

Ketamine-induced psychosis:

Ketamine, Agency and schizophrenia

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Bernard Wolfe Health
Neuroscience Fund



Early psychotic illness AND ketamine

- The world feels odd
 - Perceptions change
 - Strange things begin to feel important
 - Things seem to relate to each other in new and usual ways

From prediction error to psychosis: ketamine as a pharmacological model of delusions

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Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia

Paul C. Fletcher and Chris D. Frith^{†§}*

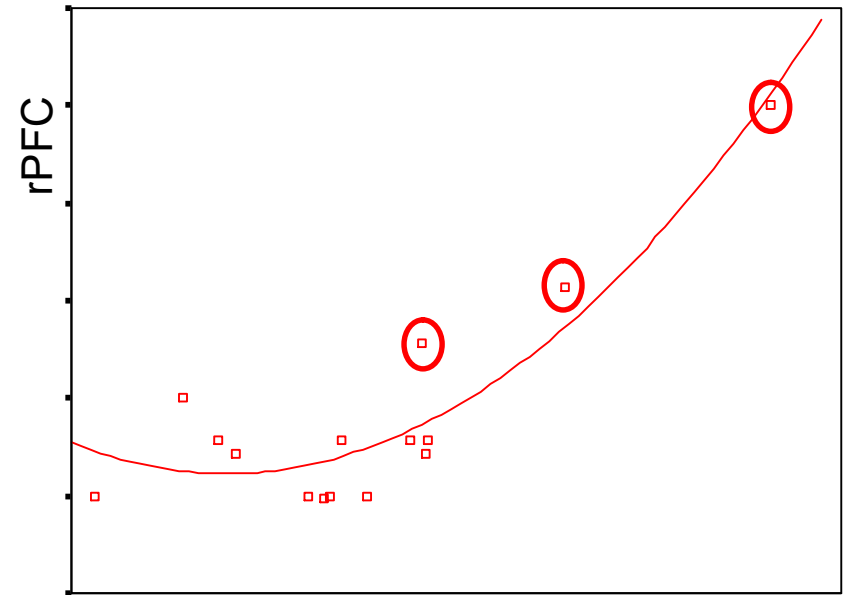
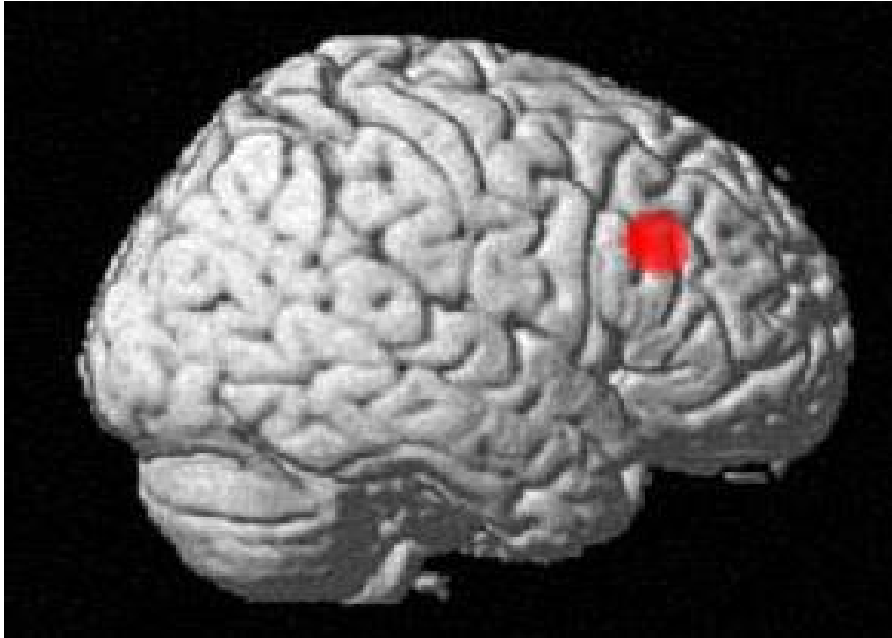
Fletcher & Frith *Nature Rev Neurosci*, 2009

Frontal Responses During Learning Predict Vulnerability to the Psychotogenic Effects of Ketamine

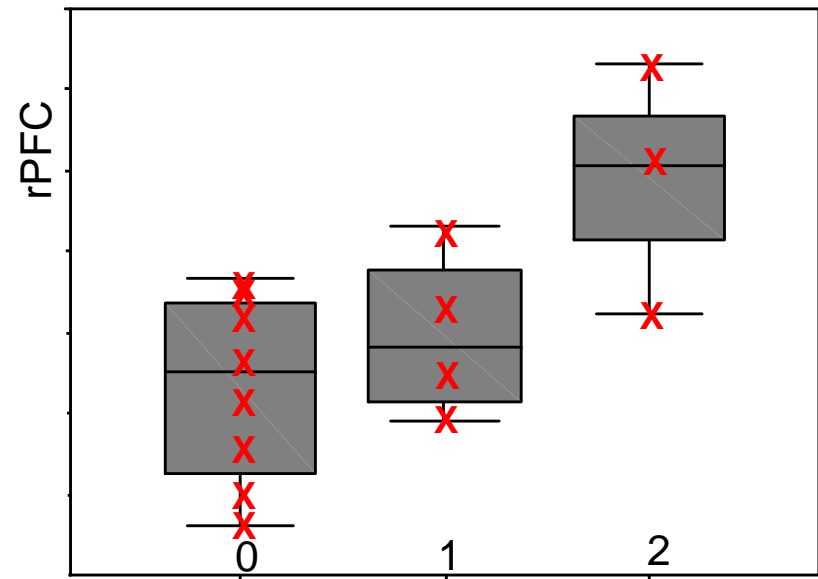
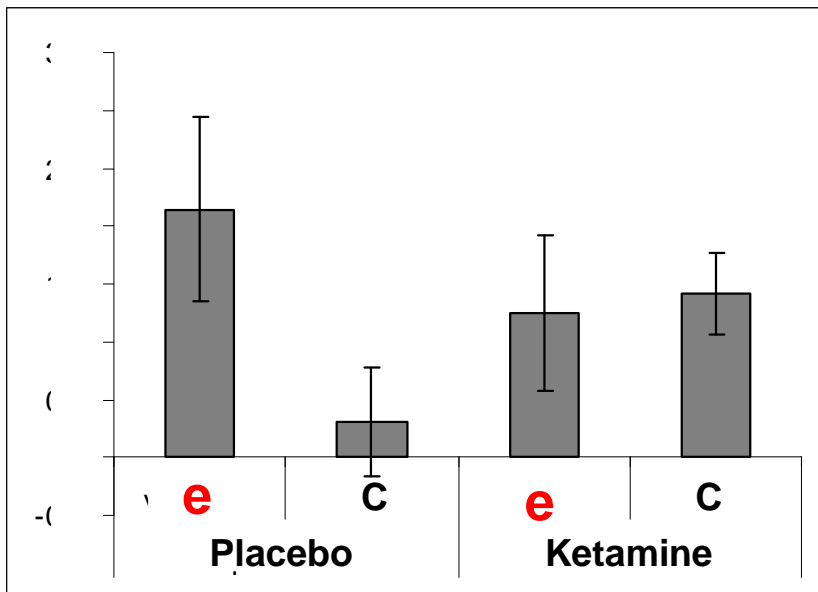
Linking Cognition, Brain Activity, and Psychosis

Philip R. Corlett, BA; Garry D. Honey, PhD; Michael R. F. Aitken, PhD; Anthony Dickinson, PhD, FRS;
David R. Shanks, PhD; Anthony R. Absalom, MB, ChB, MD, FRCA; Michael Lee, MB, BS, FRCA;
Edith Pomarol-Clotet, PhD, MRCPsych; Graham K. Murray, MRCPsych; Peter J. McKenna, PhD, MRCPsych;
Trevor W. Robbins, PhD, FRS; Edward T. Bullmore, PhD, MRCPsych; Paul C. Fletcher, PhD, MRCPsych

1. Perceptual disturbance under ketamine correlates with referential ideation
2. Ketamine attenuates neuronal signal for prediction error-dependent learning
3. Baseline measures in prediction error sensitivity predict vulnerability to changed perception and changed beliefs under ketamine



CADSS – Environmental perception



PSE Ideas of reference

Behavioral/Systems/Cognitive

Individual Differences in Psychotic Effects of Ketamine Are Predicted by Brain Function Measured under Placebo

Garry D. Honey,¹ Philip R. Corlett,¹ Anthony R. Absalom,² Michael Lee,² Edith Pomarol-Clotet,¹ Graham K. Murray,¹ Peter J. McKenna,¹ Edward T. Bullmore,¹ David K. Menon,² and Paul C. Fletcher¹

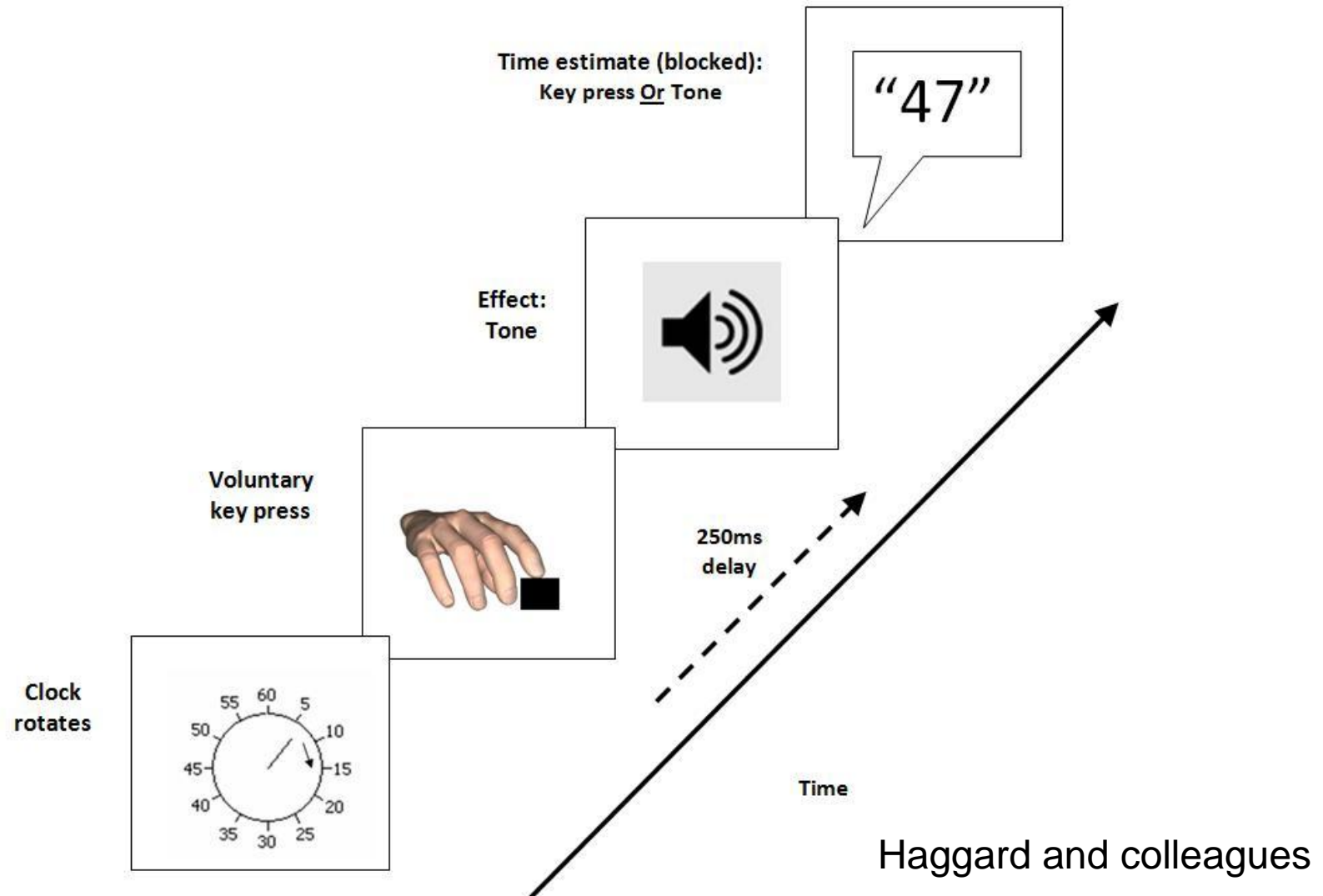
¹Brain Mapping Unit and Behavioural and Clinical Neurosciences Institute, Department of Psychiatry, University of Cambridge, School of Clinical Medicine, and ²Department of Anaesthesiology, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom

Ketamine, schizophrenia and the experience of agency: preliminary data

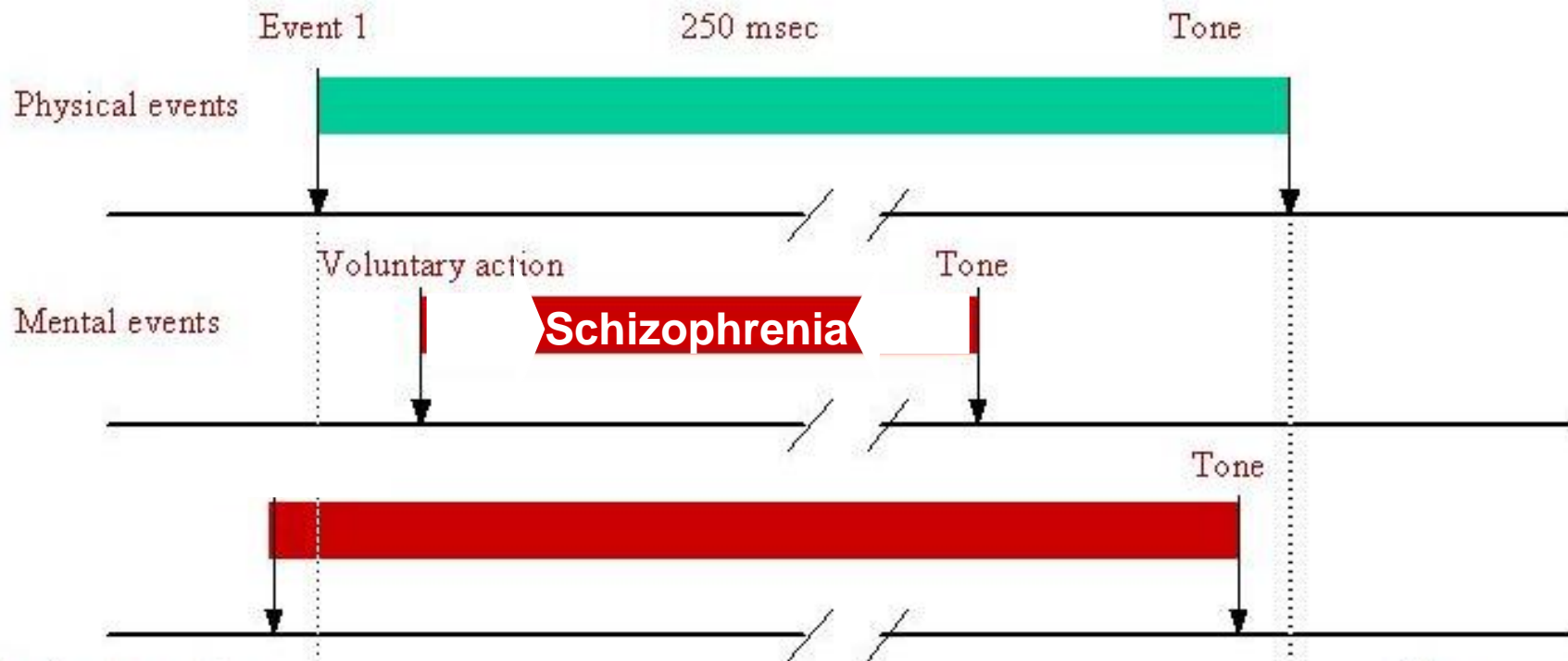
Two principles relating to experience of voluntary action...

1. When our willed action has an external consequence, the temporal experience of the interval between the action and its consequence is diminished – *binding*
2. When we act, we *predict* and *cancel* the sensory consequence of that action

Temporal binding

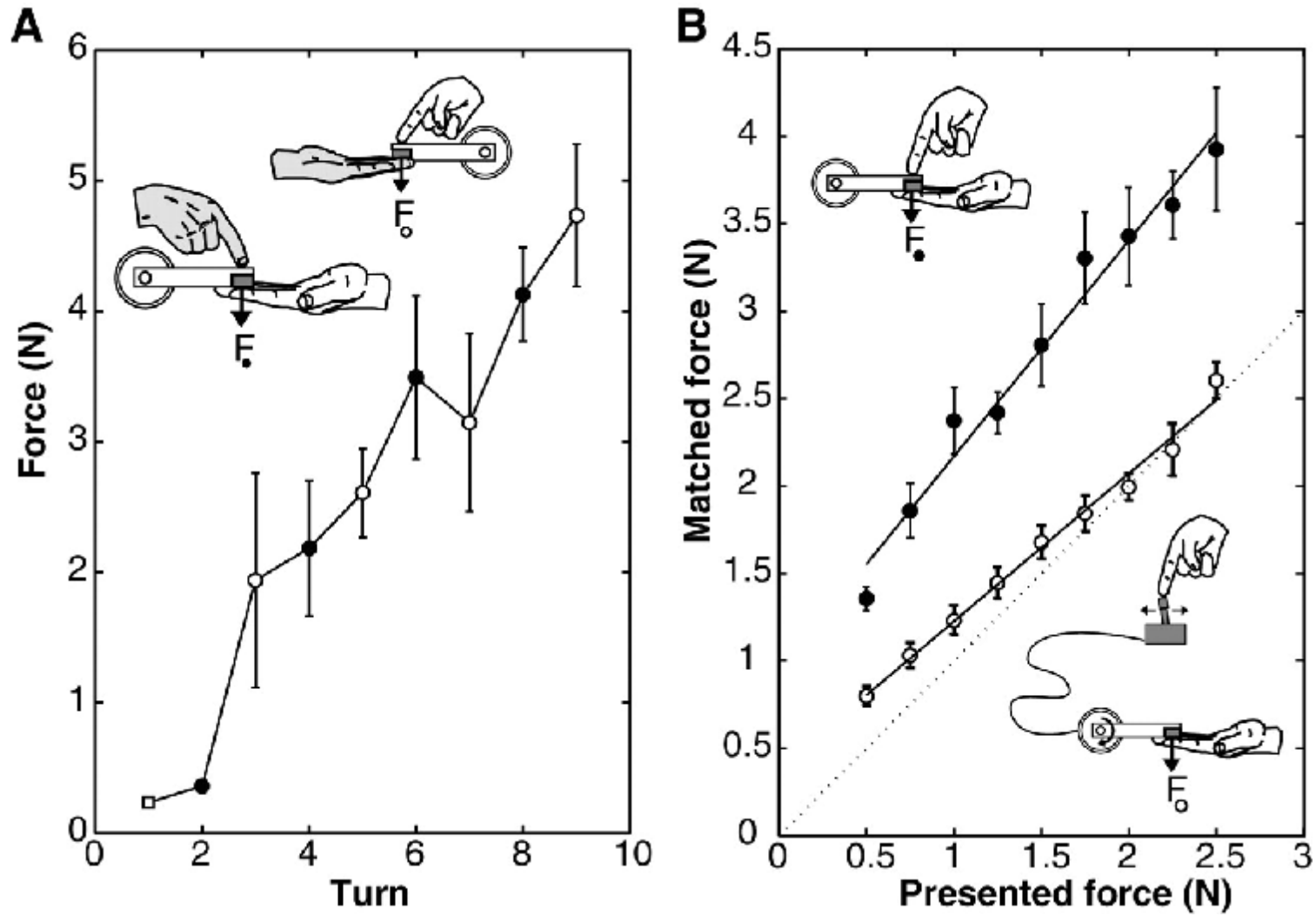


Haggard et al 2002 – results (2)

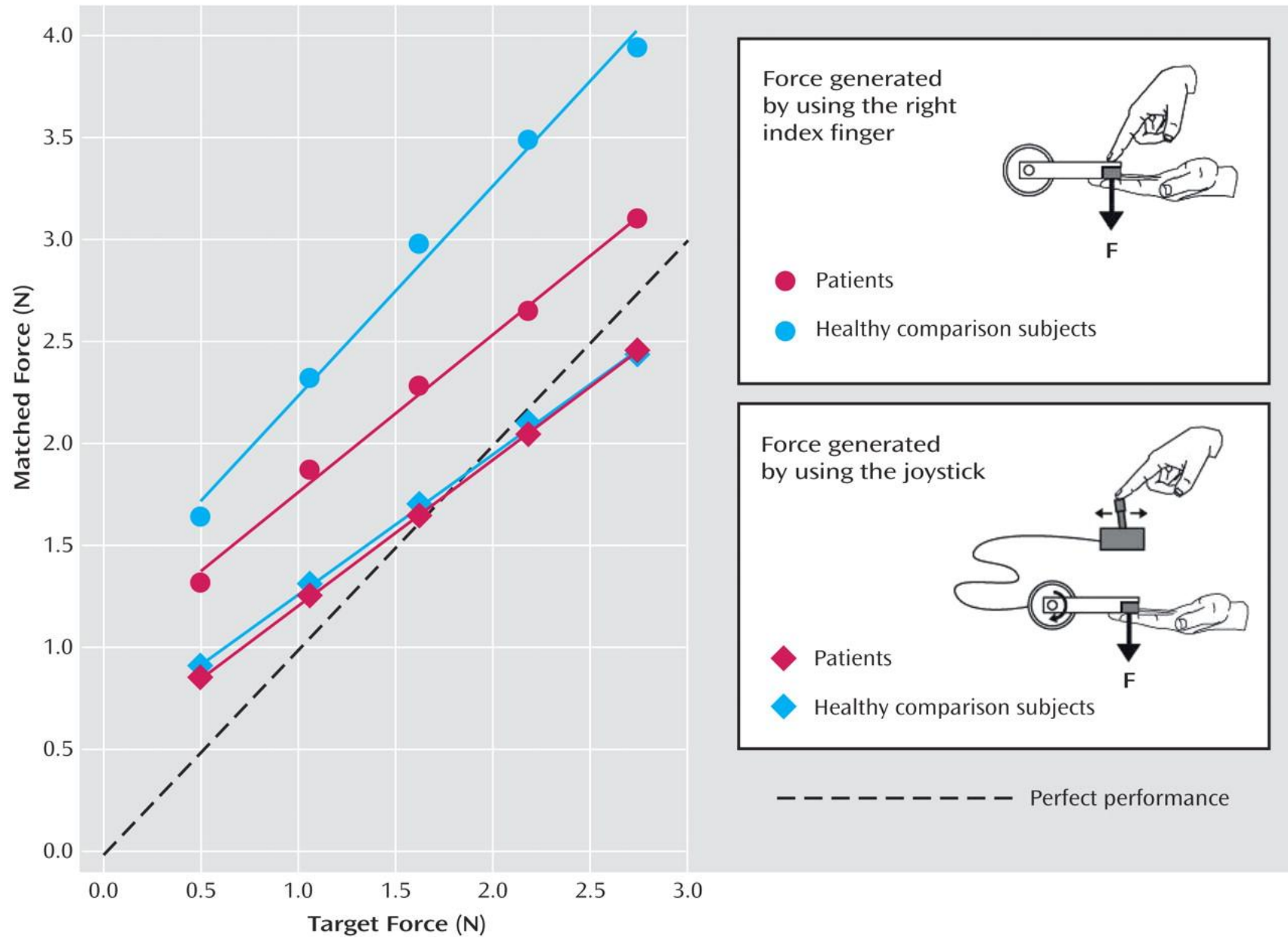


C. Frith fecit

Prediction and Cancellation



Shergill et al, Science, 2003



Shergill et al, Am J Psych, 2005

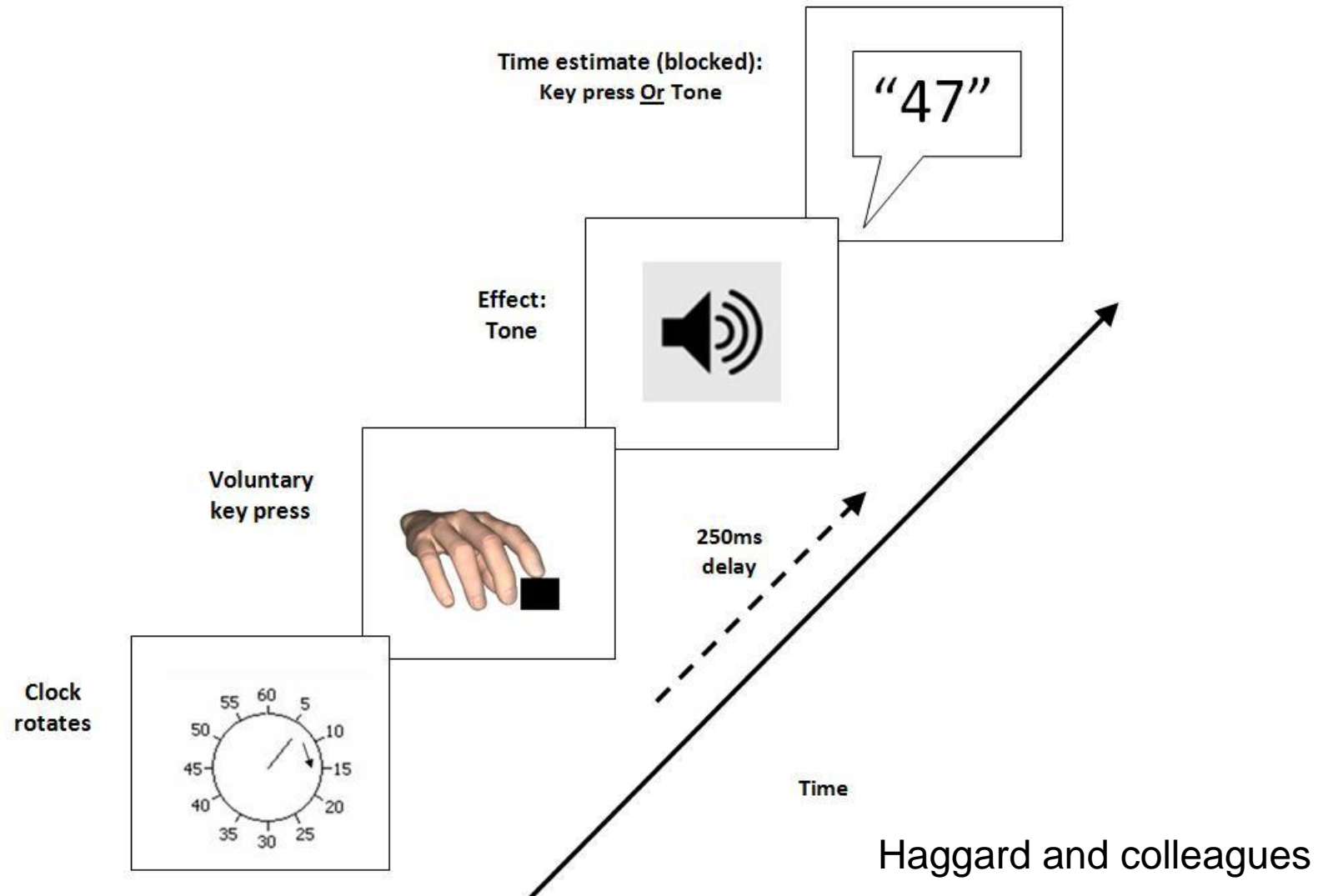
Two principles relating to experience of voluntary action...

1. When our willed action has an external consequence, the temporal experience of the interval between the action and its consequence is diminished – binding
 1. Specific to voluntary action
 2. Predictive and Postdictive
2. When we act, we predict and cancel the sensory consequence of that action
 1. Specific to self-generated actions
 2. Predictive

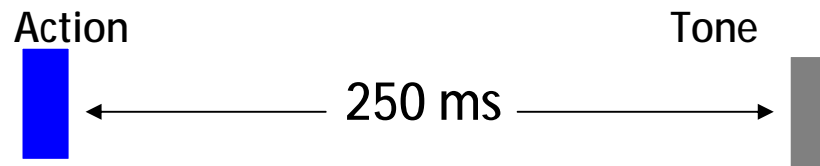
Force-matching and Action-outcome binding under ketamine

- 15 healthy volunteers
- Target controlled Infusion over 2 hour period
 - Target dose 100ng/ml plasma – **Action-outcome binding task**
 - Target dose 200ng/ml plasma – **Force-matching task**

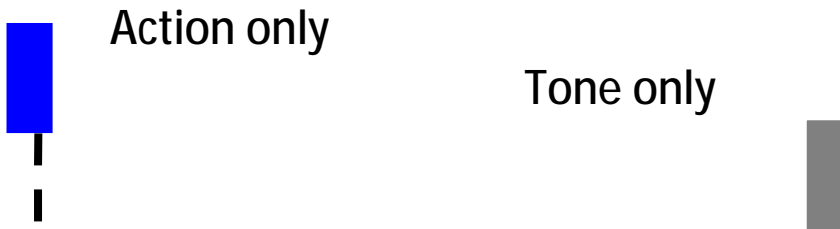
Temporal binding



A. Physical events



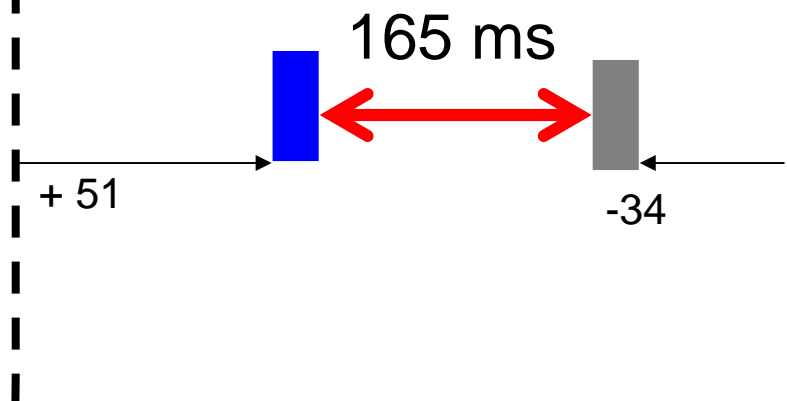
B. Baseline judgements



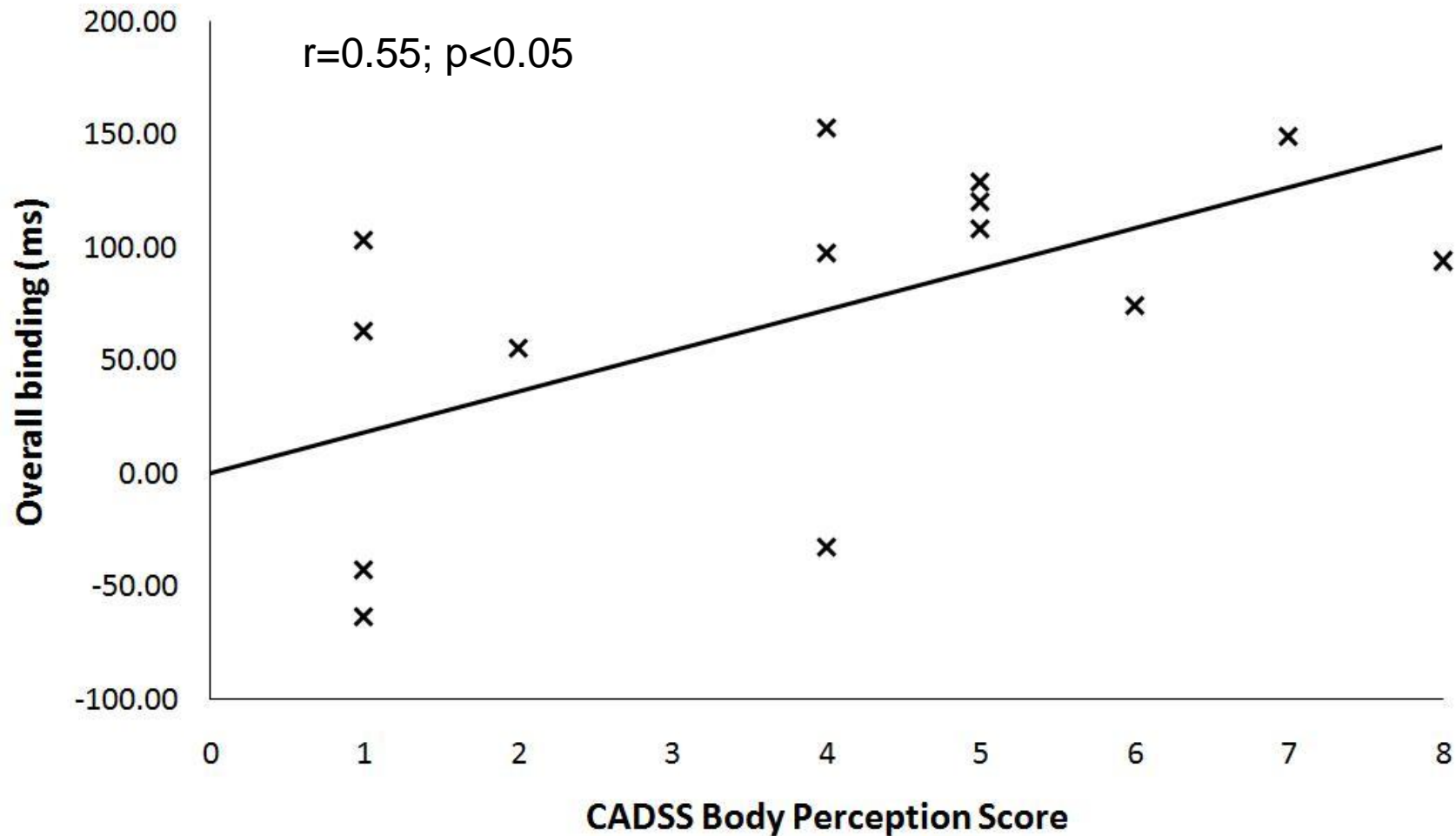
C. Intentional binding OFF Ketamine



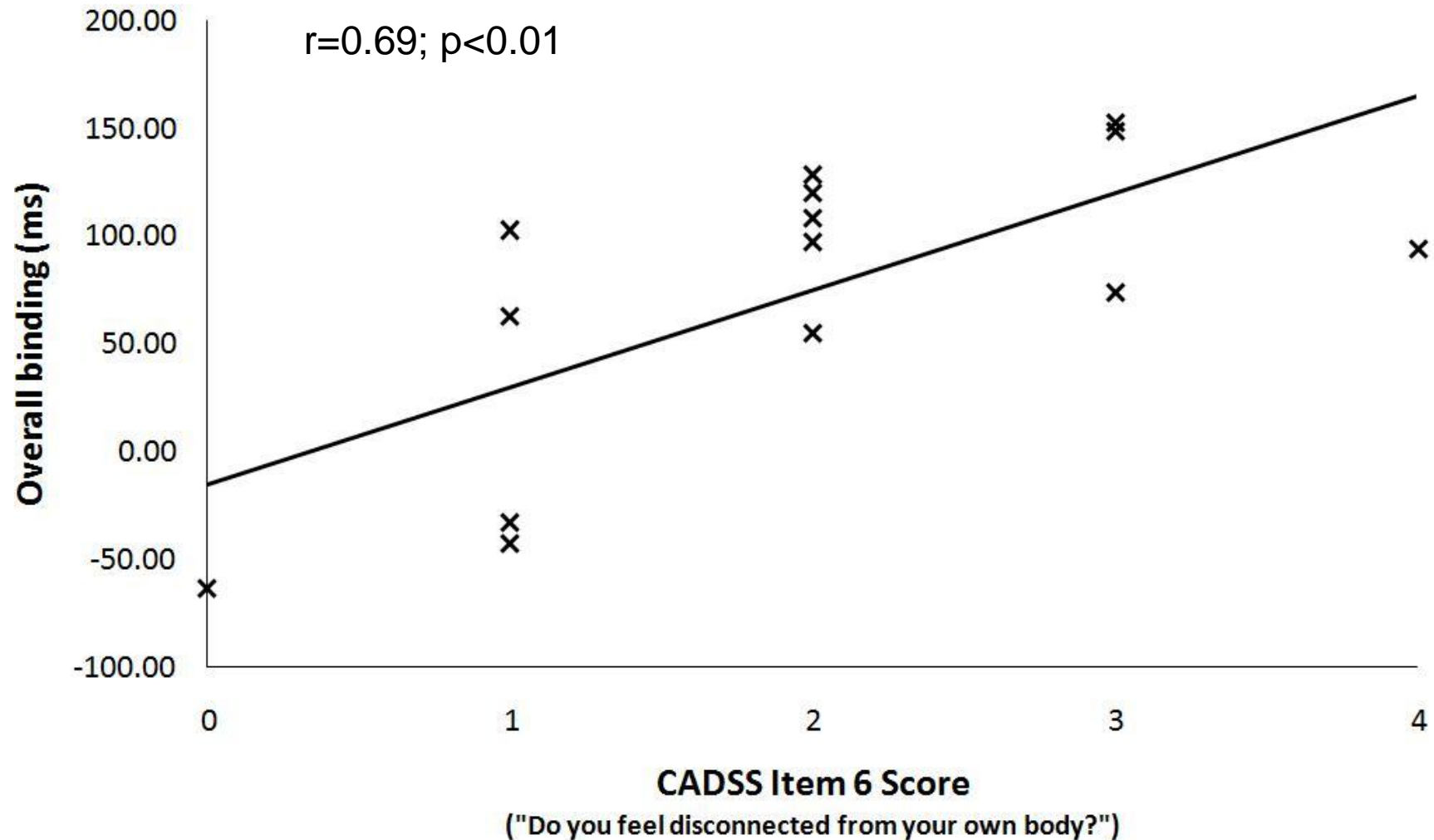
D. Intentional binding ON Ketamine



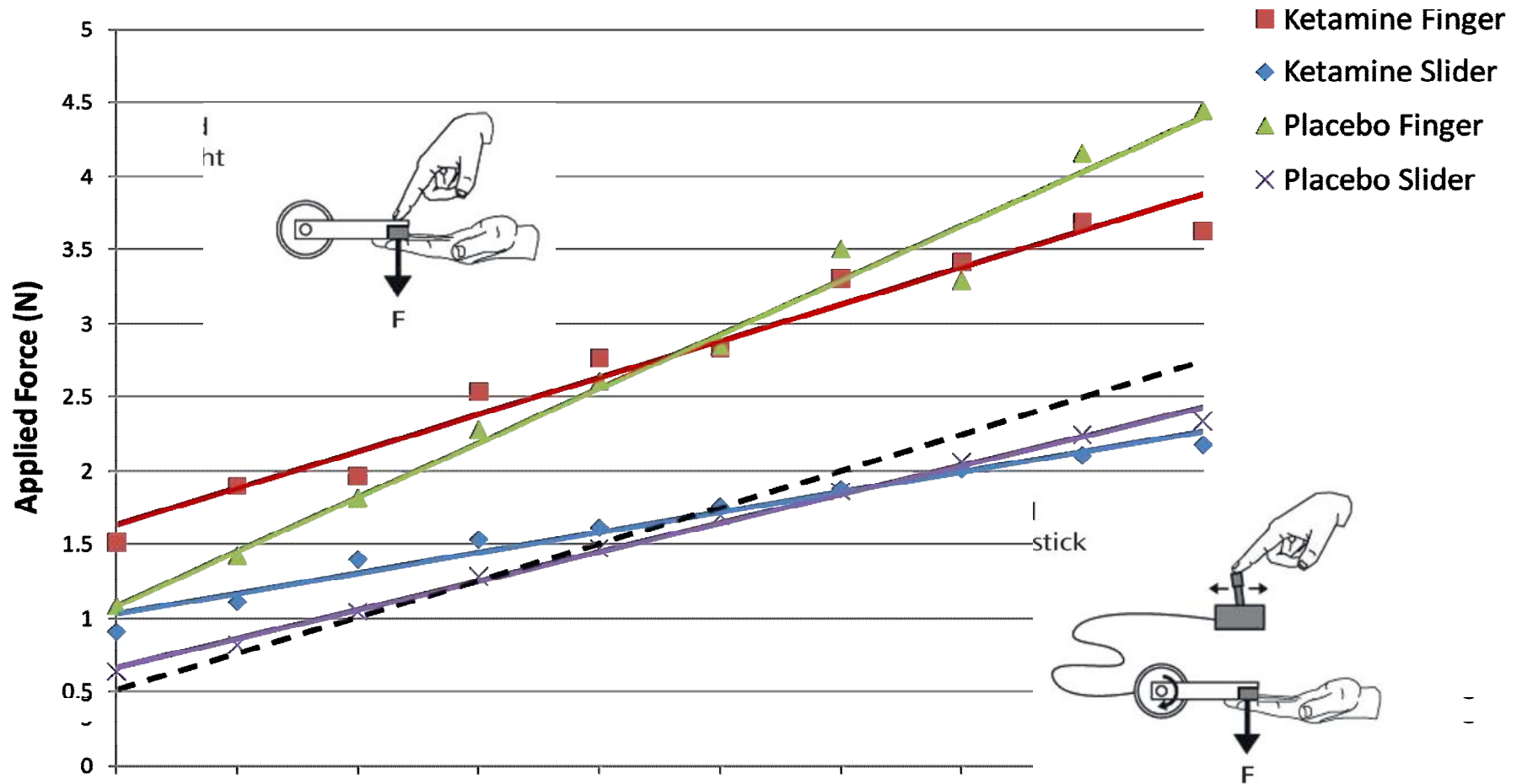
Binding and ketamine-induced experience



Binding and ketamine-induced experience



Force matching task – ketamine (200ng/ml plasma) and placebo



- Action outcome binding is increased under ketamine (comparable to schizophrenia).
- The degree of this effect correlates positively across subjects with ketamine-induced changes in body perception esp sense of “disconnection” from own movements
- Force cancellation appears to be unaffected, even at the higher dose of ketamine.

In association with...

- Cambridge
 - BCNI/Psychiatry
 - J Moore
 - FS Arana
 - PR Corlett
 - HL Morgan
 - DC Redhead
 - J Gardner
 - J Everitt
 - J Pigott
 - GK Murray
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 - A Absalom
 - R Adapa
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 - S de Wit