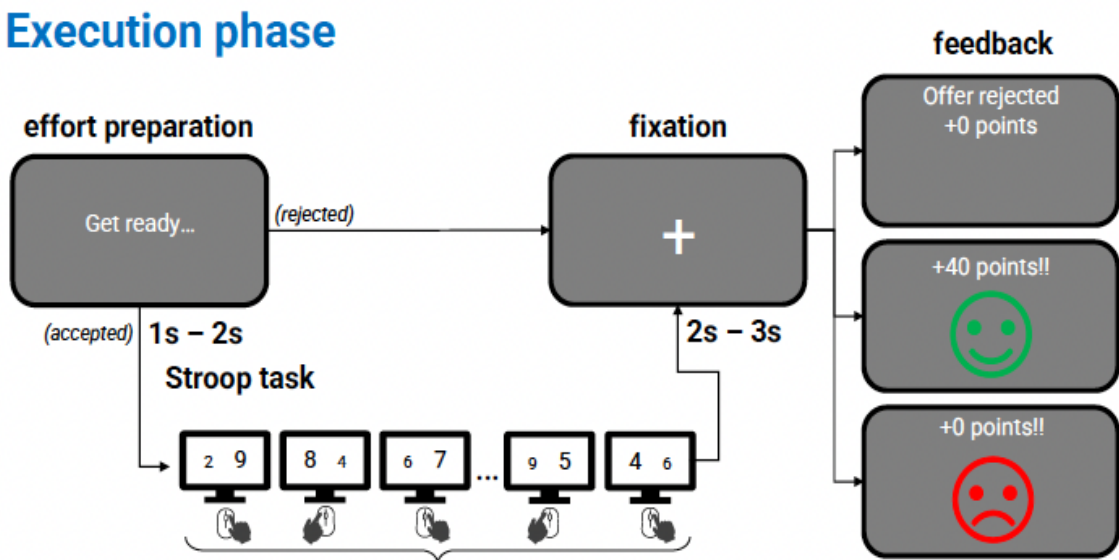
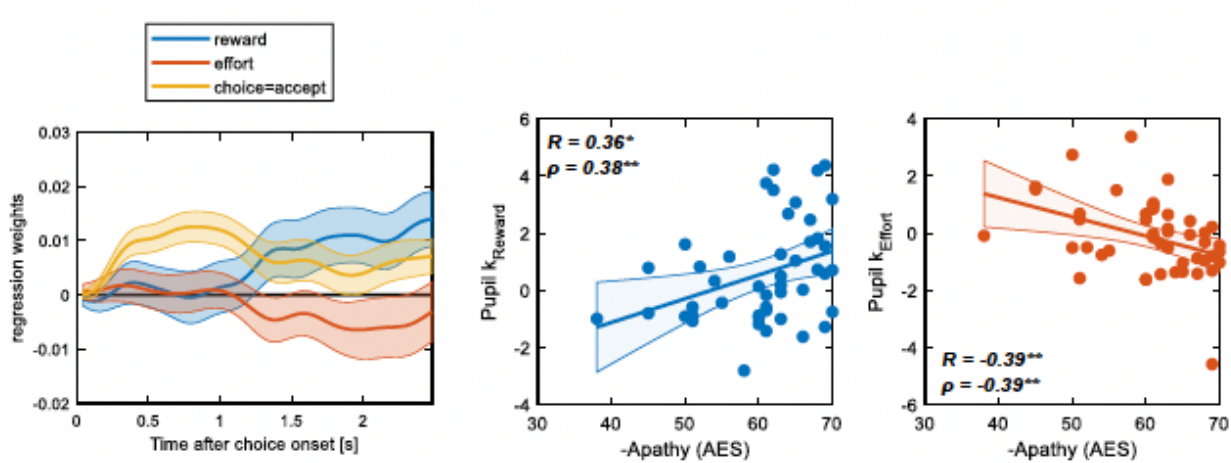
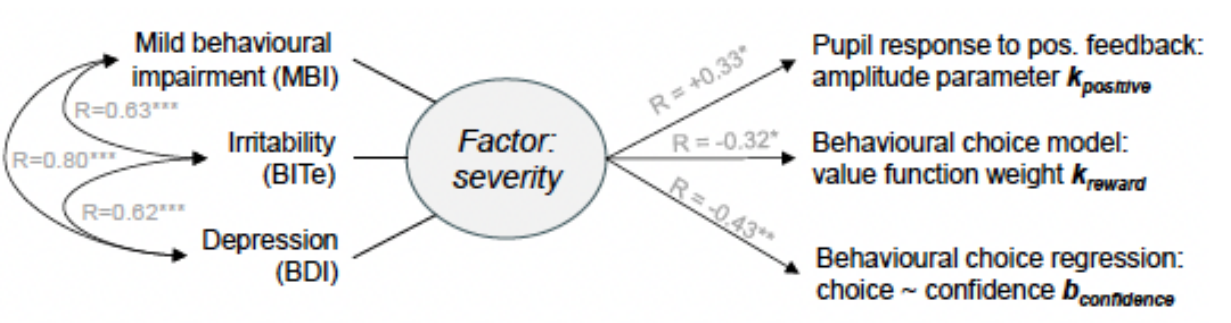
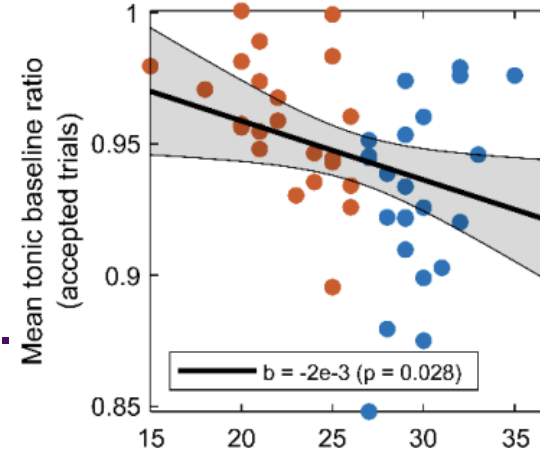


Computational and physiological markers of neuropsychiatric symptom vulnerability relevant to early Alzheimer’s disease

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Neuropsychiatric symptom vulnerability was associated with altered reward-, effort-, and feedback-related behavioural and pupillary responses, consistent with differences in LC-NA system-related processing. Baseline pupil measures were associated with cognitive impairment rather than NPS, suggesting distinct tonic and phasic LC-NA-related markers of cognitive and behavioural change relevant to early AD.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
Neuropsychiatric symptoms (NPS) are common in early Alzheimer’s disease (AD) and are associated with faster disease progression and poorer quality of life, but they are often under-recognised. The locus coeruleus-noradrenaline (LC-NA) system, which is involved in arousal, motivation, reward processing, and cognitive effort, is affected early in AD. Aim: To determine whether pupillary and behavioural markers of LC-NA function during effort, reward, and feedback processing are associated with NPS vulnerability in older adults with intact or mildly impaired cognition.	Decision phase  Execution phase  Participants completed a numerical Stroop task embedded within an effort-reward decision paradigm. On each trial, participants chose whether to accept or reject an offer requiring a specified level of cognitive effort in exchange for reward. Task difficulty was individually calibrated to equate performance across participants. Continuous pupil diameter was recorded throughout. Baseline pupil activity was measured during a 1.5-second pre-trial period. Mean pupil diameter across the entire trial was subsequently calculated, and a baseline-to-full-trial ratio was computed to quantify baseline pupil activity relative to task-evoked pupil responses. NPS vulnerability was assessed using validated questionnaires for apathy, depression, anhedonia, irritability, neuroticism, and mild behavioural impairment (MBI). Cognition was measured using the modified Telephone Interview for Cognitive Status (TICS-m). Analysis: Computational modelling was used to estimate reward and effort sensitivity. Behavioural and pupillary measures were related to NPS and cognition scores. Participants showed robust Stroop interference. Cognitive impairment was associated with slower responses but not reduced task accuracy.	Apathy was associated with: - Lower reward-related pupil responses during decision-making - Greater pupil response to effort demands  Higher depression, irritability and MBI were associated with: - Reduced influence of reward and confidence on decisions - Greater pupil dilation following positive feedback  Higher baseline pupil activity was associated with greater cognitive impairment but not NPS. 	• Altered pupillary and behavioural responses to reward, effort, and feedback were associated with greater NPS vulnerability. • Findings are consistent with differences in LC-NA-related motivational and adaptive processing. • Baseline pupil activity was linked to cognitive impairment but not NPS, suggesting that task-evoked responses may be more sensitive to NPS-related differences. • Future work is needed incorporating AD biomarkers and longitudinal follow up. <i>This project is funded by The Computational Psychiatry Prize of University College London, obtained by the authors in 2024.</i>  ALZHEIMER'S ASSOCIATION AAIC 26