# Effects of acute ketamine infusion on visual working memory encoding: a study using ERPs

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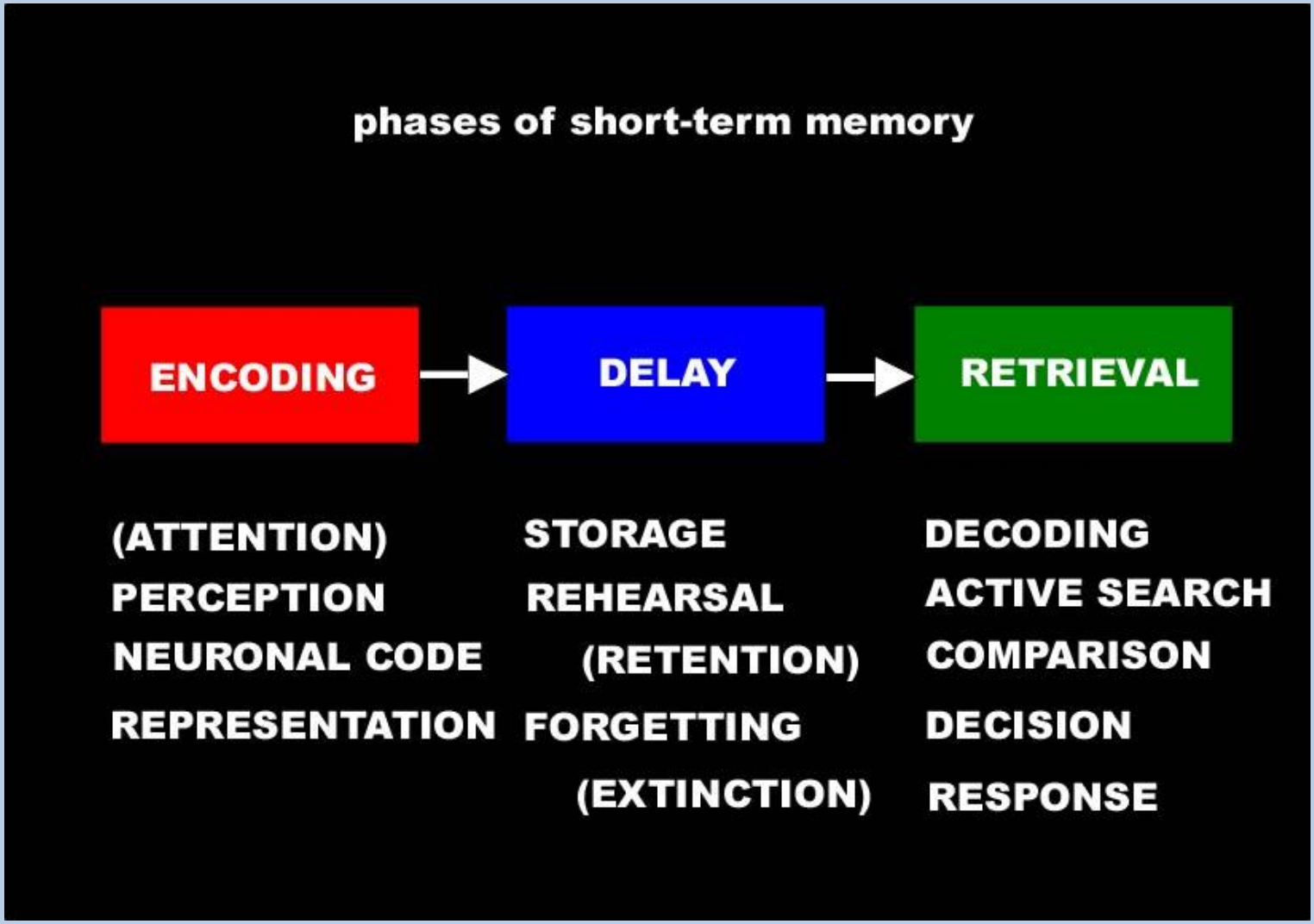
# Schizophrenia: The relevance of cognitive deficits for the understanding of schizophrenia

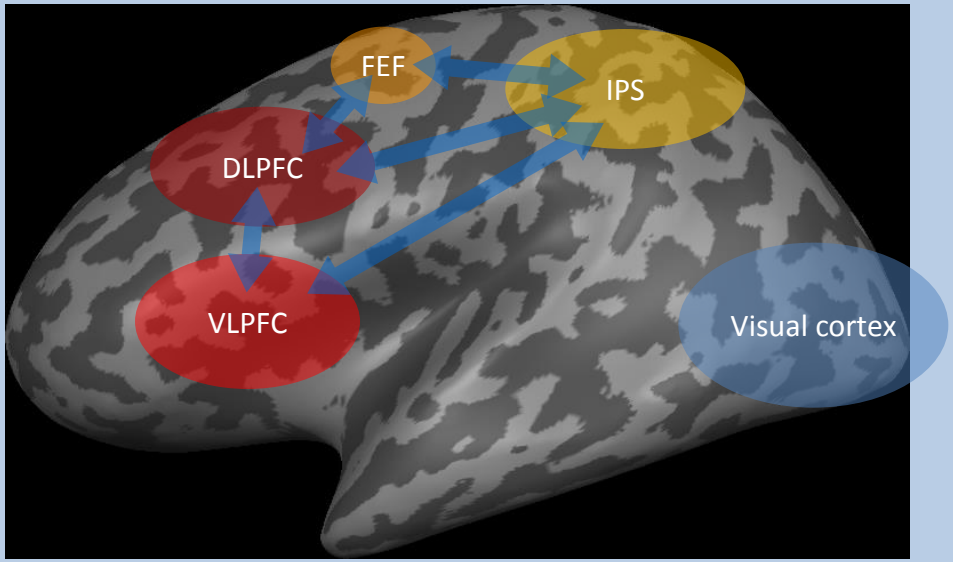
- Schizophrenia is associated with acute psychiatric symptoms (i.e. hallucinations, delusions).
- Even when free of these symptoms (which is most of the time), patients suffer from severe problems in day to day life resulting in tremendous personal and economic costs.
- These appear to be highly related to cognitive deficits associated with the disorder.
- Working Memory is one of the most fundamental processes in performing many daily tasks.
- Impaired Visual Working memory (WM) is a core deficit in schizophrenia.
- Treating WM impairments may have important practical benefits for patients (both behaviourally and with drugs).

# Impaired visual working memory (WM) is a core deficit in schizophrenia



# Visual working memory deficits in schizophrenia: Evidence from fMRI and EEG

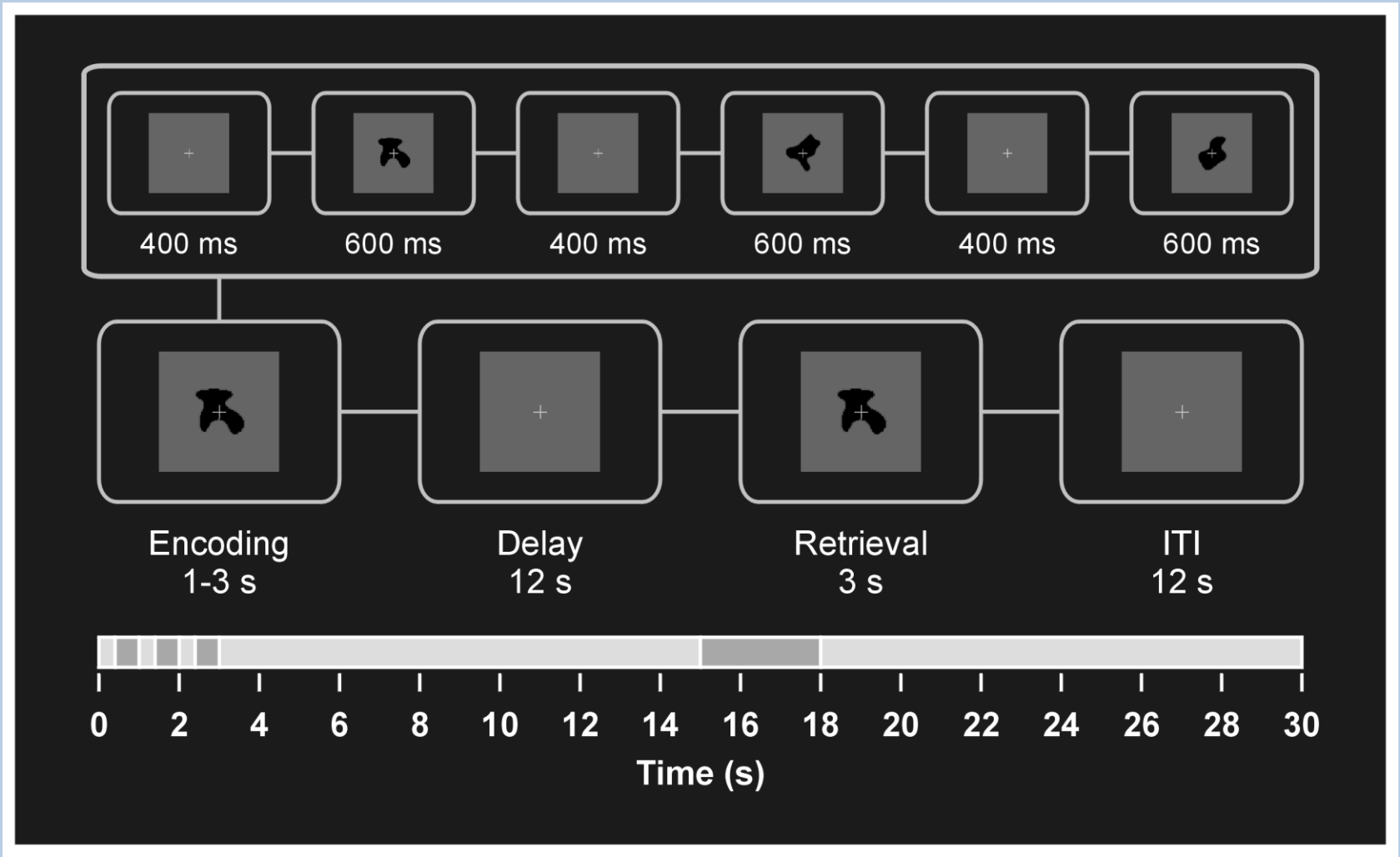
Encoding ⇒ Maintenance ⇒ Retrieval



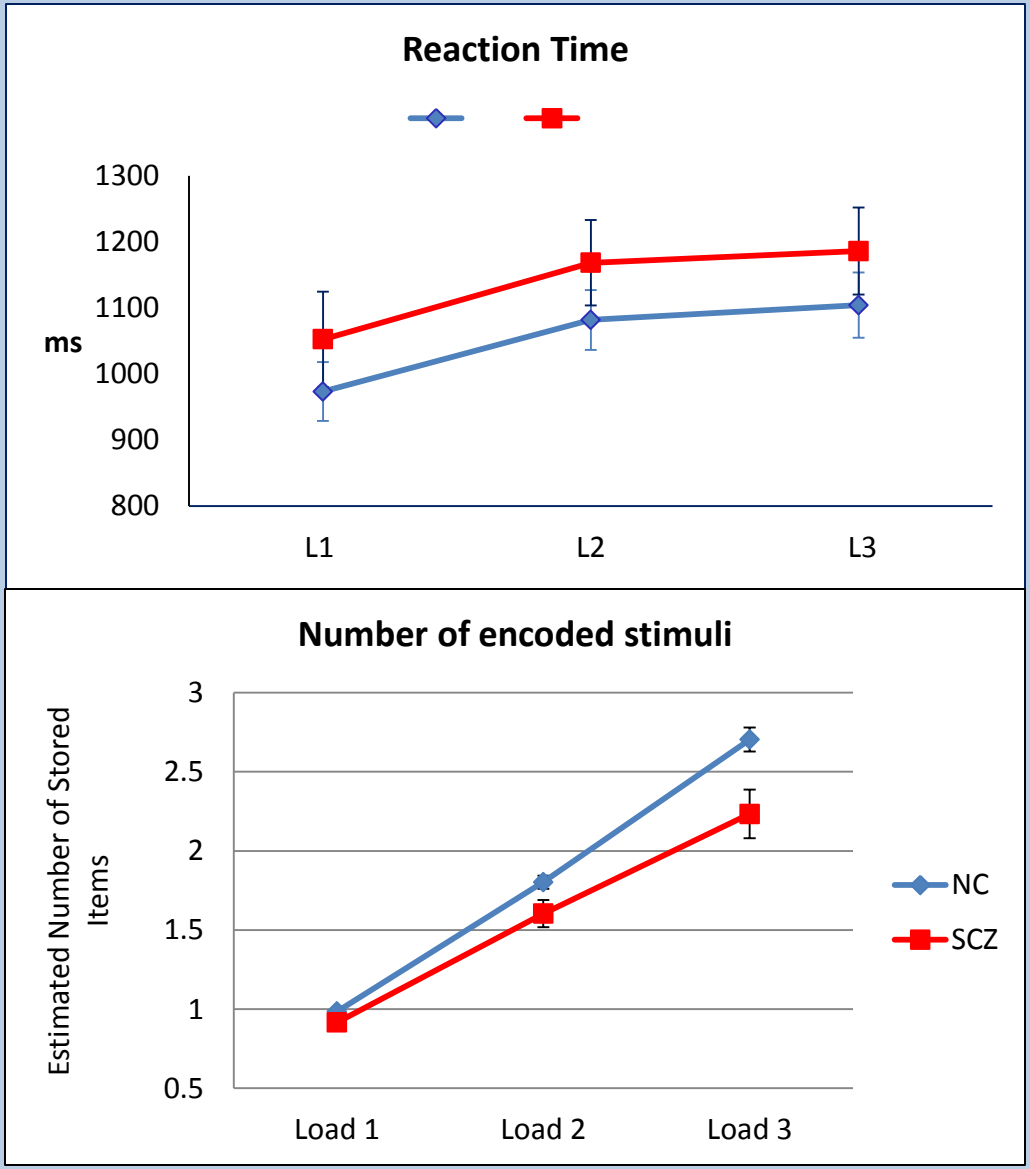

- WM deficits have mostly been attributed to maintenance and executive functions associated with prefrontal cortical dysfunction.

- More recently emphasis on the encoding stage of WM and possible deficits occurring at this stage.

# Delayed Discrimination Task



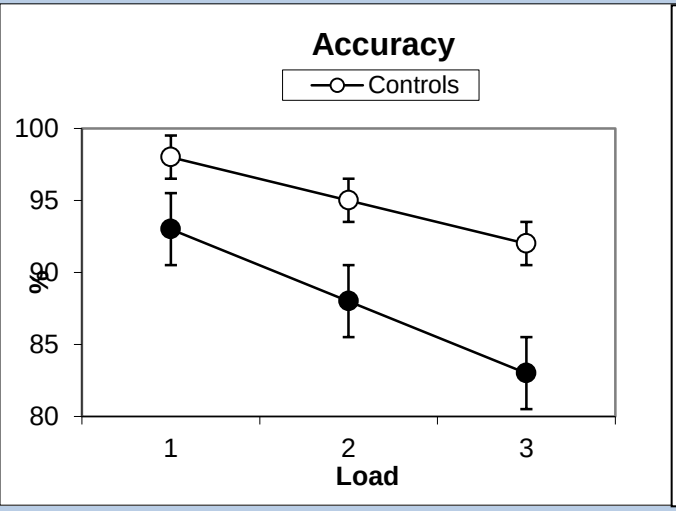
# Behavioural data: Early Onset Sz



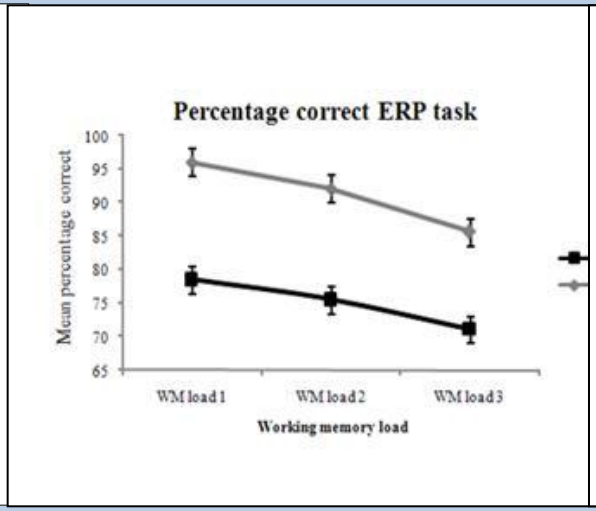

*Haenschel et al., 2007,*

# WM Performance in the SZ-spectrum

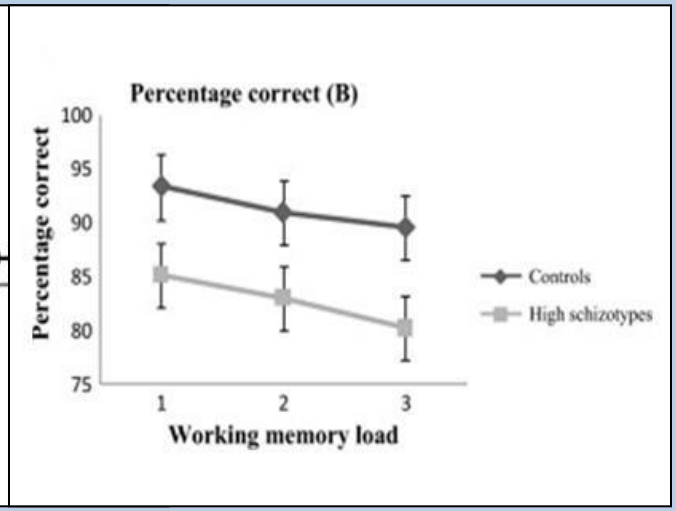
Early Onset Sz




Chronic Sz

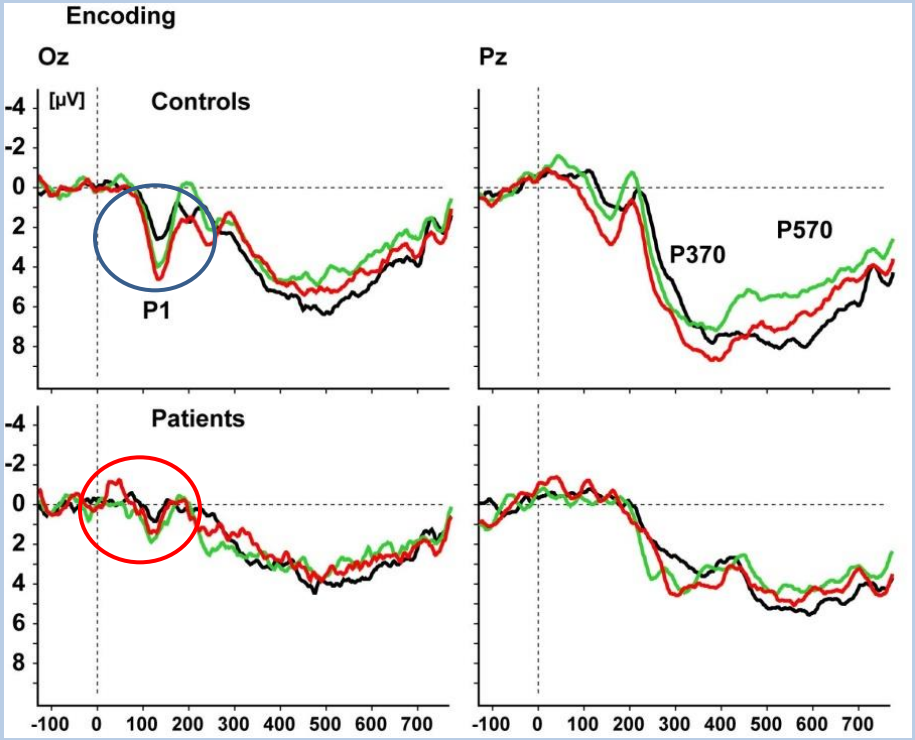



Schizotypy




*Haenschel et al., 2007, Koychev et al.* 2010; 2012

# ERPs: The importance of Encoding for successful WM and its Dysfunctions

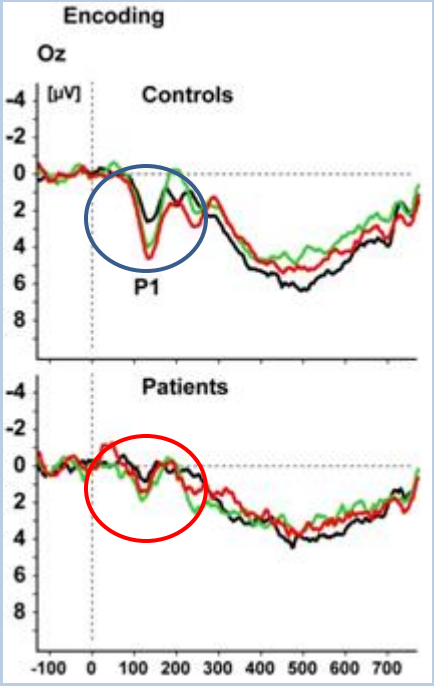


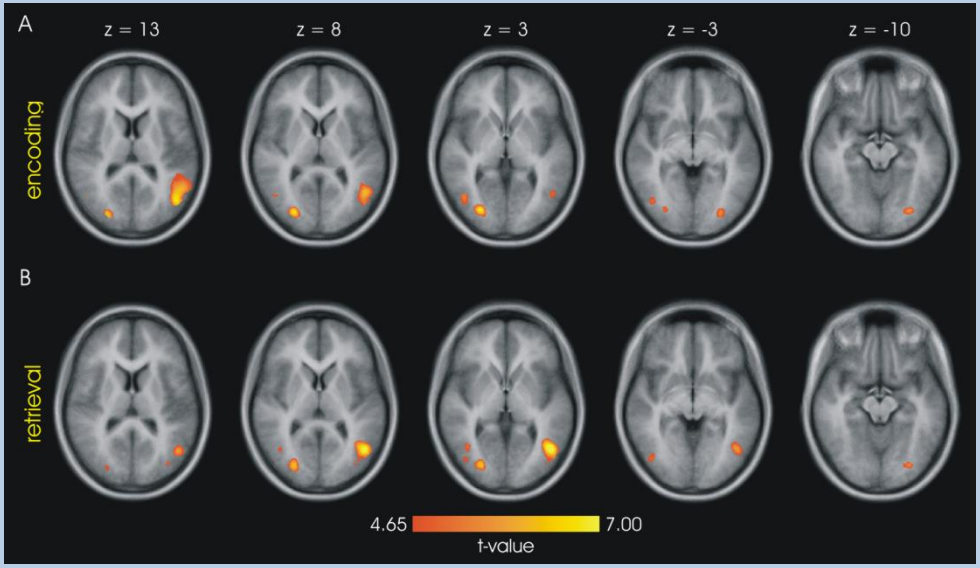

P1 ERP component increases with load predicting performance in controls

**but** is severely reduced in early onset schizophrenia.

*Haenschel et al., Arch Gen Psych 2007*

# ERPs: P1 as a biomarker of the disorder?



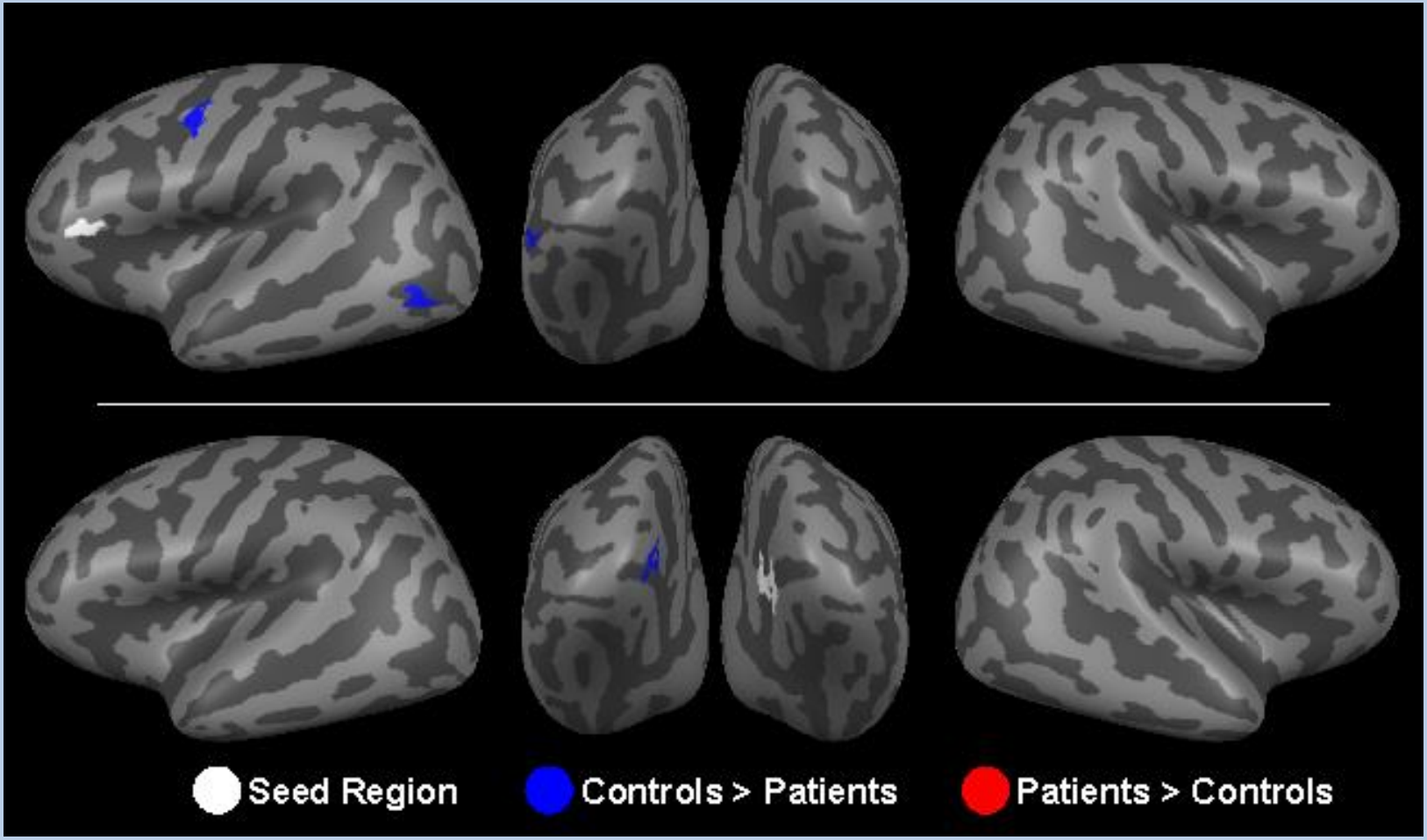

P1 ERP component increases with load predicting performance in controls

**but** is severely reduced in early onset schizophrenia.

fMRI revealed reduced activation in the middle occipital gyrus in early onset schizophrenia.

*Haenschel et al., Arch Gen Psych 2007,*

# Functional connectivity between frontal and visual areas during Encoding

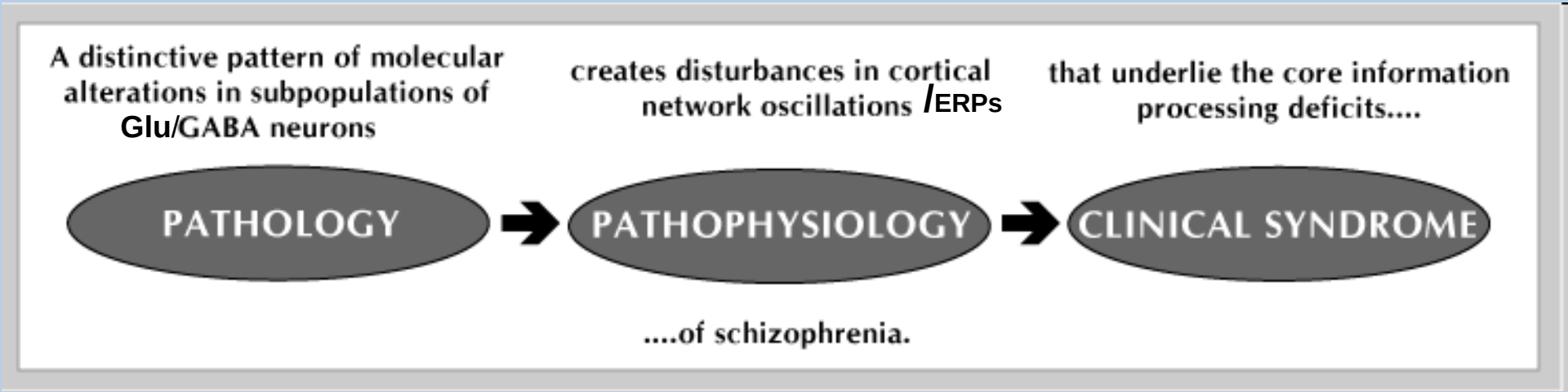



Reduced functional connectivity between left VLPFC and the left LOC & between right extrastriate visual cortex and left early visual cortex in patients!

*Bittner, Linden, Haenschel, 2014*

# Neurochemical background of WM encoding?

- Disturbances in Dopamine, GABA, Glutamate (NMDA receptors) have been found in schizophrenia.




DA Lewis: http://www.ccnmd.pitt.edu/Pages/Research/researchov.html

# Ketamine

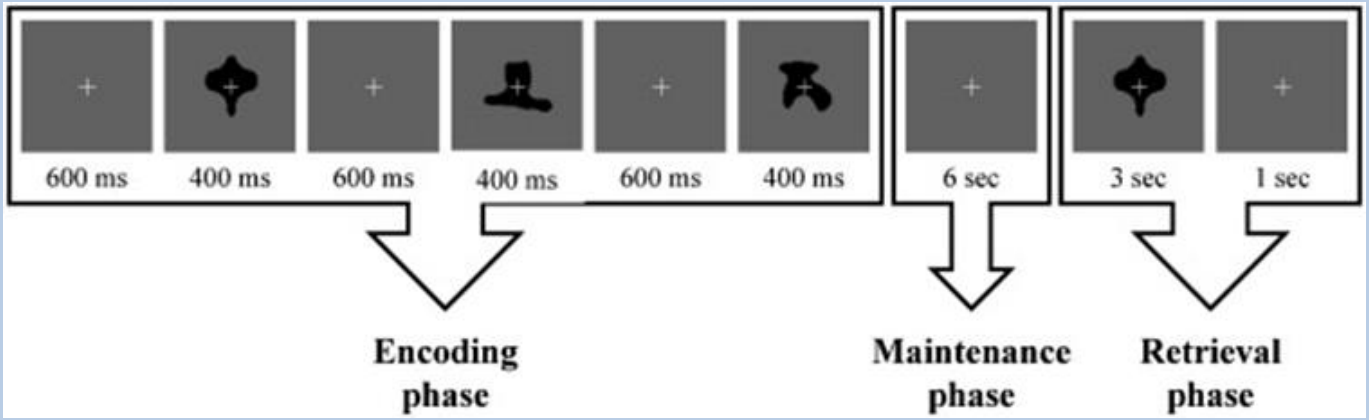
- Ketamine is a well-established pharmacological model of schizophrenia
- This has been attributed to its NMDA antagonism and likely involves disinhibition of glutamatergic pyramidal neurons and consequent downstream dysregulation of the striatal dopamine system.

Question: Will ketamine reproduce both the working memory and visual information processing deficits?

# Methods: WM & EEG

•Randomised & Blind: Continuous Intravenous infusion of placebo (0.9% normal saline) or Ketamine (100ng/ml) Infusion randomised by Pharmacy.

After 5 Min Infusion → 2 WM runs → 2 Min Rest & CADS → 2 WM runs → Rest & BPRS → 2 WM runs




CADS: Clinician Administered Dissociative Symptom Scale; BPRS: Brief Psychiatric Rating scale

# Methods EEG ketamine

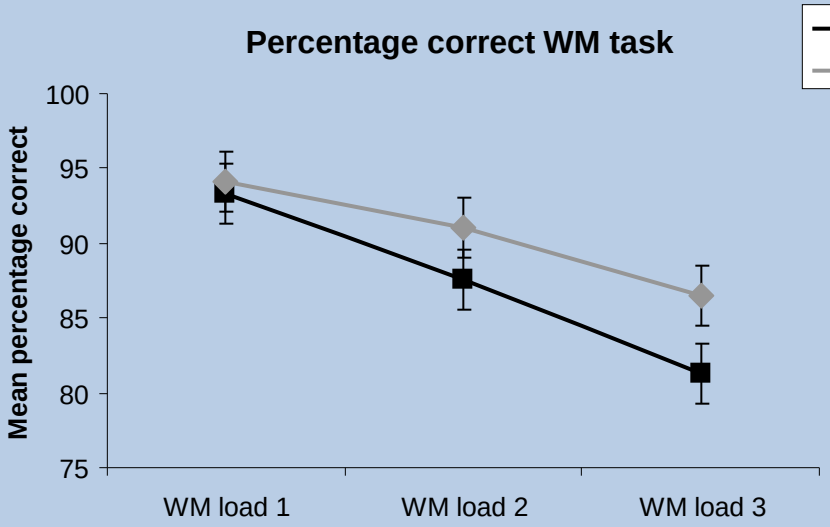
| | Drug | N | Mean | SD | SE |
|---|---|---|---|---|---|
| BPRS | Ketamine | 22 | 19.9091 | 2.06810 | .44092 |
| | Placebo | 22 | 18.4545 | 1.10096 | .23473 |
| CADSS | Ketamine | 22 | 4.1818 | 3.85000 | .82082 |
| | Placebo | 22 | 1.4545 | 1.81861 | .38773 |
| Age | Ketamine | 22 | 23.6818 | 6.02682 | 1.28492 |
| | Placebo | 22 | 23.4091 | 3.92379 | .83655 |
| Education | Ketamine | 22 | 15.1818 | 2.15222 | .45885 |
| | Placebo | 22 | 15.8636 | 1.55212 | .33091 |
| SPQ | Ketamine | 22 | 3.1364 | 5.04546 | 1.07570 |
| | Placebo | 22 | 6.3636 | 6.12991 | 1.30690 |
| NART | Ketamine | 18 | 114.0556 | 4.42895 | 1.04391 |
| | Placebo | 21 | 114.0381 | 5.62419 | 1.22730 |

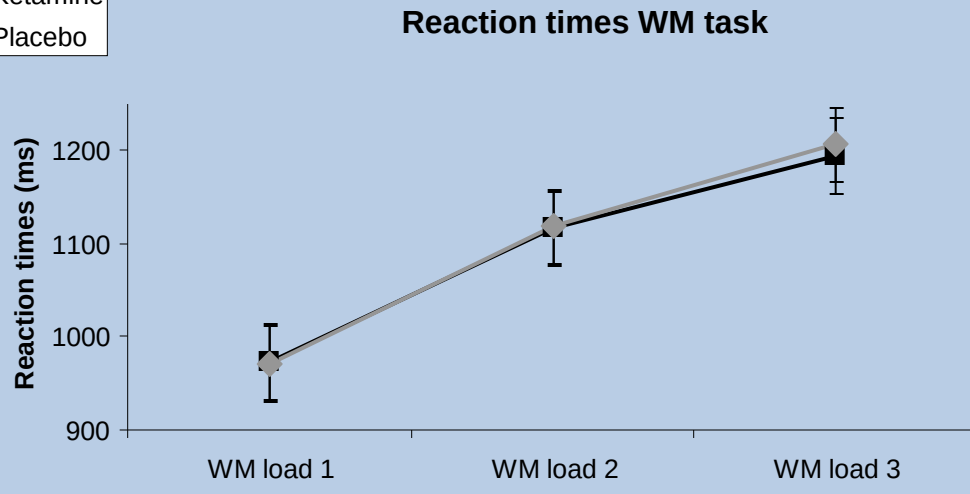
| | t | df | Sig. (2-tailed) |
|---|---|---|---|
| BPRS | 2.912 | 32.018 | .006 |
| CADSS | 3.004 | 29.927 | .005 |
| Age | .178 | 42 | .860 |
| Education | -1.205 | 42 | .235 |
| SPQ | -1.907 | 42 | .063 |
| NART | .011 | 37 | .992 |

Koychev, Deakin, El-Deredy, Haenschel, in prep.

# Behavioural results

44 healthy volunteers (22 ketamine, 22 placebo)

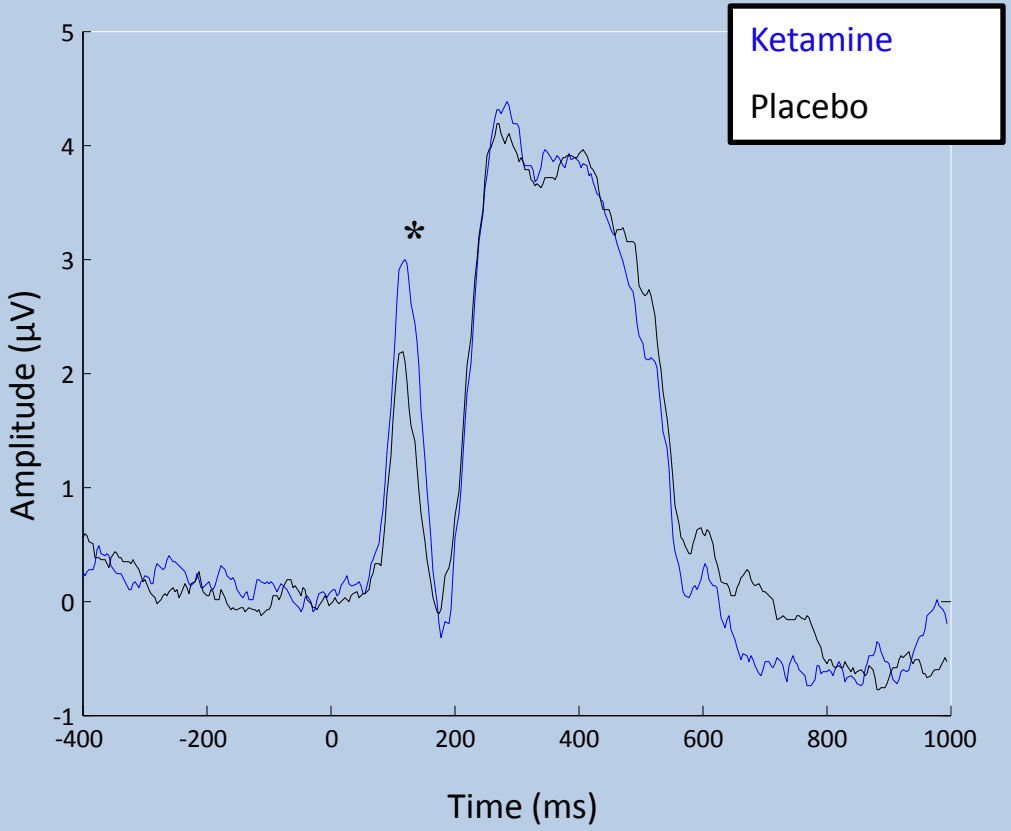



*Group effect: Clinician Administered Dissociative States Scale* (*CADSS*): p=0.005 & BPRS: p= .006

Koychev, Deakin, El-Deredy, Haenschel, in prep.

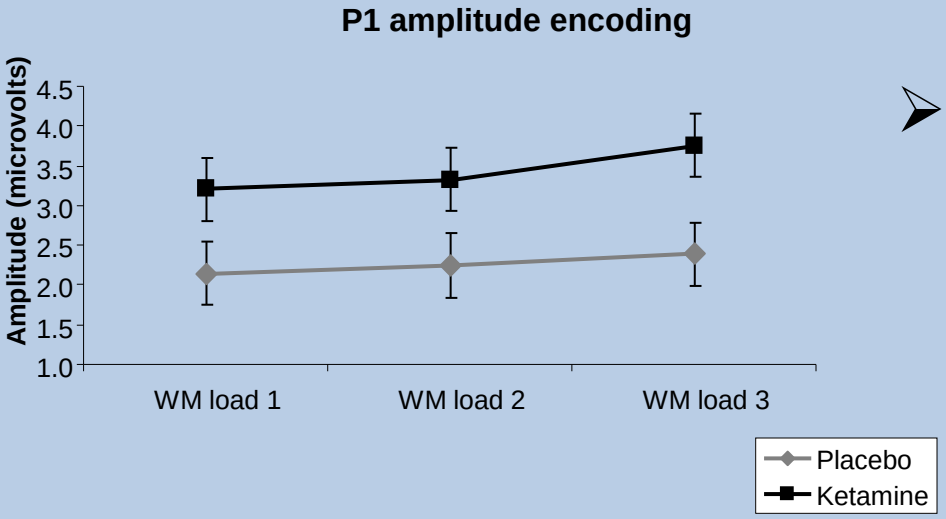
# Results: ERP occipital electrodes



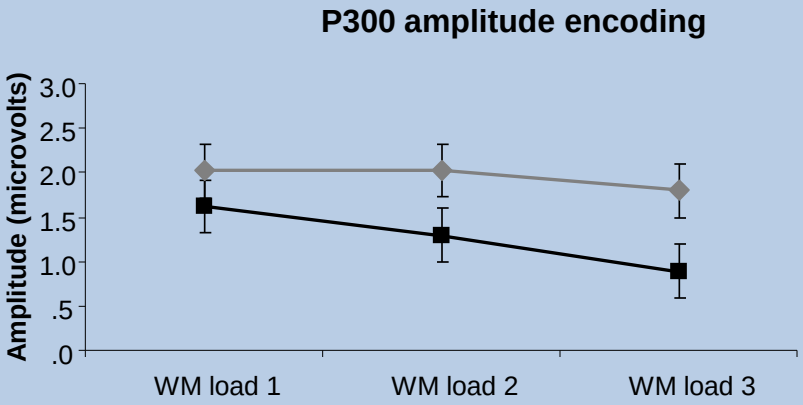

* $F(1,42) = 6.673$, $p = .04$; partial $eta^2 = 0.1$

Koychev, Deakin, El-Deredy, Haenschel, in prep.

# Effects of acute Ketamine on WM encoding




- Increase in P1




- But a later decrease in P300

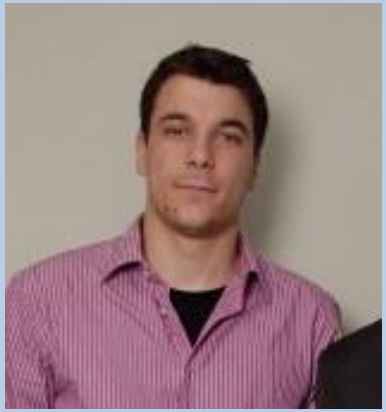
Koychev, Deakin, El-Deredy, Haenschel, in prep.

# Discussion

- Ketamine induces cognitive impairment similar to the one found in psychosis and schizotypy
- Early visual evoked responses are however augmented
- Later EEG components (P300) are significantly reduced in amplitude
- Visual cortex disinhibition caused by ketamine associated with higher order disturbance?

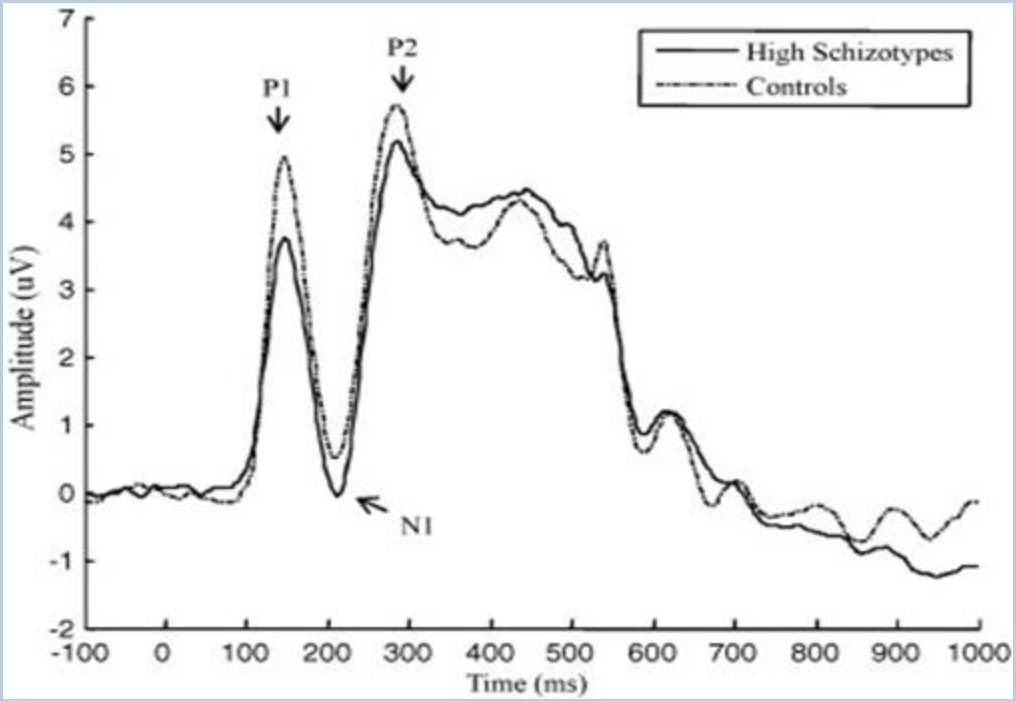
# Acknowledgements

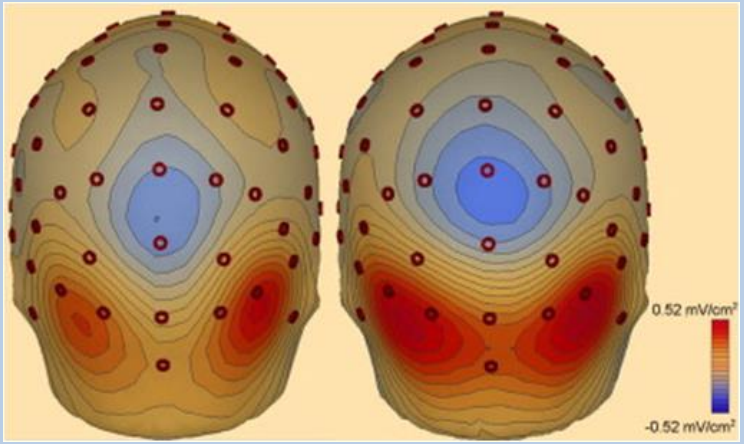
IOP



Thank you for your attention!

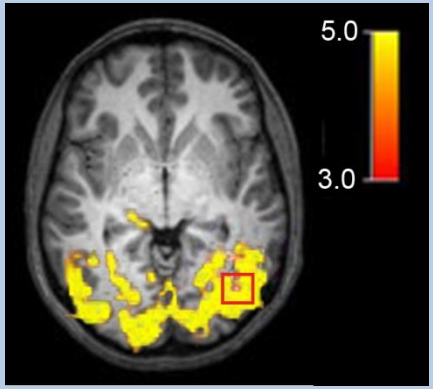
# P1 as a biomarker: SCHIZOTYPY



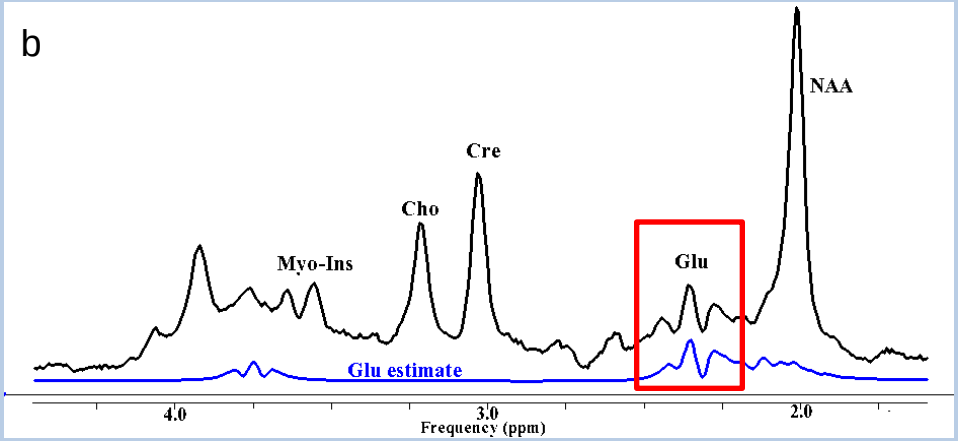




*Koychev et al. Neuropsychologia* 2010 Jun;48(7):2205-14

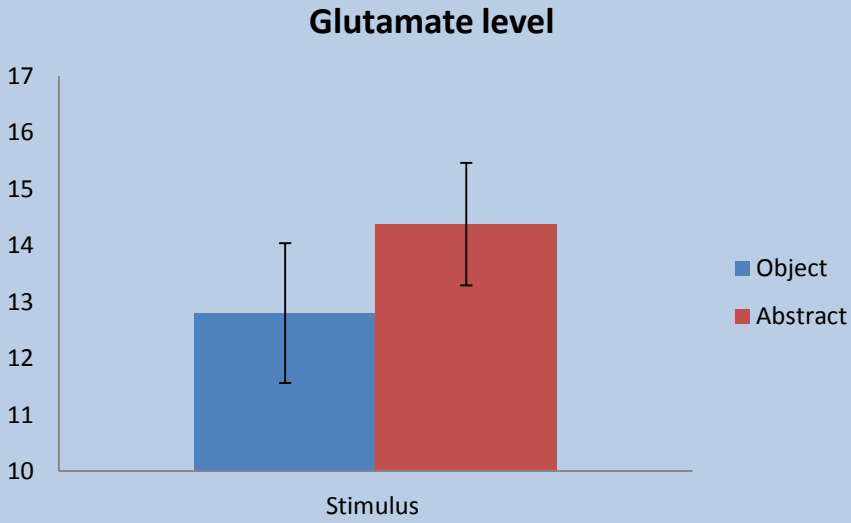
a


5.0
3.0

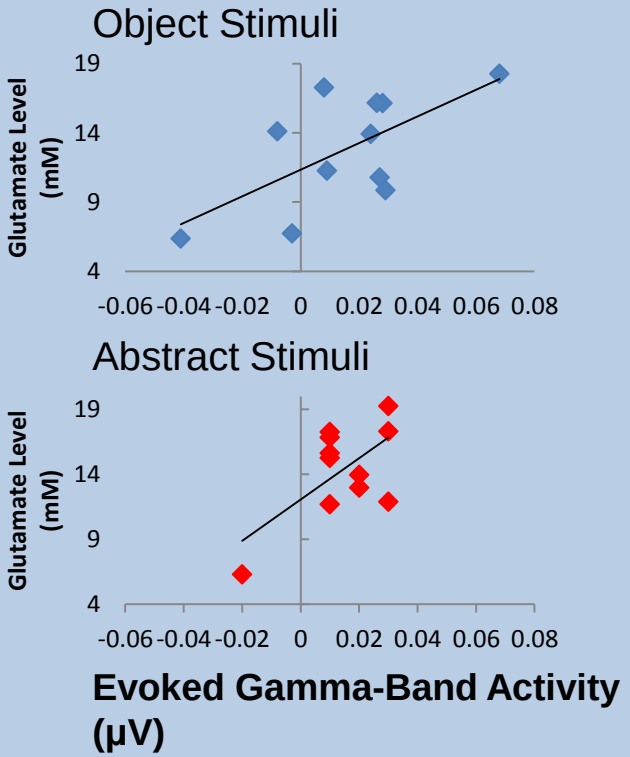
b


NAA
Cre
Cho
Myo-Ins
Glu
Glu estimate
4.0
3.0
2.0
Frequency (ppm)

c


Glutamate level
17
16
15
14
13
12
11
10
Stimulus
Object
Abstract

d


Object Stimuli
Glutamate Level (mM)
19
14
9
4
-0.06 -0.04 -0.02 0 0.02 0.04 0.06 0.08
Abstract Stimuli
Glutamate Level (mM)
19
14
9
4
-0.06 -0.04 -0.02 0 0.02 0.04 0.06 0.08
Evoked Gamma-Band Activity (μV)

# Combining measures of electrophysiology and neurotransmitters in humans?

- Different ways of investigating possible relationship
  - Use measures of EEG/MEG and MR-spectroscopy to measure neurotransmitter concentration (Lally et al., 2014)
  - Using drugs that block or enhance specific transmitters, for example ketamine, a NMDA antagonists

# Methods

- The influence of ketamine on WM using EEG.

Participants were randomised to receive an intravenous infusion of placebo (0.9% normal saline) or Ketamine.

•Ketamine was administered to achieve a dose of 100ng/ml