THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Schizophrenia as a Cognitive Disorder: Insights from Cognitive Neuroscience

Pat Michie
School of Psychology and
Centre for Translational Neuroscience and Mental Health Research
University of Newcastle.

Schizophrenia as a Cognitive Illness?

Clinical Review & Education

Special Communication

Schizophrenia Is a Cognitive Illness
Time for a Change in Focus

René S. Kahn, MD, PhD; Richard S. E. Keefe, PhD

Schizophrenia is currently classified as a psychotic disorder. This article posits that this emphasis on psychosis is a conceptual fallacy that has greatly contributed to the lack of progress in our understanding of this illness and hence has hampered the development of adequate treatments. Not only have cognitive and intellectual underperformance consistently been shown to be risk factors for schizophrenia, several studies have found that a decline in cognitive functioning precedes the onset of psychosis by almost a decade. Although the question of whether cognitive function continues to decline after psychosis onset is still debated, it is clear that cognitive function in schizophrenia is related to outcome and little influenced by antipsychotic treatment. Thus, our focus on defining (and preventing) the disorder on the basis of psychotic symptoms may be too narrow. Not only should cognition be recognized as the core component of the disorder, our diagnostic efforts should emphasize the changes in cognitive function that occur earlier in development. Putting the focus back on cognition may facilitate finding treatments for the illness before psychosis ever emerges.

JAMA Psychiatry. 2013;70(10):1107-1112. doi:10.1001/jamapsychiatry.2013.155
Published online August 7, 2013.

Editorial page 1009

Author Affiliations: Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, the Netherlands (Kahn); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina (Keefe).

Corresponding Author: René S. Kahn, MD, PhD, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, Heidelberglaan 100, 3508 GA Utrecht, PO Box 85500, the Netherlands (r.kahn@umcutrecht.nl).

From Kahn & Keefe, JAMA Psychiatry, 2013

Schizophrenia as a Cognitive Illness?

From Kahn & Keefe, JAMA Psychiatry, 2013

Schizophrenia is currently classified as a psychotic disorder. This article posits that this emphasis on psychosis is a conceptual fallacy that has greatly contributed to the lack of progress in our understanding of this illness and hence has hampered the development of adequate treatments. Not only have cognitive and intellectual underperformance

EDITORIAL

What Is the Core of Schizophrenia?

Stephan Heckers, MD

Most clinicians agree that schizophrenia is a useful diagnosis, but few agree on what it is. We have embraced schizophrenia to classify some peculiar mental states and to manage some unusual, bizarre, and, at times, frightening behaviors. But there is little agreement on the mechanism of disease. In this issue of *JAMA Psychiatry*, Kahn and Keefe[1] claim that we have gotten it all wrong: "schizophrenia is not primarily a psychotic disorder, it is a cognitive illness." They forcefully state that the focus on psychosis has held us back from finding better treatments for schizophrenia. Ironically, they list Emil

Related article page 1107

ing was influenced by the reactionary mindset of imperialist Germany, making it easy for him to think about degeneration and irreversible brain damage as the cause of mental illness.[4] We do not want to go back there.

After making their case, Kahn and Keefe give 5 recommendations: (1) cognitive decline prior to onset of psychosis should be part of the diagnosis and (2) central in treatment guidelines, (3) schizophrenia should be reclassified as a cognitive disorder, (4) early recognition and intervention have to be moved to an earlier age at onset, and (5) cognitive underperformance rather than psychosis proneness is the proper risk phenotype.

Schizophrenia as a Cognitive Illness?

Heckers, JAMA Psychiatry, 2013

Kahn & Keefe propose that

"the whole concept of schizophrenia as an illness that presents with psychosis should be discarded." This is a bold request. Is it helpful?

Cognitive deficits in schizophrenia – a brief history

- Kraepelin, 1893 – *dementia praecox* – early cognitive decline.
- Bleuler, 1911 – *schizophrenia* – loosening of associative thinking.

- Early 1920s to late 1990s – cognitive deficits ignored.
- Despite many reports of impairments on standard neuropsychological batteries

Neuropsychology
1998, Vol. 12, No. 3, 426–445

Copyright 1998 by the American Psychological Association, Inc.
0894-4105/98/$3.00

Neurocognitive Deficit in Schizophrenia: A Quantitative Review of the Evidence

R. Walter Heinrichs and Konstantine K. Zakzanis
York University

The neurocognitive literature on test performance in schizophrenia is reviewed quantitatively. The authors report 22 mean effect sizes from 204 studies to index schizophrenia versus control differences in global and selective verbal memory, nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and interhemispheric tactile-transfer test performance. Moderate to large raw effect sizes ($d > .60$) were obtained for all 22 neurocognitive test variables, and none of the associated confidence intervals included zero. The results indicate that schizophrenia is characterized by a broadly based cognitive impairment, with varying degrees of deficit in all ability domains measured by standard clinical tests.

Cognitive deficits in schizophrenia –

- Meta-analyses – Heinrichs & Zaksanis, 1998. Moderate to large effect sizes - largest for verbal memory (initial learning)
- Subsequent meta-analysis and large cohort studies of patients vs controls (WAFSS, ASRB) replicated these findings

- Patients have deficits in a number of cognitive domains – **memory & learning, executive functions, attention, processing speed, working memory**

Why cognitive deficits in schizophrenia should not be ignored?

1. Cognitive impairment is a risk factor for the development of schizophrenia – low IQ increases risk in dose dependent manner – evident by early teens.
2. Cognitive decline begins well before the onset of psychosis – evident at ages 7, 9, 11, & 13 (Dunedin cohort). Gap increased over 7 – 13 yrs
3. Individuals at ultra-high risk (UHR) or in at at-risk-mental state (ARMS) show cognitive impairments.

Cognitive deficits in ARMS vs Healthy Controls: Means (SDs) The Minds in Transition Study (MinT)

Measure	ARMS	Healthy controls
WASI: 2 Subscale IQ	54.33 (11.71)	62.26 (8.42)***
CVLT-II:		
List A Trials 1-5 T Score	51.92 (12.29)	55.76 (8.17)*
List A Short Delay Cued Recall Std Score	-0.178 (1.07)	0.169 (0.93)**
List A Long Delay Cued Recall Std Score	-0.212 (1.1)	0.129 (0.99)*
WMS-III: Digit Span Scaled	9.93 (2.77)	11.53 (3.26)**
Visual Pattern Test	8.57 (2.31)	10.33 (1.85)**
D-KEFS:		
Trail Making Test Condition 4 (Number – Letter Sequencing) Scaled	8.87 (3.3)	10.43 (2.77)*
Verbal Fluency Test Condition 3 (Category Switching) Total Correct Scaled	12.04 (2.87)	12.9 (2.88)*
Colour Word Interference Test Condition 3 (Inhibition) Scaled	8.9 (3.53)	12.14 (2.44)***
GAF	54.1 (12.61)	85.18 (6.68)***
SOFAS	58.32 (13.88)	84.47 (7.54)***

* p<.05, **p<.01, ***p<.001

Atkinson et al 2013

4. Cognitive impairments may get worse with duration of illness but few good prospective studies.
5. Despite initial optimism, second generation antipsychotics do not ameliorate cognitive deficits.

What Are the Functional Consequences of Neurocognitive Deficits in Schizophrenia?

Michael Foster Green, Ph.D.

Objective: *It has been well established that schizophrenic patients have neurocognitive deficits, but it is not known how these deficits influence the daily lives of patients. The goal of this review was to determine which, if any, neurocognitive deficits restrict the functioning of schizophrenic patients in the outside world.* *Method:* *The author reviewed studies that have evaluated neurocognitive measures as predictors and correlates of functional outcome for schizophrenic patients. The review included 1) studies that have prospectively evaluated specific aspects of neurocognition and community (e.g., social and vocational) functioning (six studies), 2) all known studies of neurocognitive correlates of social problem solving (five studies), and 3) all known studies of the neurocognitive correlates and predictors of psychosocial skill acquisition (six studies).* *Results:* *Despite wide variation among studies in the selection of neurocognitive measures, some consistencies emerged. The most consistent finding was that verbal memory was associated with all types of functional outcome. Vigilance was related to social problem solving and skill acquisition. Card sorting predicted community functioning but not social problem solving. Negative symptoms were associated with social problem solving but not skill acquisition. Notably, psychotic symptoms were not significantly associated with outcome measures in any of the studies reviewed.* *Conclusions:* *Verbal memory and vigilance appear to be necessary for adequate functional outcome. Deficiencies in these areas may prevent patients from attaining optimal adaptation and hence act as "neurocognitive rate-limiting factors." On the basis of this review of the literature, a series of hypotheses are offered for follow-up studies.*

(Am J Psychiatry 1996; 153:321–330)

6. Most importantly – **cognitive impairments are a better predictor of functional outcomes than psychotic symptoms** (Green, 1996)
   - Outcomes - Community functioning, social problem solving and psychosocial skill acquisition
   - Verbal memory → all outcomes
   - Sustained attention → social problem solving and skill acquisition.
   - Cognitive flexibility → community functioning
   - Negative symptoms associated with social problem solving but not skill acquisition

In summary: Cognitive deficits are a core aspect of schizophrenia:

- EF sizes of 1 – 2 SDs in established illness
- A risk factor for schizophrenia
- Occur in first degree relatives
- Increased decline evident some years prior to onset of psychosis
- Occur in young people at risk (UHR/ARMS)
- Better predictor of functional outcomes than psychotic symptoms
- And not alleviated to any marked degree by antipsychotics

But should schizophrenia be no longer classified as a psychotic disorder – is it helpful to define it as a cognitive illness?

How would it change treatment if focus shifted to cognition rather than psychosis?

- Not clear that other non-pharma treatments of cognitive deficits (eg cognitive remediation / rehabilitation) work any better
- Nothing new in terms of antipsychotics but maybe we could learn something from AD?
- No doubt that more targeted research on understanding cause(s) of cognitive deficits would occur

Cognitive Neuroscience contribution – understanding the neurobiological basis of impaired cognition

Neurobiological basis of these deficits – focus on electrophysiology

Three indices derived from the EEG:

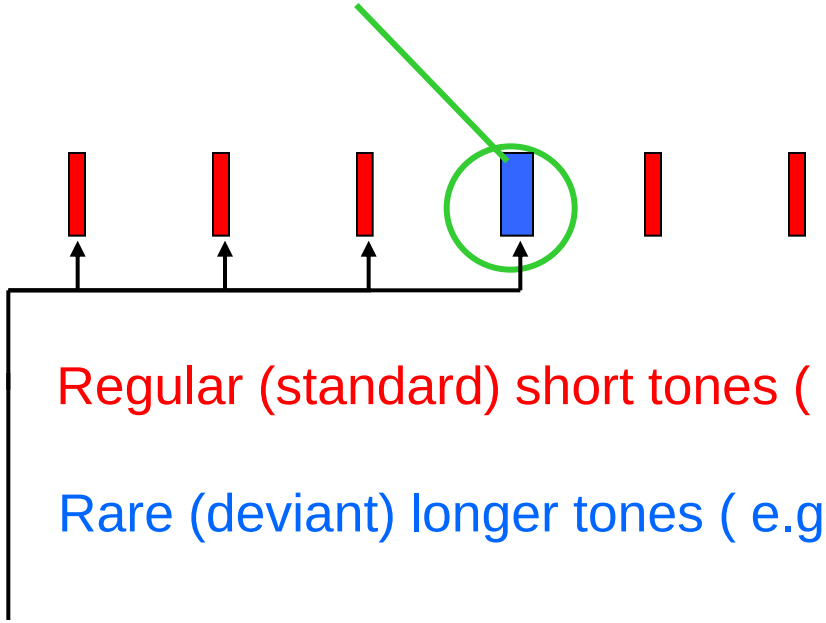
- Mismatch negativity or MMN – an automatic event-related potential to deviant sounds in a background of standard sounds
- Auditory N1 at slow delivery rates
- Gamma oscillations – EEG activity in range of 30Hz and above.

What has MMN revealed about schizophrenia? (Michie, 2001)

What is Mismatch Negativity (MMN)?

Mismatch Negativity (MMN) occurs when the auditory system recognises a change in some regularity of acoustic stimulation

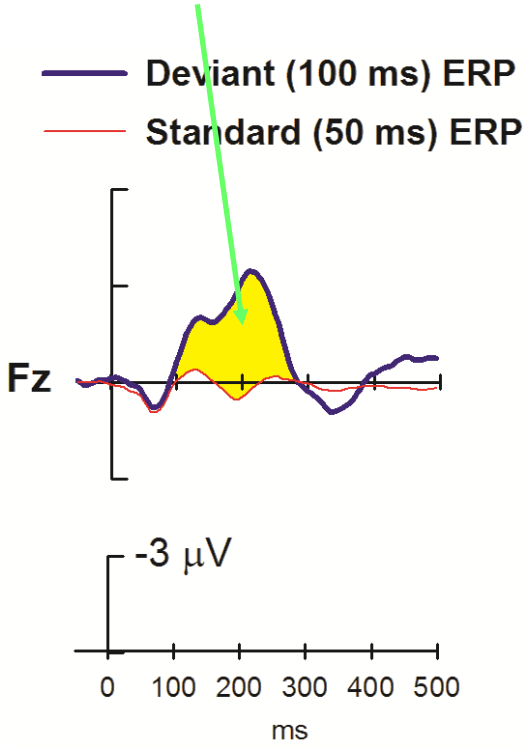
DURATION
or
FREQUENCY
CHANGE

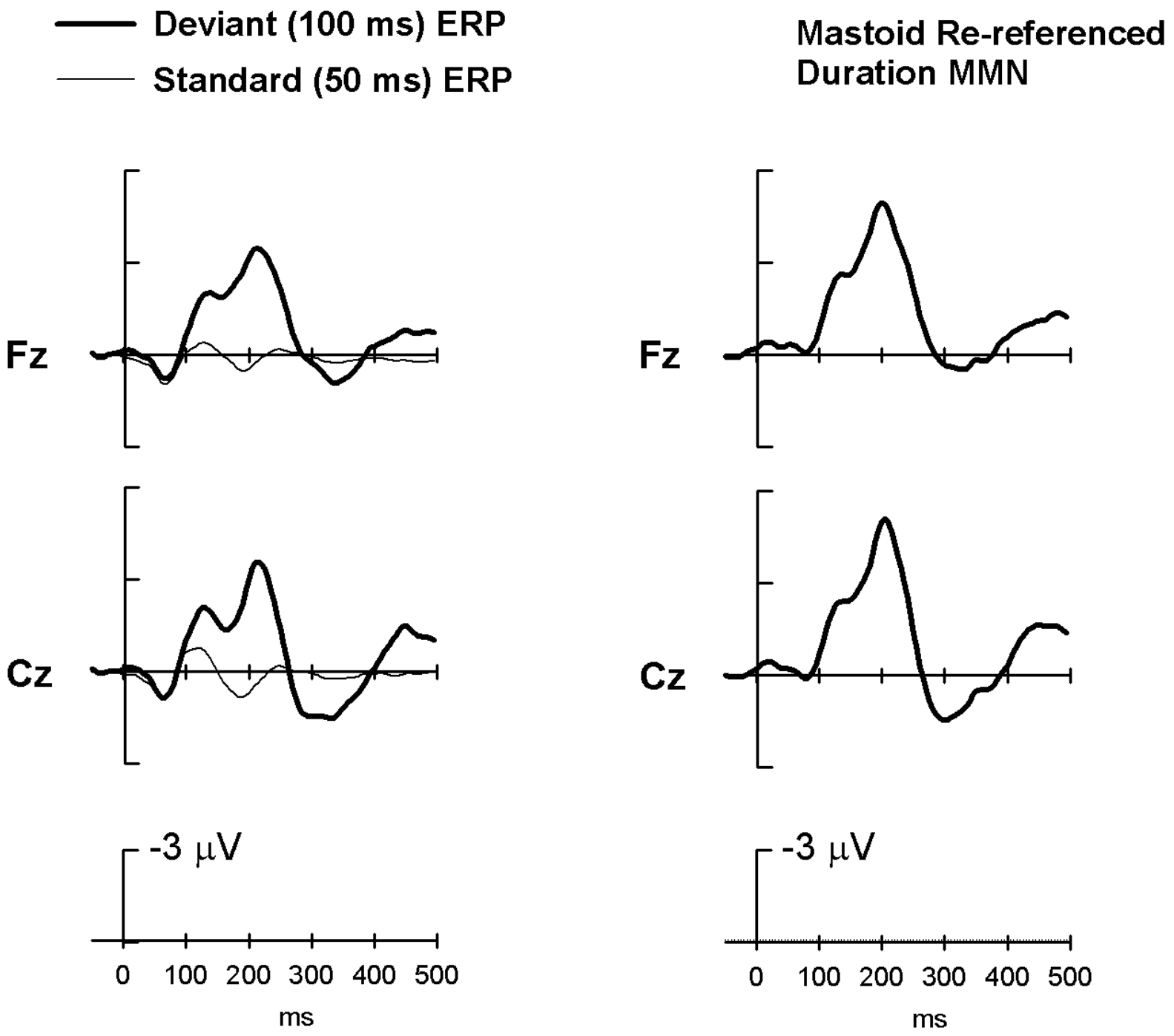


Regular (standard) short tones (e.g., 50 ms)

Rare (deviant) longer tones (e.g., 100 ms)

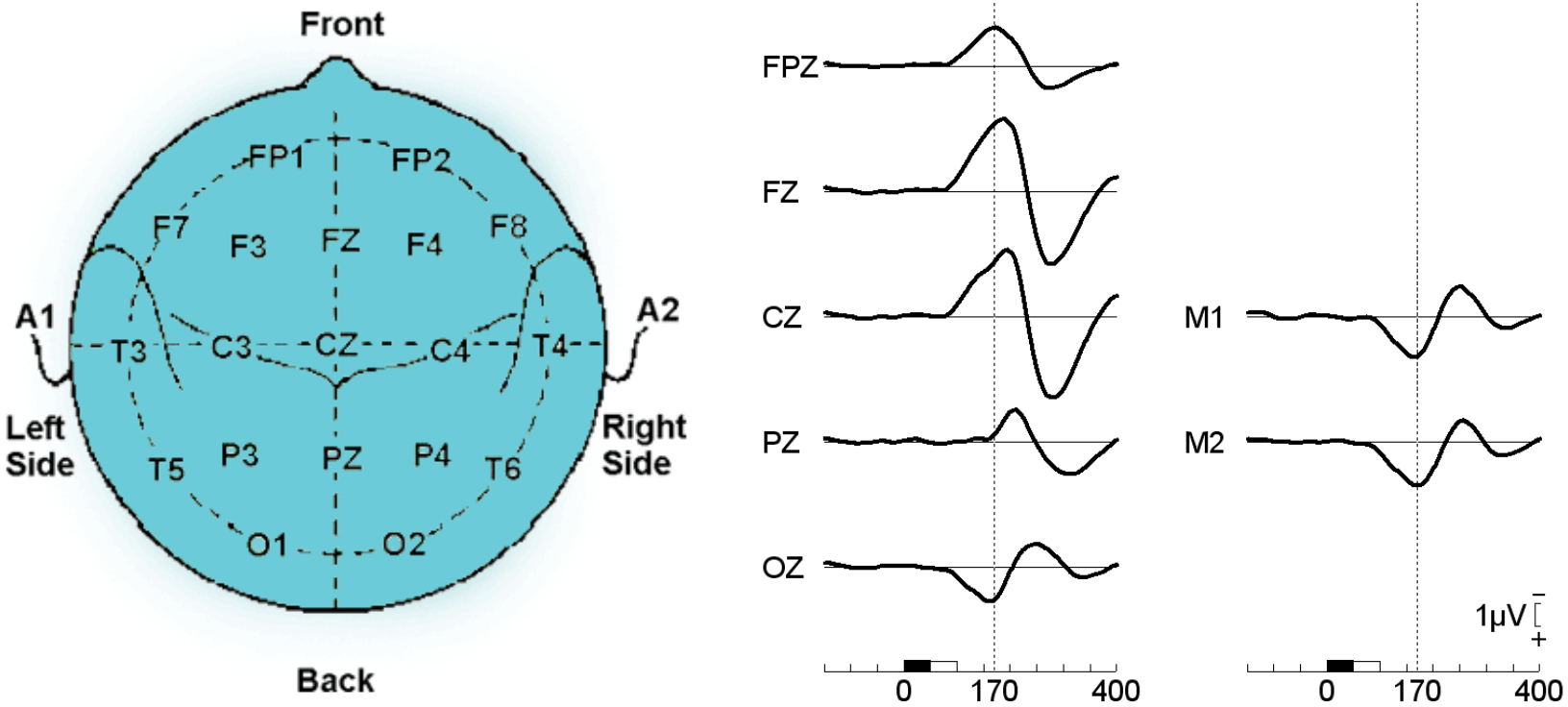
MMN – difference between deviant and standard ERPs




Deviant (100 ms) ERP
Standard (50 ms) ERP
Mastoid Re-referenced
Duration MMN
Fz
Cz
Fz
Cz
-3 μV
0 100 200 300 400 500
ms
-3 μV
0 100 200 300 400 500
ms

Characteristics of human MMN

- MMN elicited by any violation of regularity in background sounds -> a model comparison process
- MMN reflects prediction error & updating of model
- An automatic deviance detection mechanism



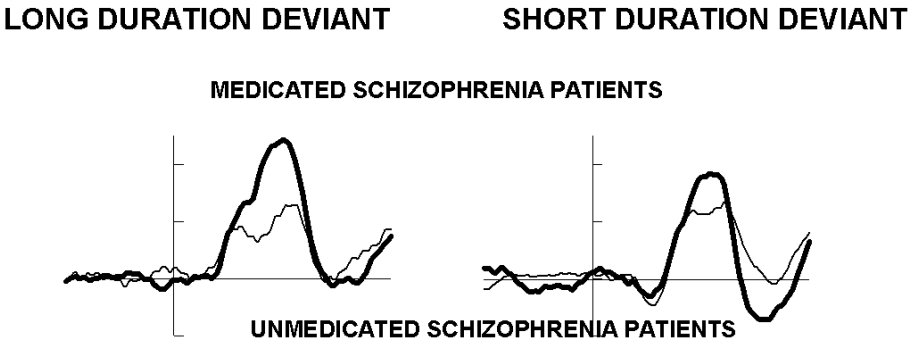
Why examine MMN in schizophrenia?

- Ideal tool for clinical studies and for probing auditory system functioning
- Human pharmacological studies - MMN provides an index of the integrity of the glutamate NMDA receptor system
  - Ketamine challenge reduces MMN in healthy individuals
- Animal studies: administration of PCP reduced intra-cortically recorded MMN in macaques without affecting exogenous ERP components.

Why is NMDAR link important?

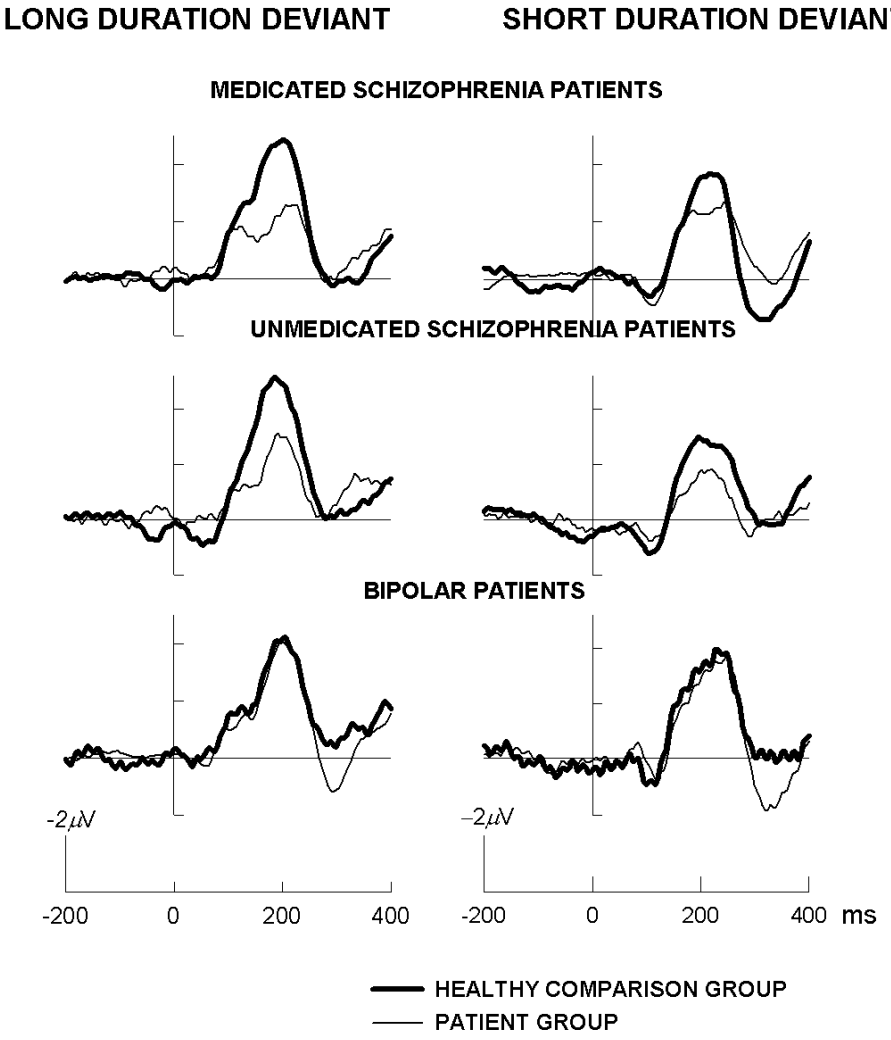
- PCP and ketamine produce cognitive deficits and psychotic like symptoms in healthy individuals
- PCP and ketamine noncompetitively block NMDA receptors
- Led to models of the aetiology and pathophysiology of schizophrenia focussing on glutamate NMDA receptor (NMDAR) hypofunction

Reduced MMN in patients reported in 1991-



Shelley et al, 1991

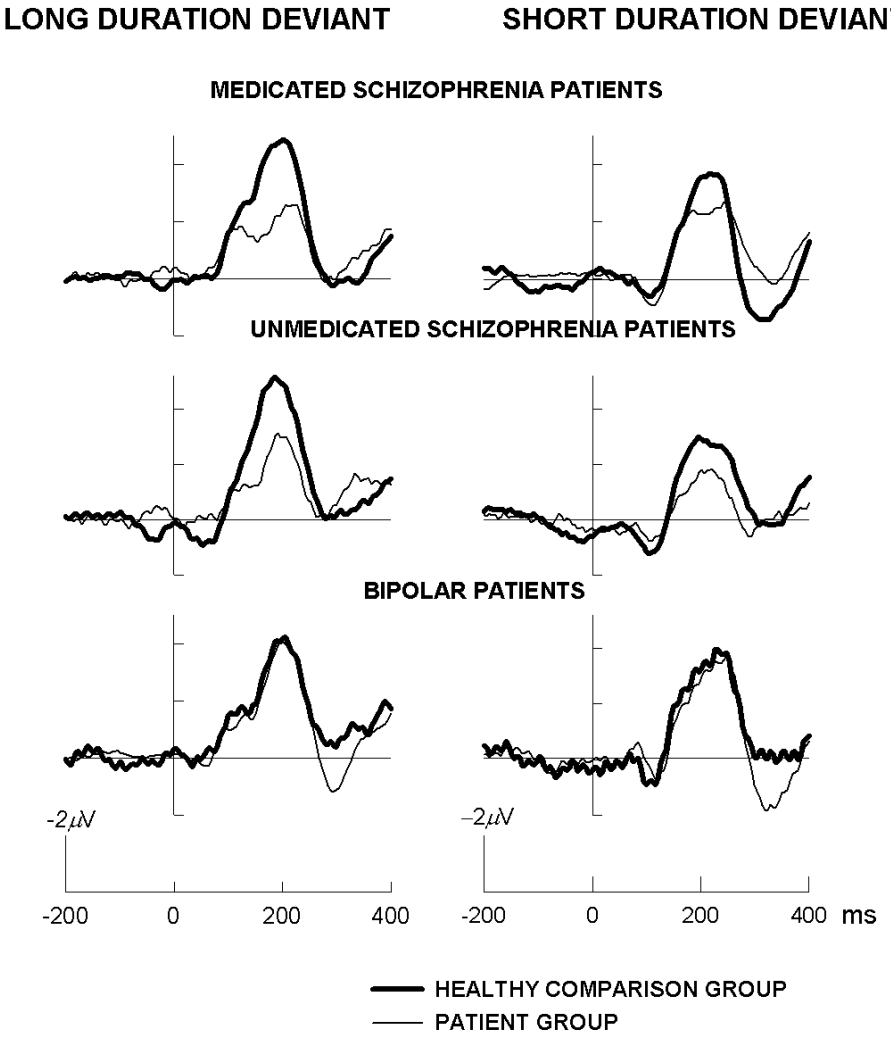
Reduced MMN in patients reported in 1991-



Shelley et al, 1991

Catts et al., 1995

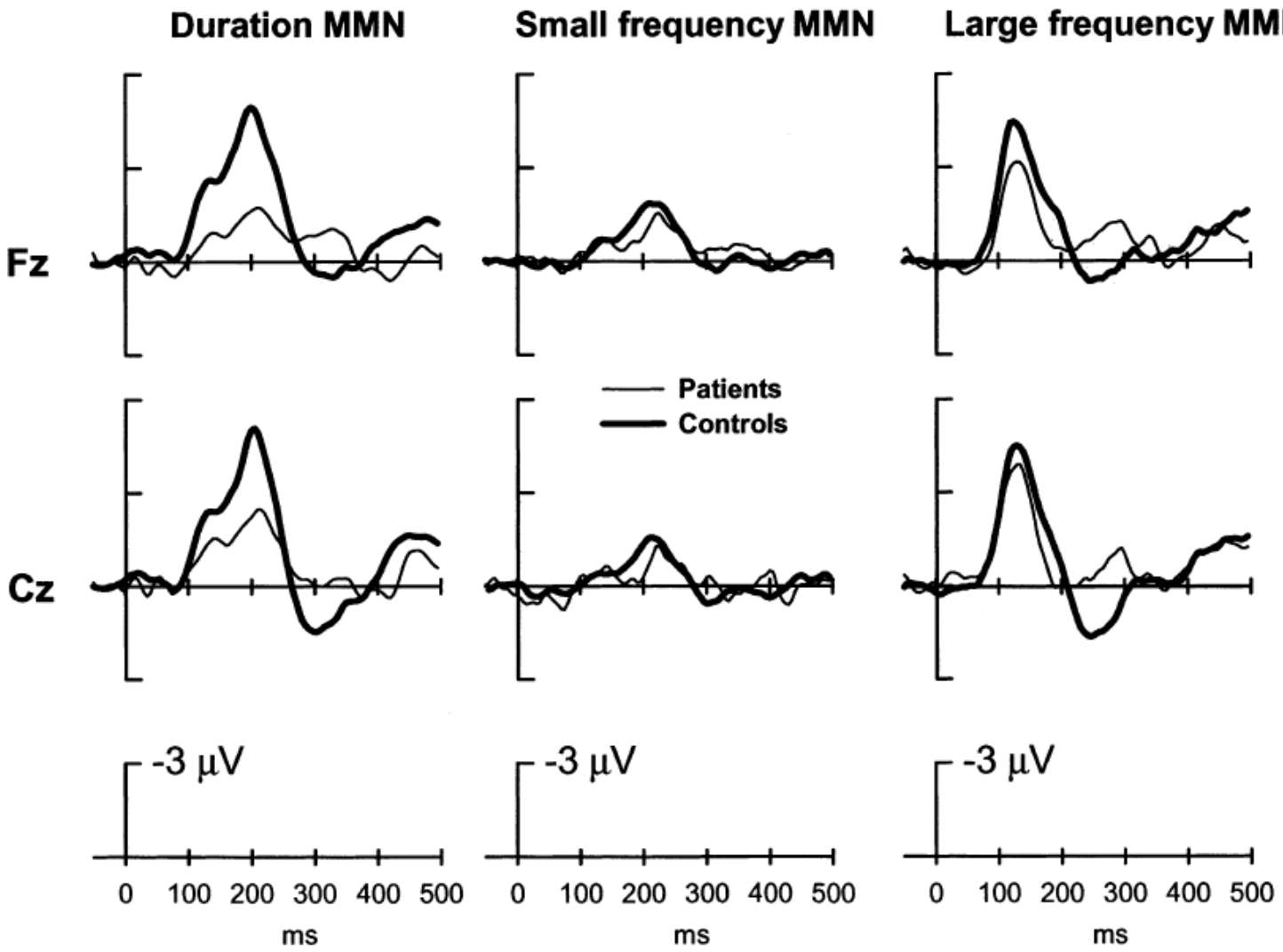
Reduced MMN in patients reported in 1991- not due to medication & specific to schizophrenia psychosis



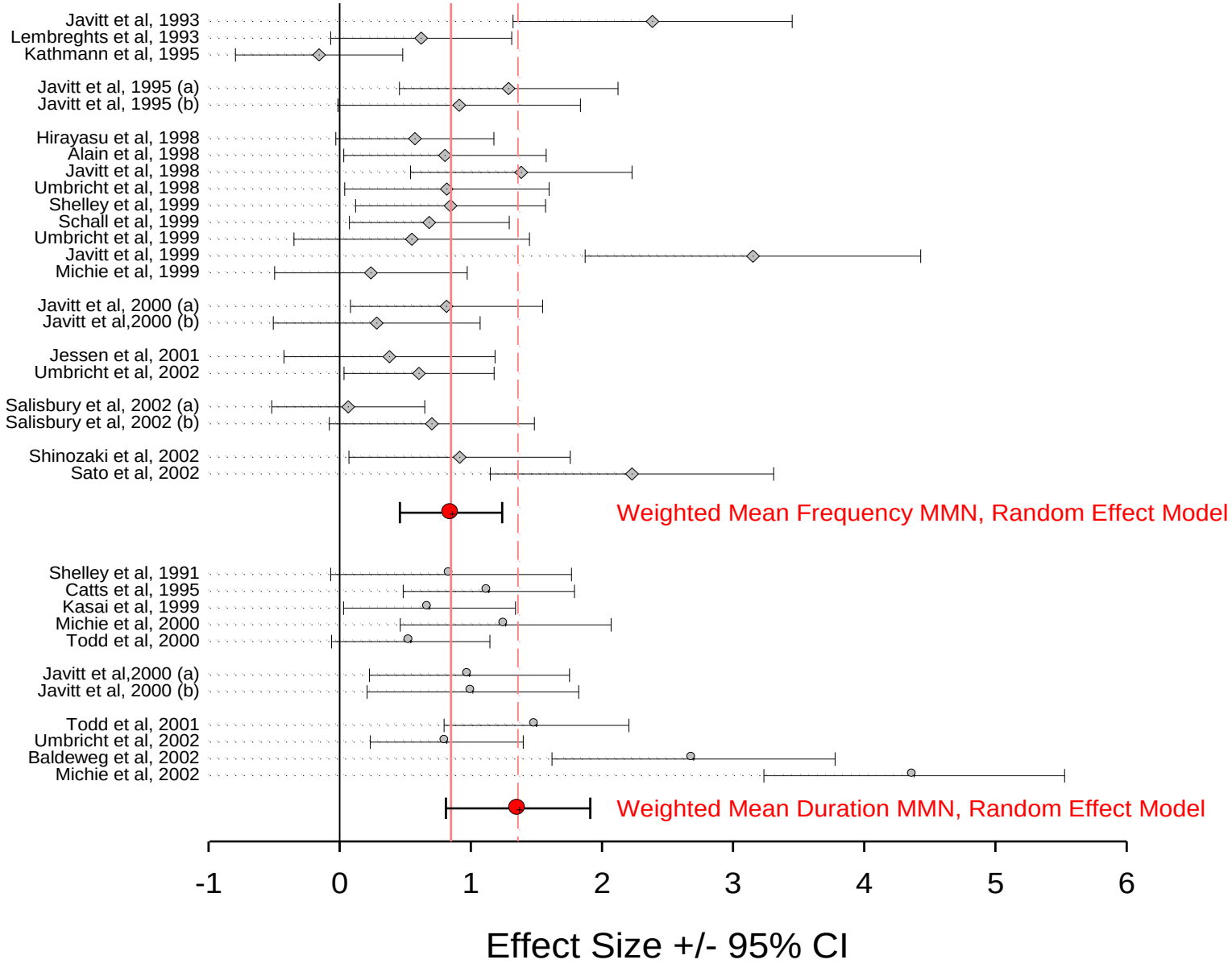
Shelley et al, 1991

Catts et al., 1995

MMN to duration deviants particularly affected

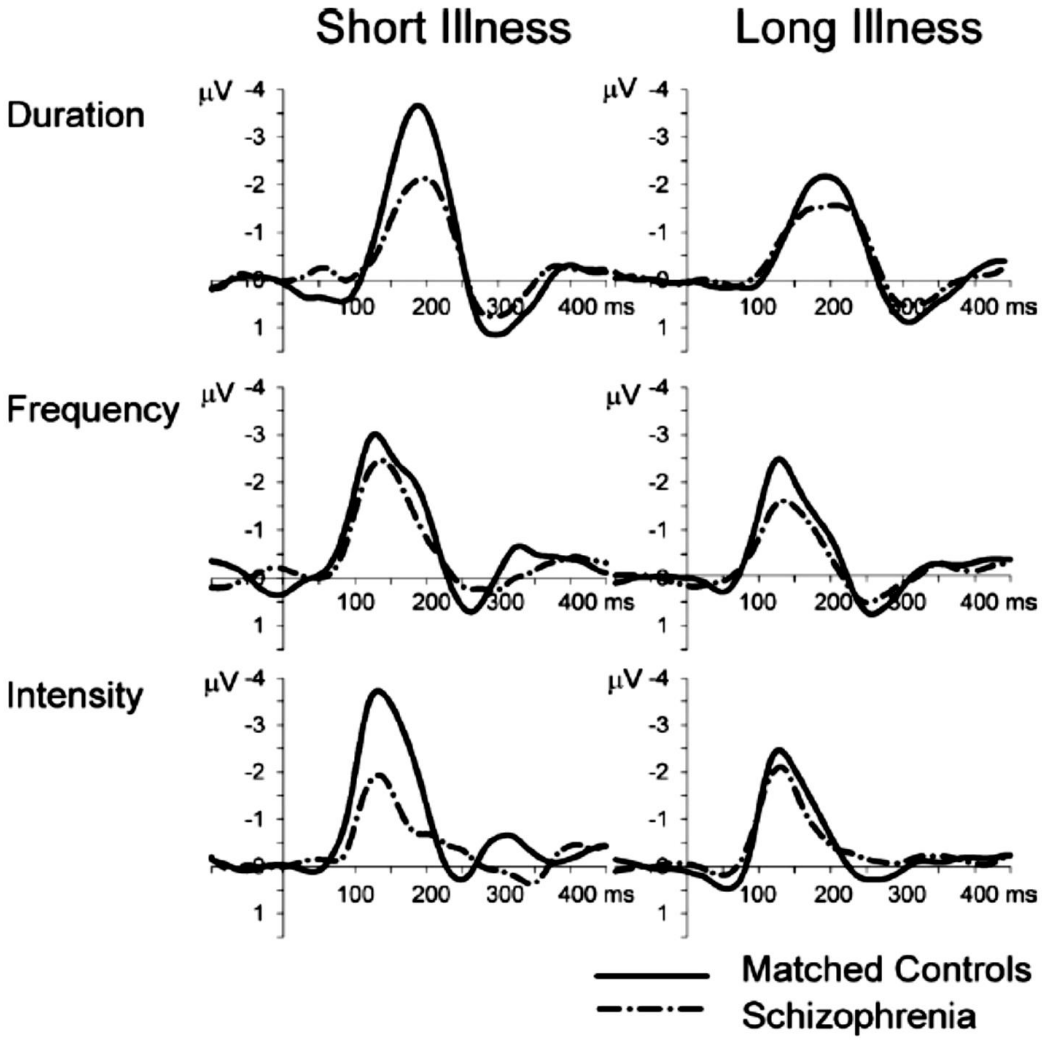


Michie et al., 2000

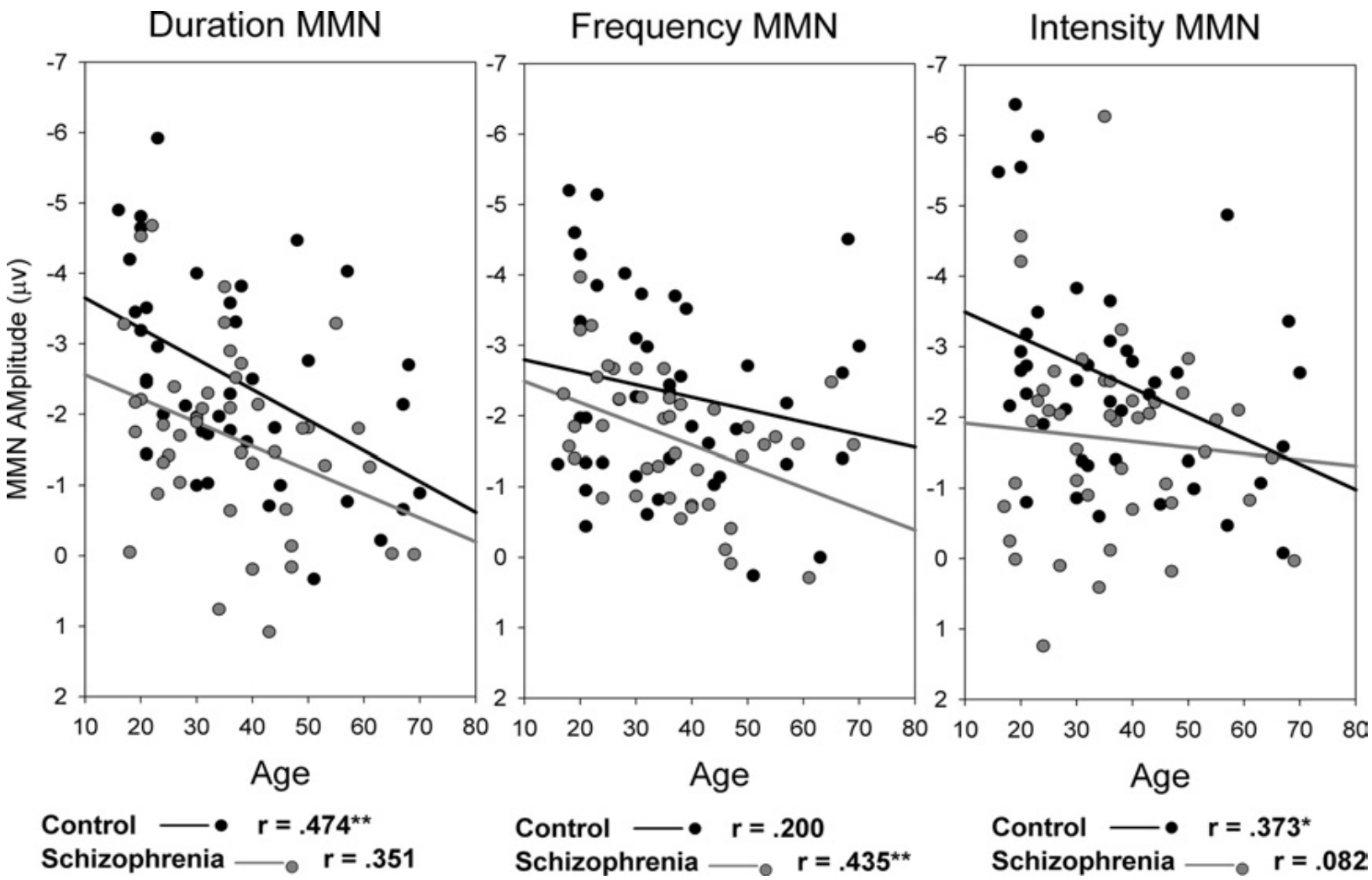


Krjles & Umbricht 2005

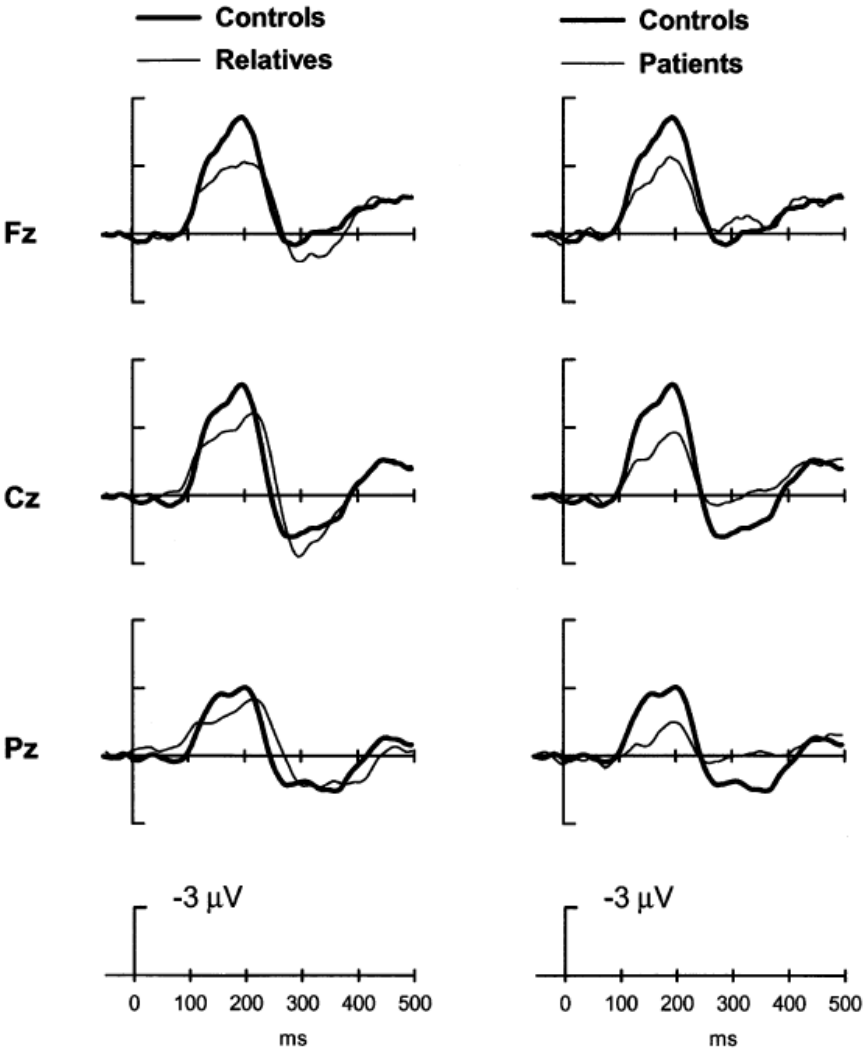
Duration MMN affected early in illness, frequency later in illness in those with an established illness



Todd et al., 2008

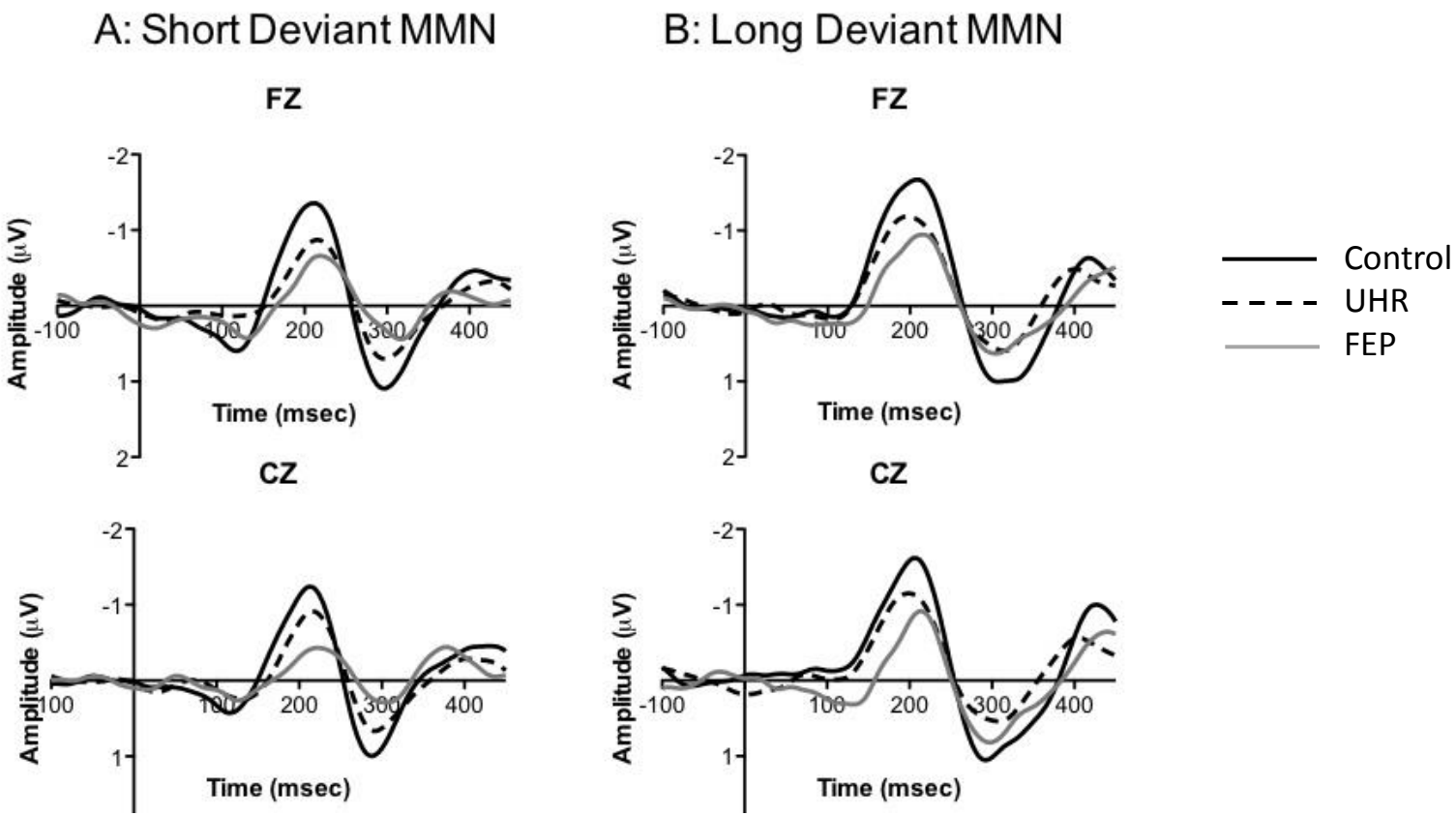

Duration MMN
Frequency MMN
Intensity MMN
MMN AMplitude (μv)
-7
-6
-5
-4
-3
-2
-1
0
1
2
10
20
30
40
50
60
70
80
Age
Control
Schizophrenia
r = .474**
r = .351
r = .200
r = .435**
r = .373*
r = .082

At-risk individuals: reduced duration MMN possibly also occurs in unaffected family members (relatives)



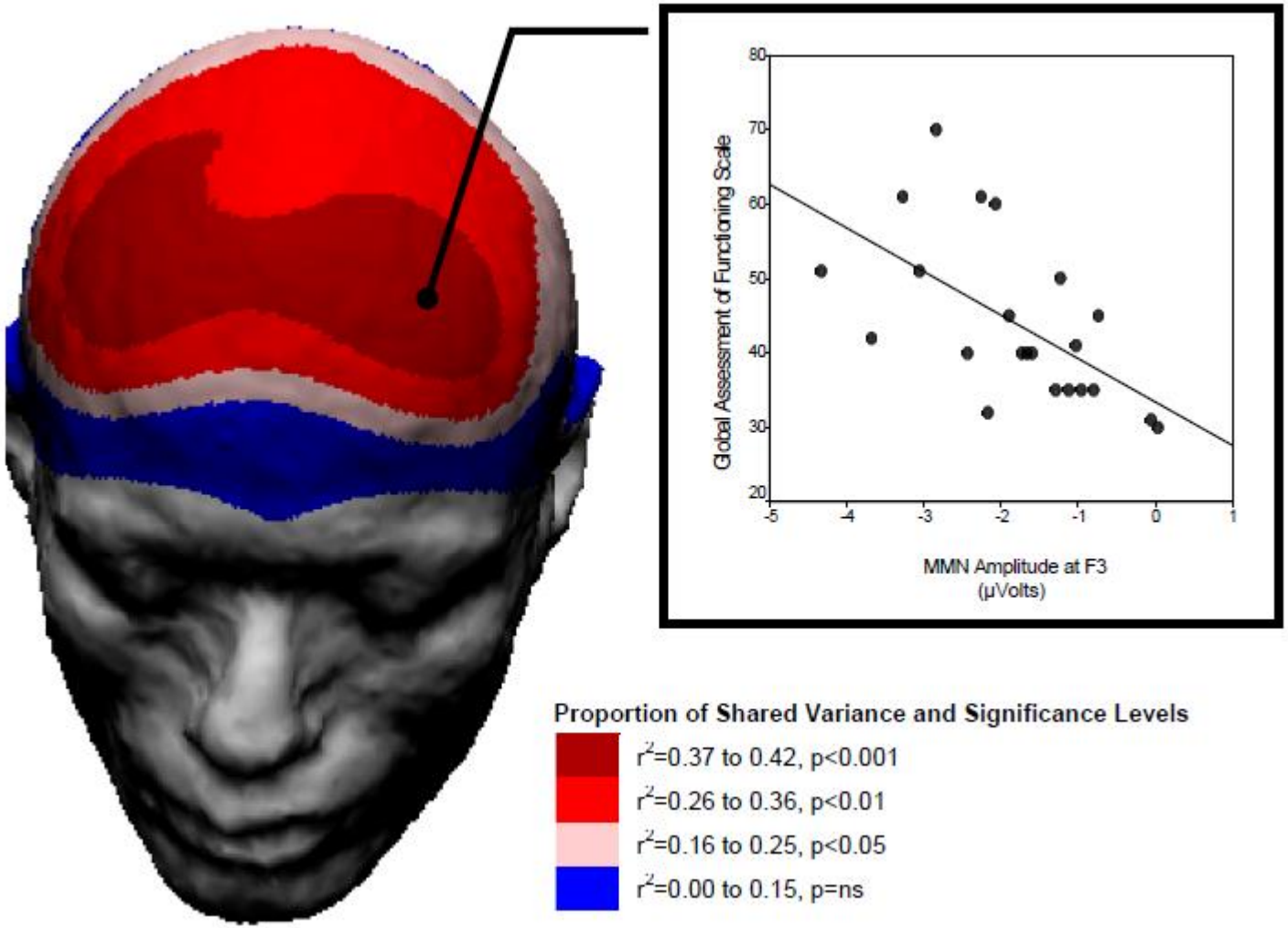
Michie et al., 2002

At-risk individuals: reduced duration MMN in help-seeking young people identified as at-risk (UHR) of developing schizophrenia

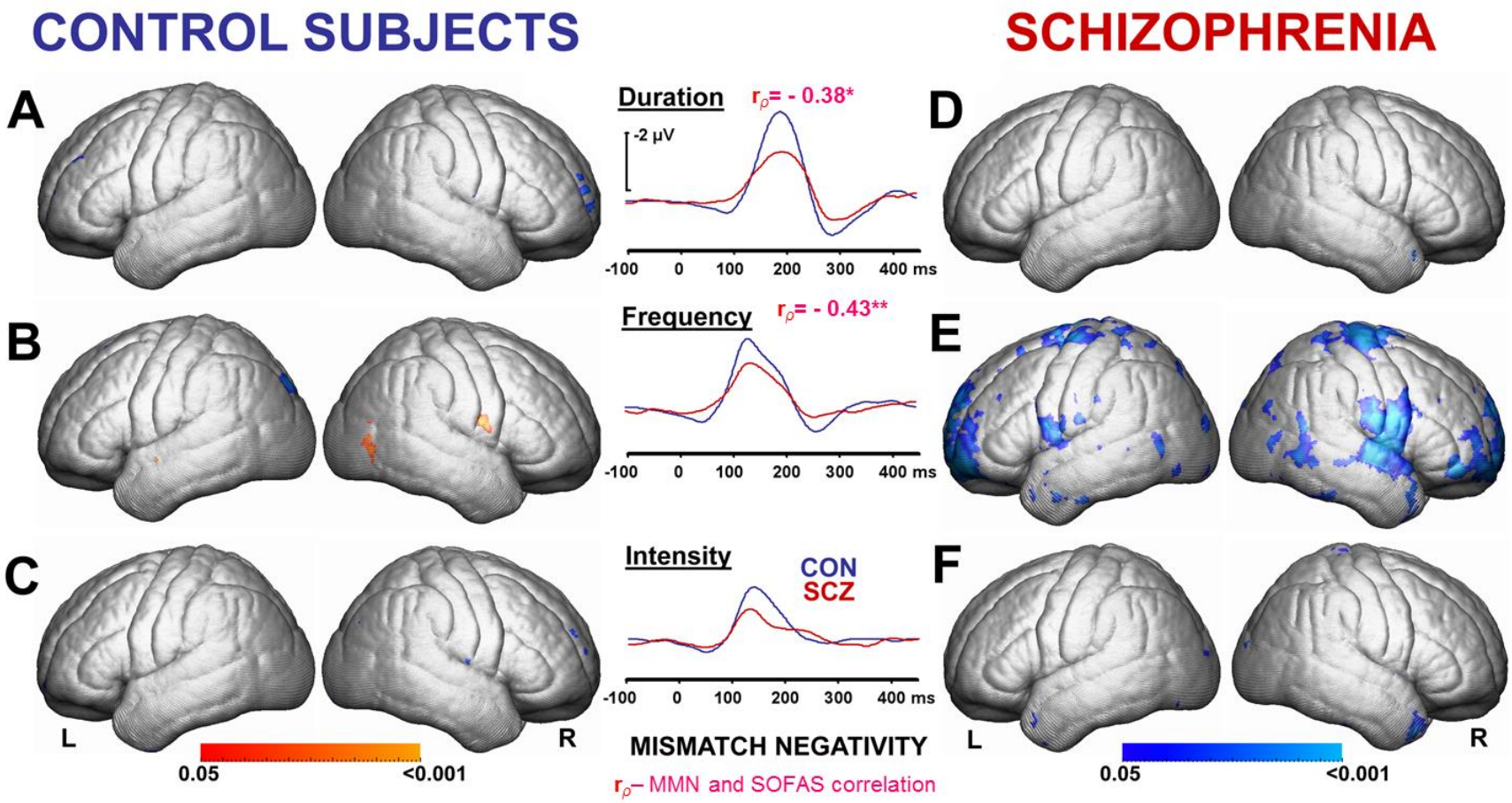


Atkinson et al., 2012
See also Bodatsch et al 2011

Reduced MMN correlates with low scores on Global Assessment of Function (GAF) scale But not symptom ratings Light & Braff 2005



MMN correlates with SOFAS and grey matter loss



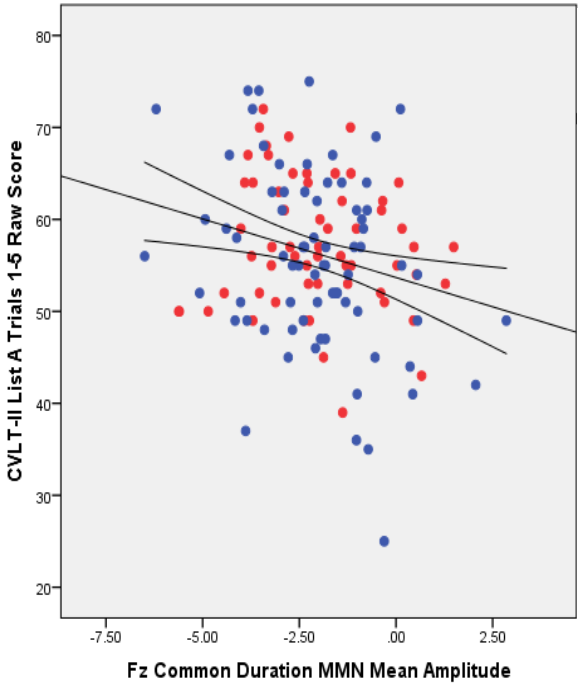
No correlation between grey matter loss & frequency MMN

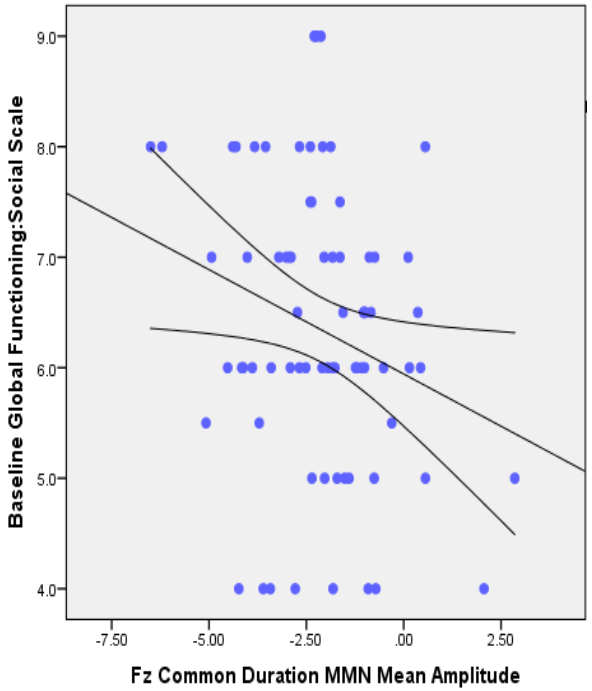
Correlation between grey matter loss & frequency MMN

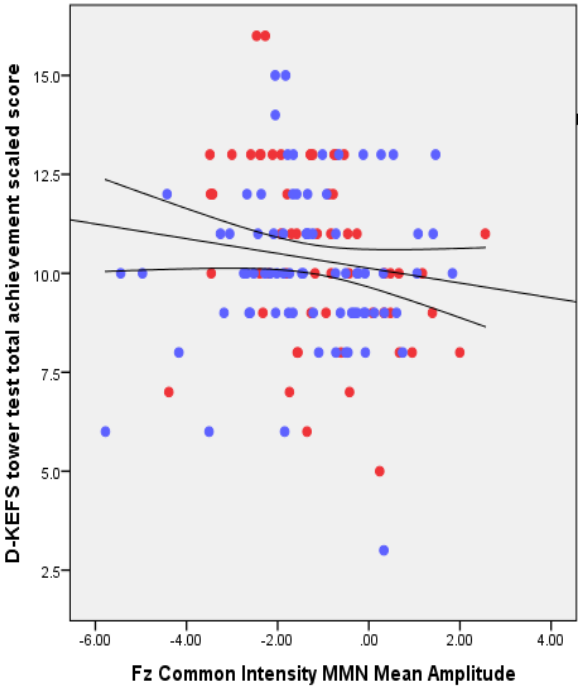
Rasser et al, 2011

Reduced MMN also correlates with cognitive deficits

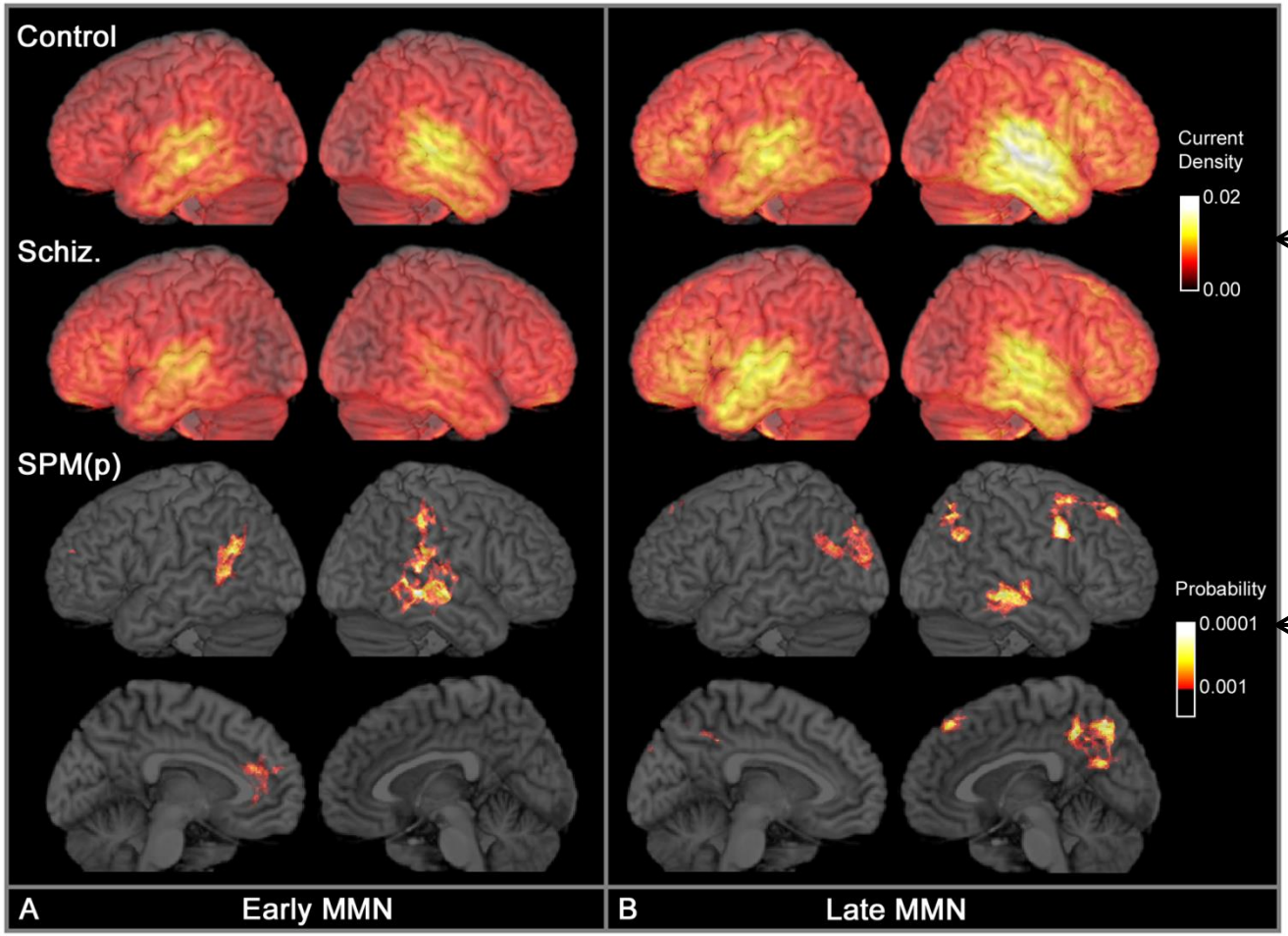
- Duration MMN correlates with verbal learning and executive functions in established illness (Kiang, et al 2007)
- And in those at risk – from MinT project (Atkinson et al 2013)







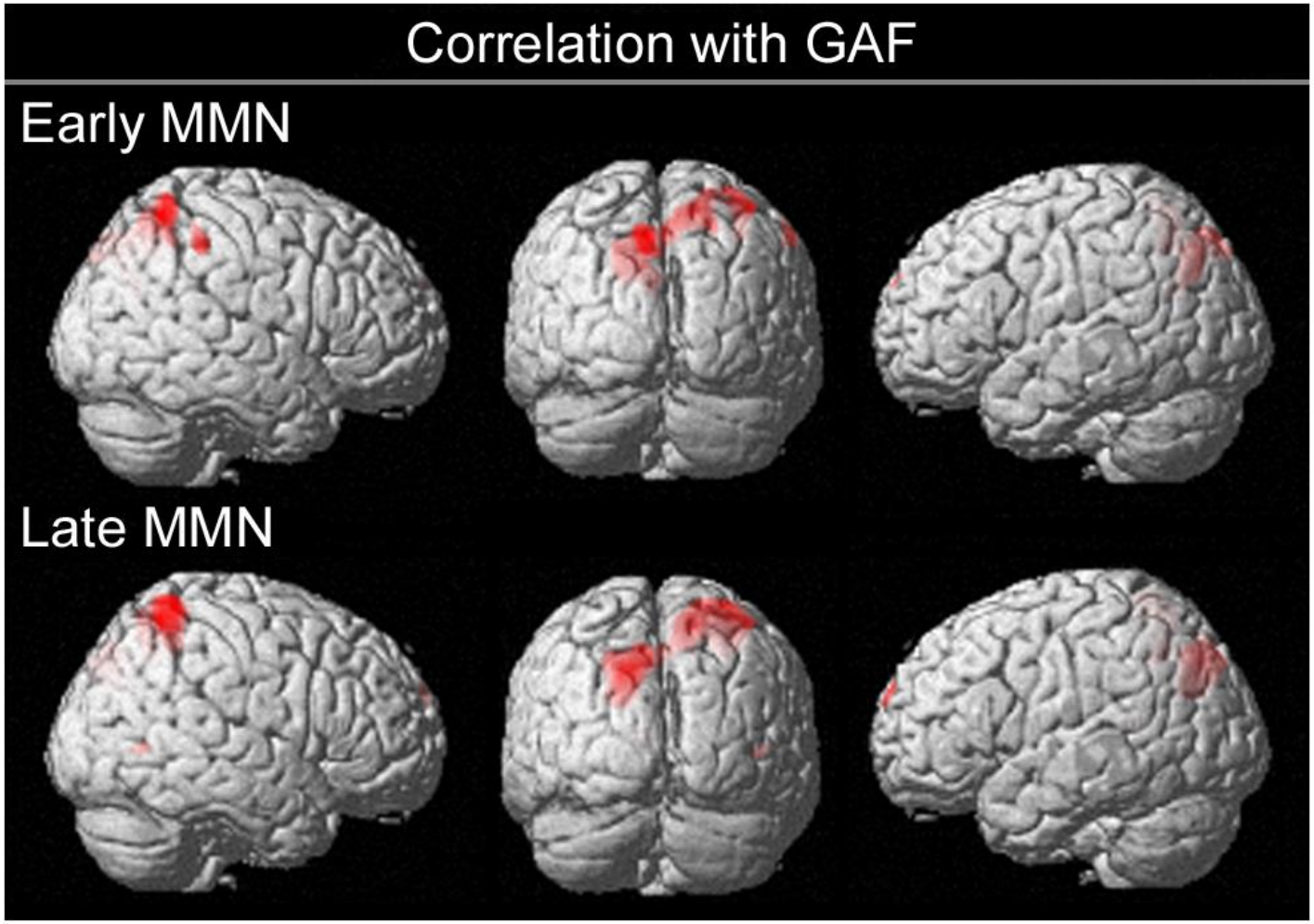
But we can do more with MMN: Comparison of CSD in controls and patients during Early MMN (110-160 ms), and Late MMN (160-210 ms). Fulham et al 2014



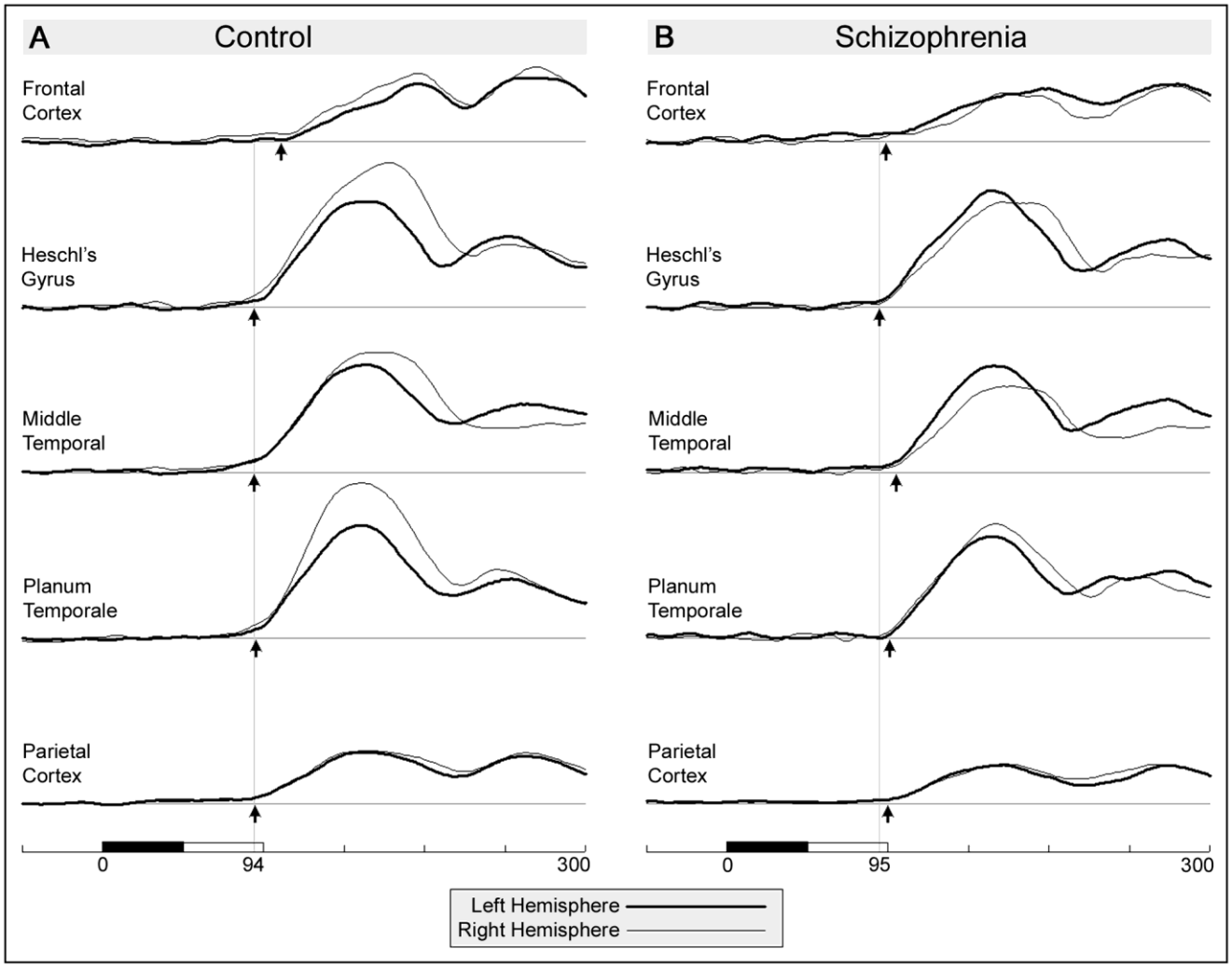
CSD magnitude

SPM of group differences (p < .001 uncorrected).

Correlation between GAF and CSD in schizophrenia patients - bilateral parietal cortex clusters for both early and late MMN intervals. SPM ($p < .001$ uncorrected).



Time course of CSD in five ROIs for control and schizophrenia groups



Controls: frontal response onsets 17 ms later than temporal and parietal response.

Patients: onset of MMN **d**elayed in secondary, but not primary AC, smaller amplitude in both primary and secondary AC particularly right hemisphere

What have we learnt so far from MMN:

- Reduced MMN in schizophrenia is very robust finding
- MMN reduced in at-risk groups (UHR individuals and possibly first degree relatives)
- Duration MMN reduced early in illness; frequency MMN over the course of illness
- Smaller MMN predicts transition to schizophrenia
- Smaller MMN correlates with poor global functioning, grey matter loss, and cognitive deficits.

Latency delays suggest

- relatively intact deviance detection at or below the level of the primary auditory cortex
- but impaired cortico-cortical or thalamo-cortical communication

Interpretation of these findings

Reduced MMN amplitude suggests a dysfunctional glutamate-NMDA receptor system may underpin cognitive deficits in patients.

Latency delays consistent with proposition that schizophrenia is a dysconnectivity disorder affecting grey and white matter at different scales

- Neurotransmitter and synaptic level
- White matter tracts and myelin dysfunction

Where to from here?

Mechanistic studies in animal models- how to proceed?

What we know:

- Reduced MMN amplitude in schizophrenia is one of the most robust neurobiological findings in the literature → endophenotype?
- Pharmacological studies - MMN provides an index of the integrity of NMDA-R system
- Consistent with models of pathophysiology of schizophrenia that focus on glutamate NMDAR hypofunction

Animal models would allow an investigation of NMDA related molecular and cellular mechanisms underpinning reduced MMN → new treatment targets

Mechanistic studies in animal models- how to proceed?

Hurdles before we can move into animal models:

- lack of consensus on whether MMN (or deviance detection more generally) occurs in rodents
- Selection of an animal model of schizophrenia that has
  - High construct, face & predictive validity
  - Demonstrated involvement of NMDAR system

Criteria for determining if "true" MMN and deviance detection occurs

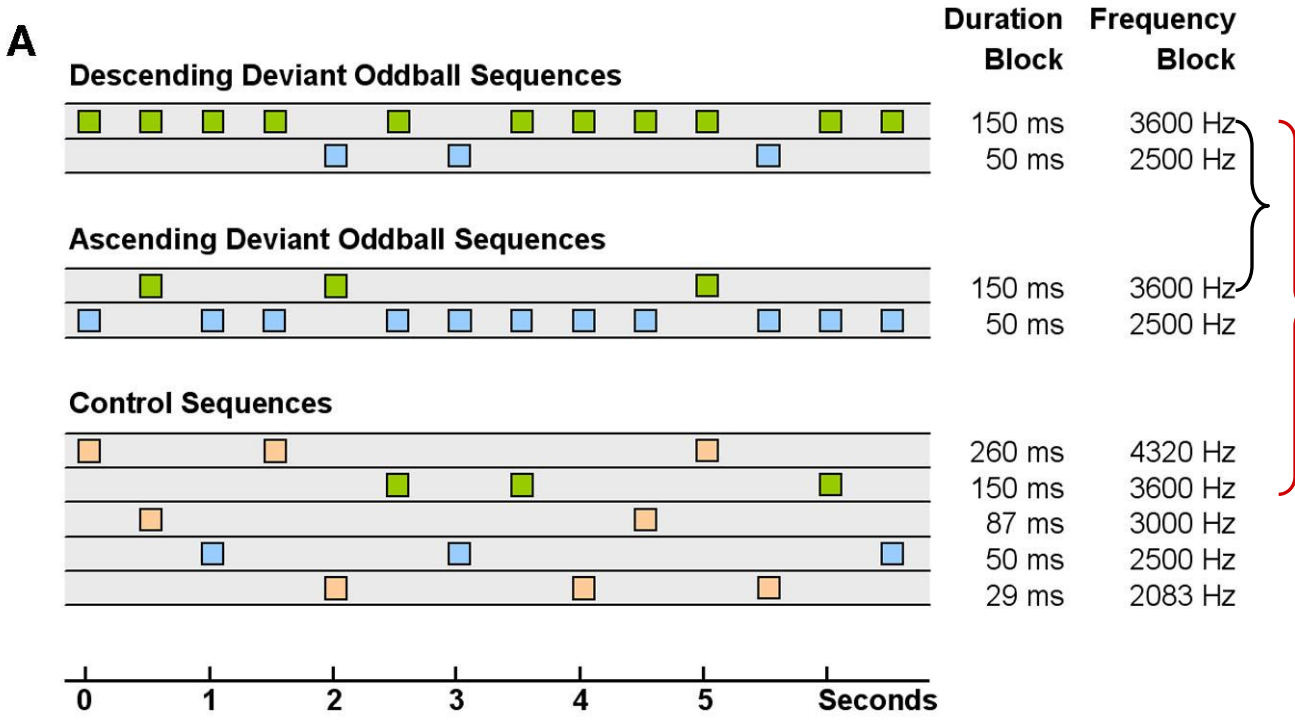
Deviant vs. standard difference:

- cannot be attributed to stimulus differences (between standard and deviant)
- not simply neuronal adaptation
- reflects a model-based-comparison process

A comparison condition that controls for adaptation differences

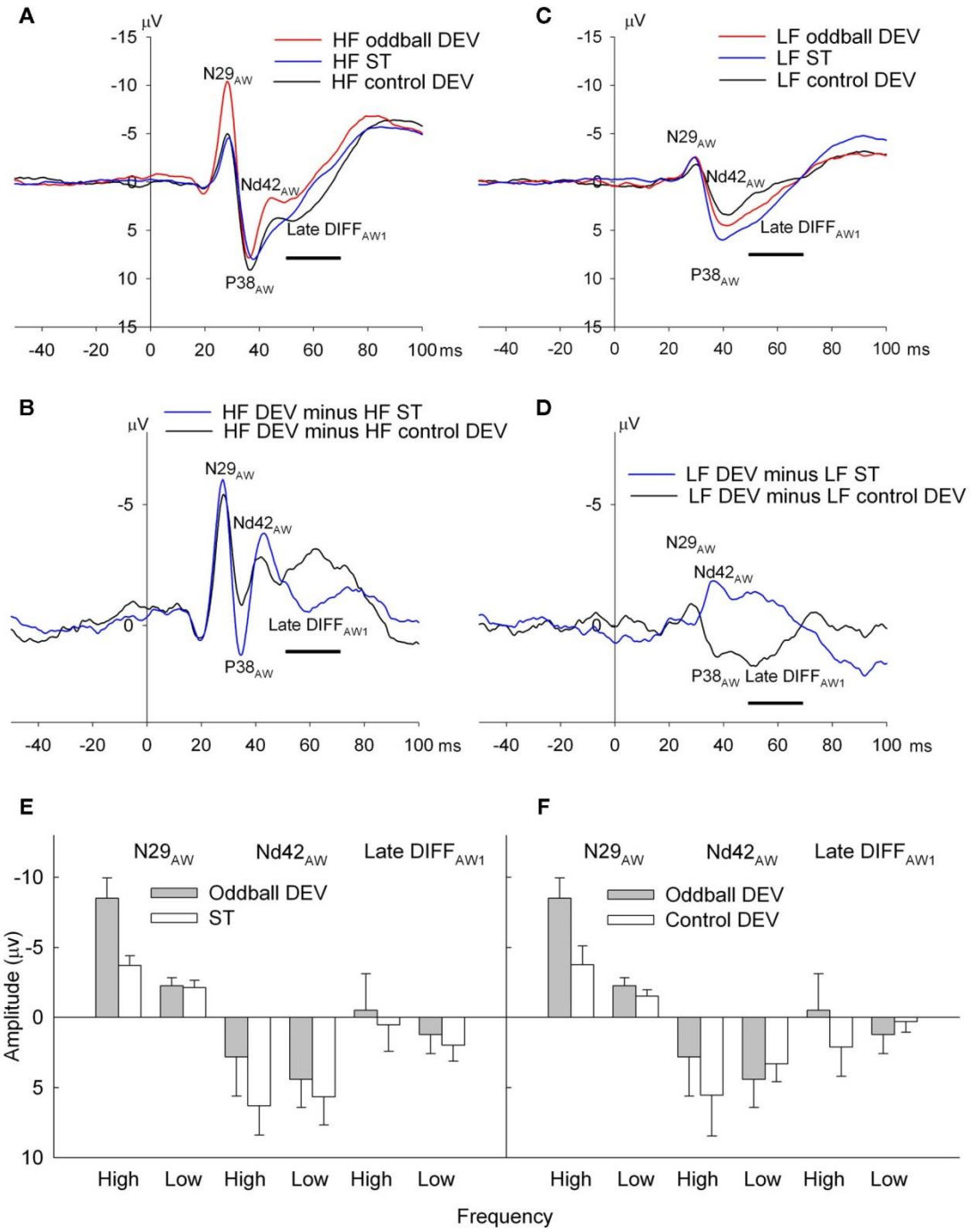
- where intervening sounds occur between deviant sounds but with no regularity that can be modelled

Nakamura et al. 2011 design.



Flip flop design: Allows control of stimulus attributes but not adaptation effects

Many standards control: allows control of stimulus attributes and adaptation, but with no regularity that can be modelled.



Deviance detection = Response to deviant – Response to control

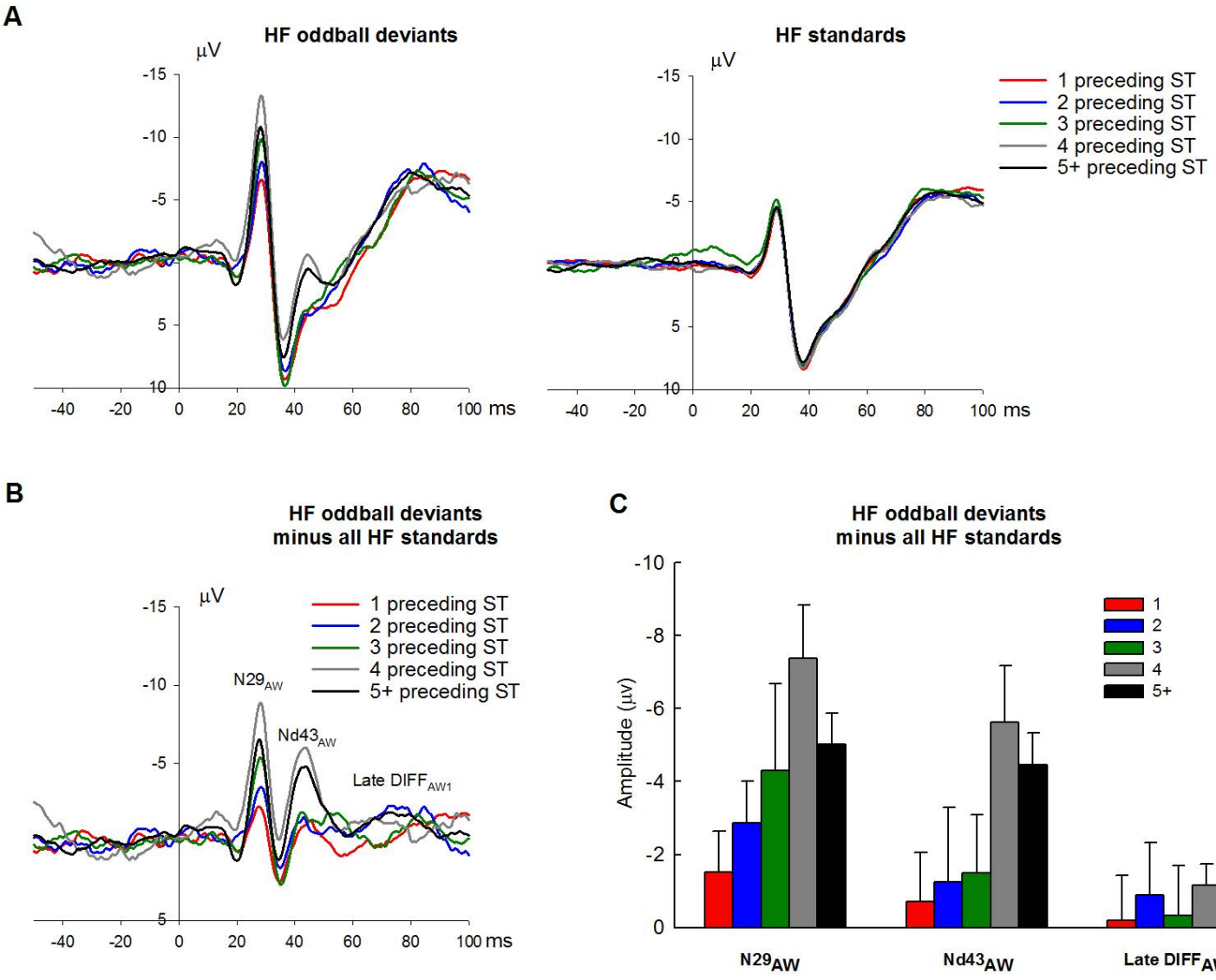
Nakamura et al 2011

Deviance detection effects on early and late components in awake rats:

All negative components

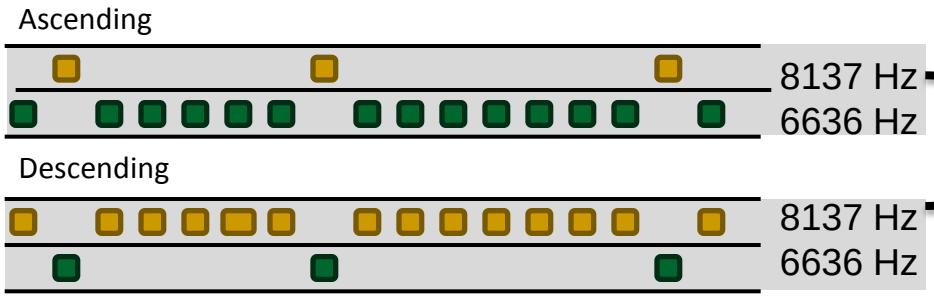
- N29
- Nd42
- Late Diff: 50 – 70 ms

But only for High Frequency (HF) stimuli.

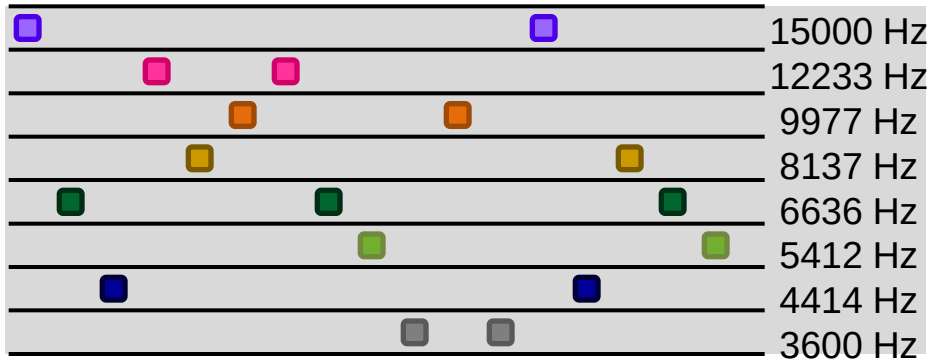

A
HF oddball deviants
HF standards
μV
-15
-10
-5
5
10
-40
-20
0
20
40
60
80
100 ms
1 preceding ST
2 preceding ST
3 preceding ST
4 preceding ST
5+ preceding ST
B
HF oddball deviants
minus all HF standards
N29AW
Nd43AW
Late DIFFAW1
C
HF oddball deviants
minus all HF standards
Amplitude (μv)
-10
-8
-6
-4
-2
0
1
2
3
4
5+
N29AW
Nd43AW
Late DIFFAW1

Harms et al. (in revision) design

Oddball Sequences – Flip-Flop Design



Control Sequence – Many-Standards Design

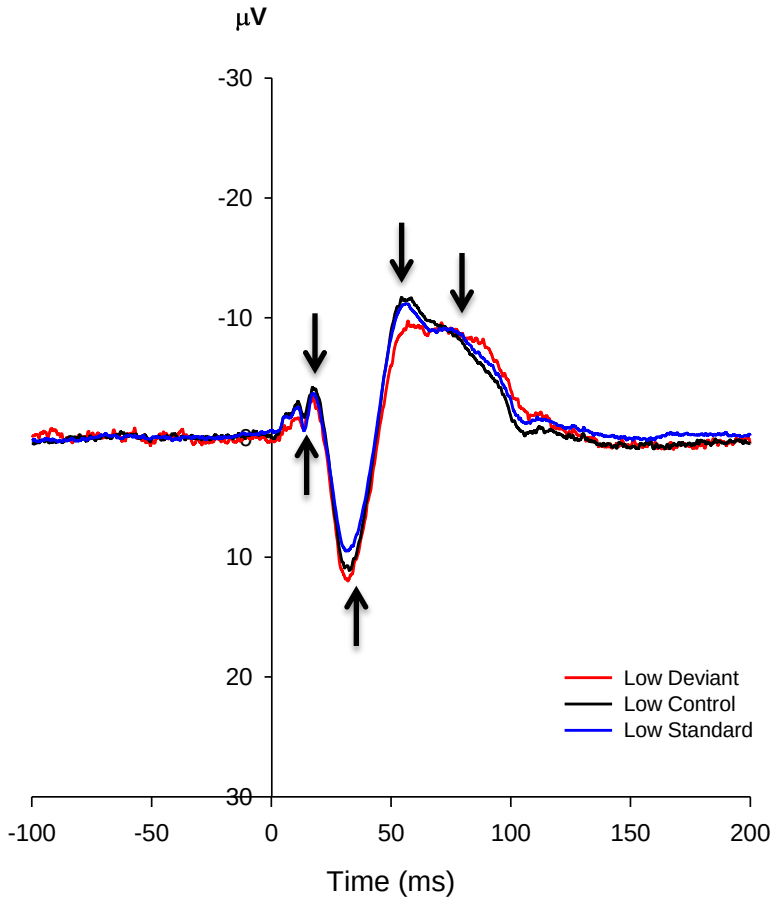


Changes to design

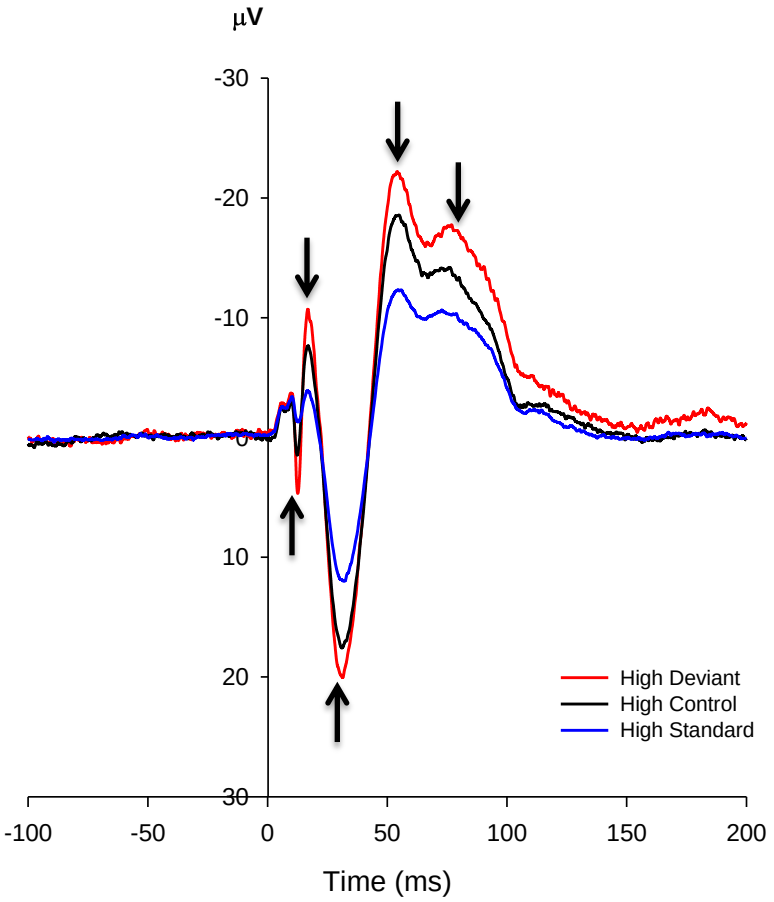
- Higher frequencies (Hz)
- Lower deviant probability 12.5%
- Minimum number of standards prior to each deviant was 3
- SOA unchanged

Skull screw electrodes as opposed to probe on dura.
5 recording sites.

Low frequencies

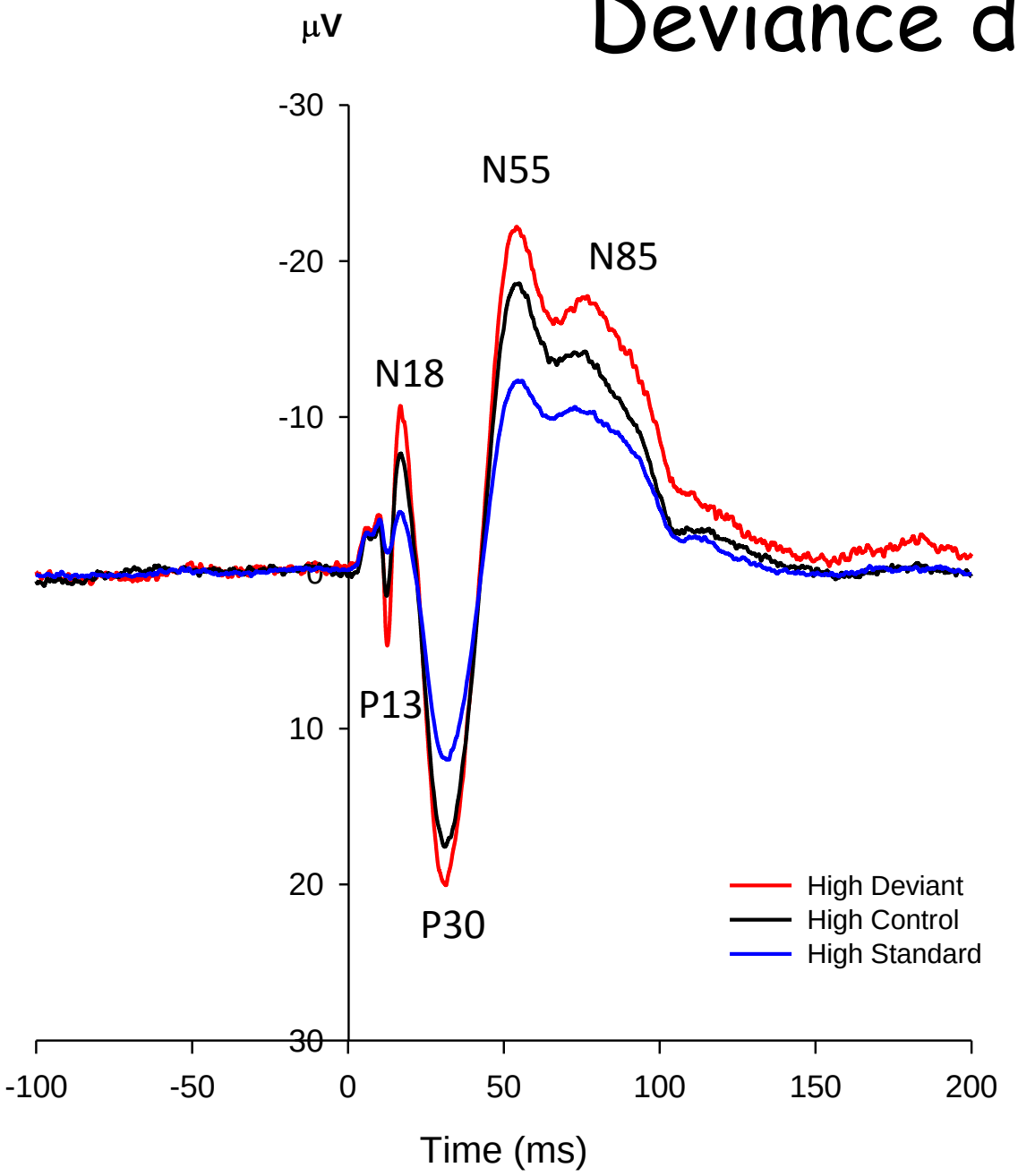


High Frequencies



P13: 11-15ms **N18:** 15-22ms **P30:** 22-43ms **N55:** 43.5-65.5ms **N85:** 65.5-105.5ms

Deviance detection



Deviance detection = Response to deviant – Response to control

Only HF deviants

- P13
- N18

Equivalent to MLR effects

- N55
- N85

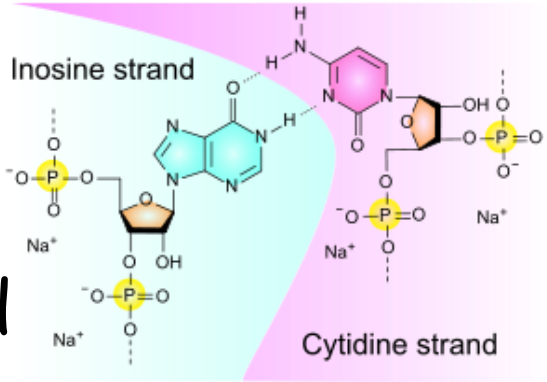
MMN-like

No effects on LF deviants

What animal model of schizophrenia?

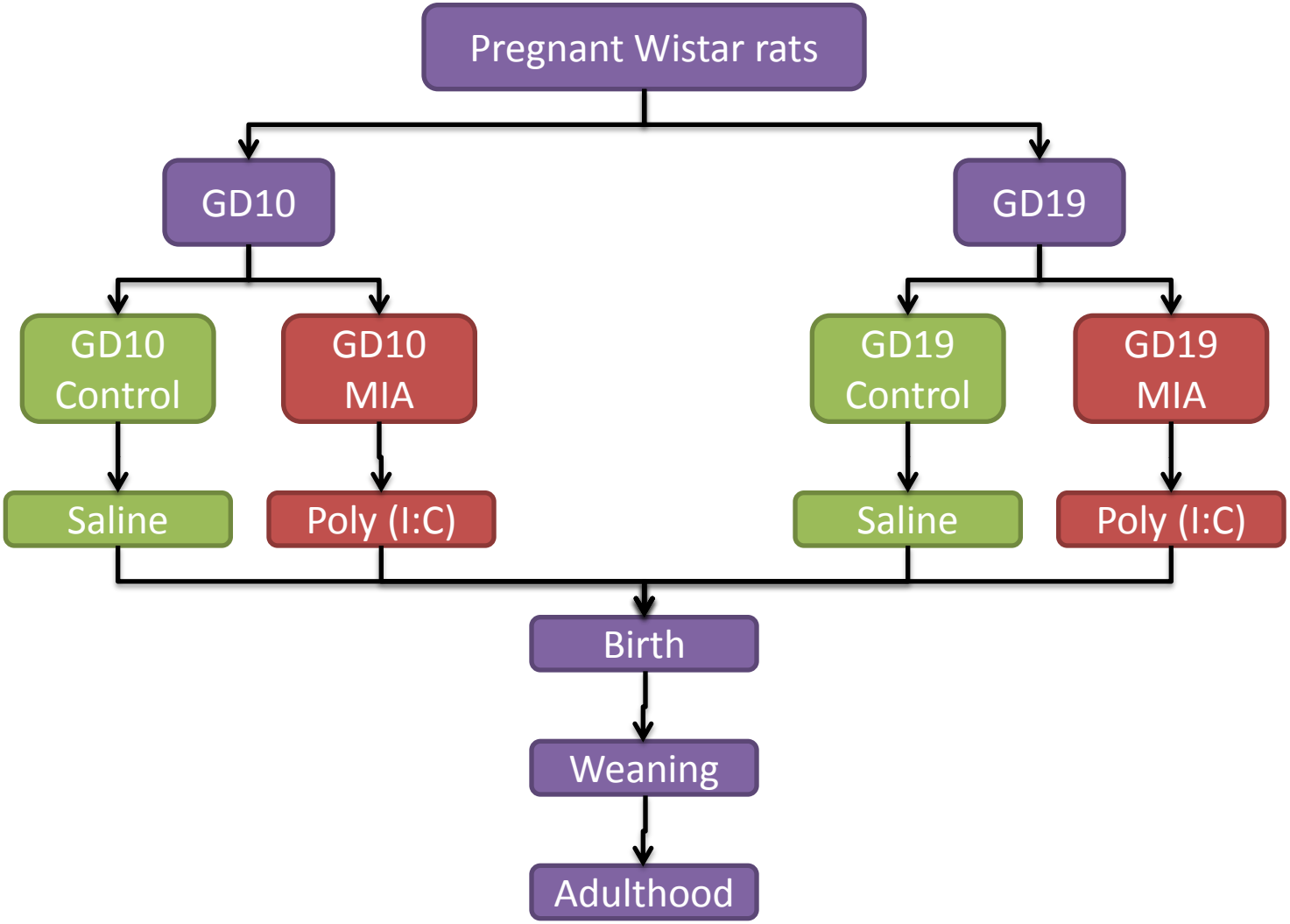
The Maternal Immune Activation (MIA) Animal Model

- Epidemiological findings: maternal infection during gestation associated with increased risk of schizophrenia
- Viral infections
- Viral mimic: Poly (I:C)



- Mouse model:
  - Early gestation (GD9) – dopamine?
  - Late gestation (GD17) – glutamate /NMDA/ GABA

Study Design

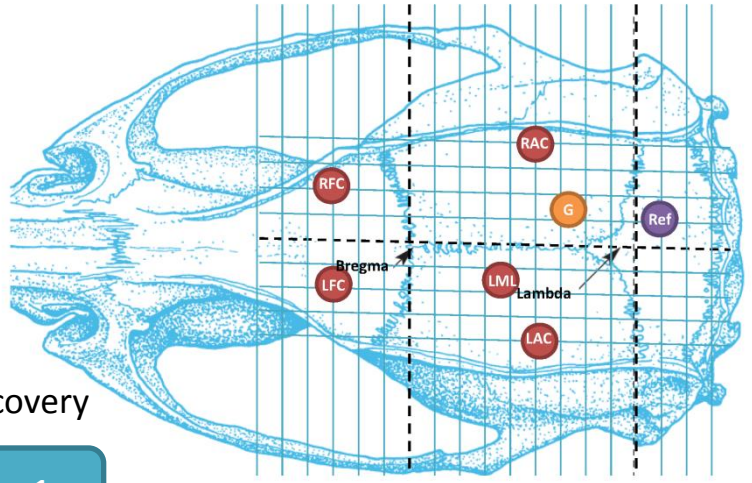


Study Design

Adulthood (12 weeks)

Surgery

1 week recovery



MMN baseline session 1

MMN baseline session 2

MMN baseline session 3

MK-801 session 1 (0.1mg/kg)

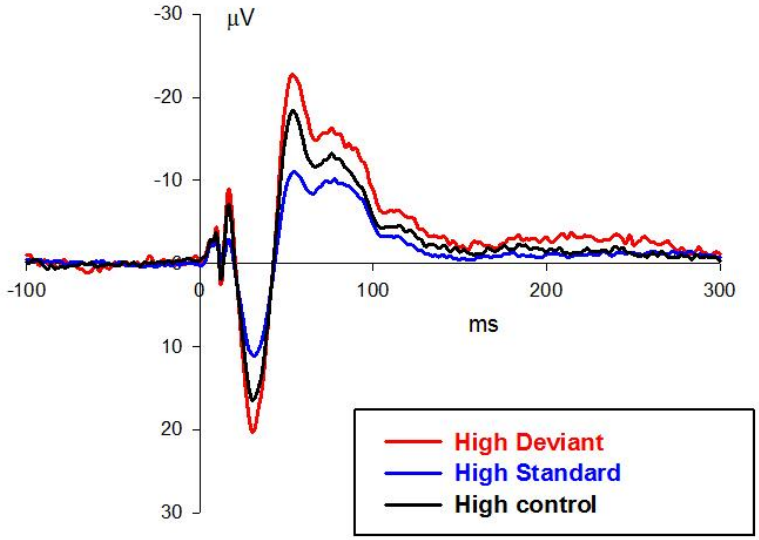
5 days washout

MK-801 session 1 (0.3mg/kg)

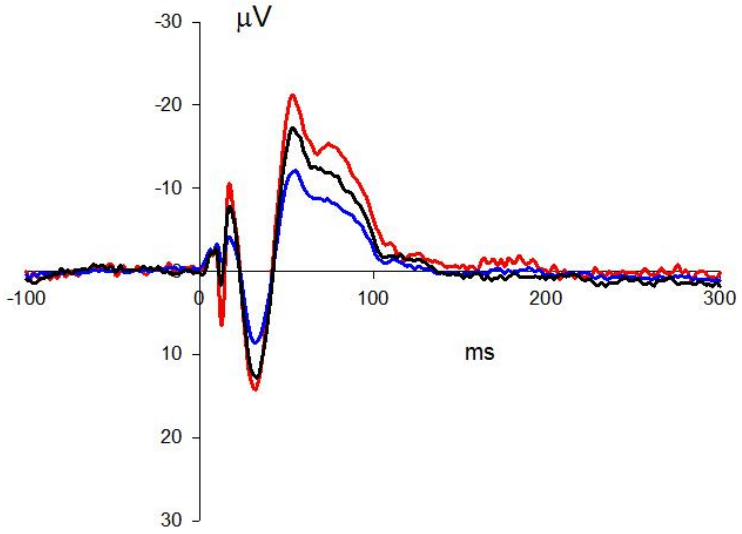
5 days washout

MK-801 session 1 (0.5mg/kg)

GD10_Control

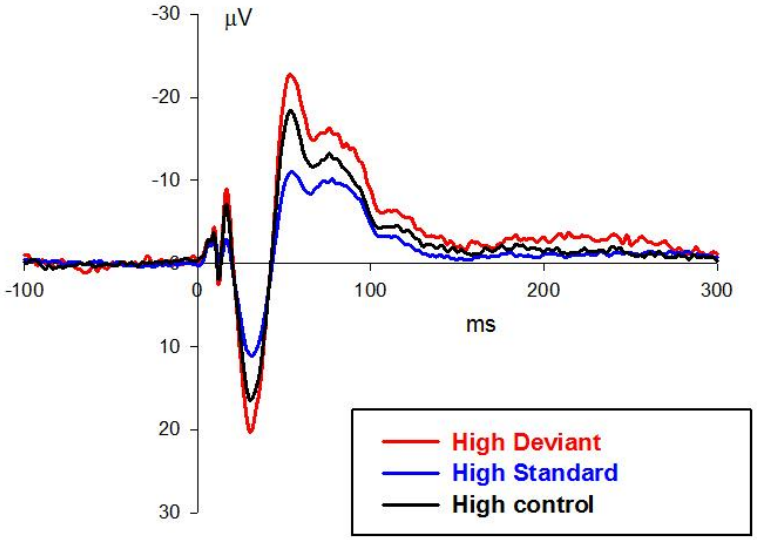


GD19_Control

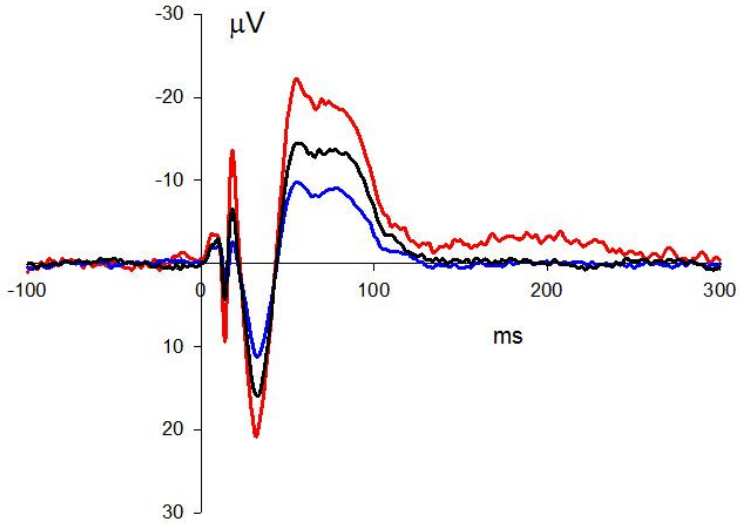


Left Frontal Cortex

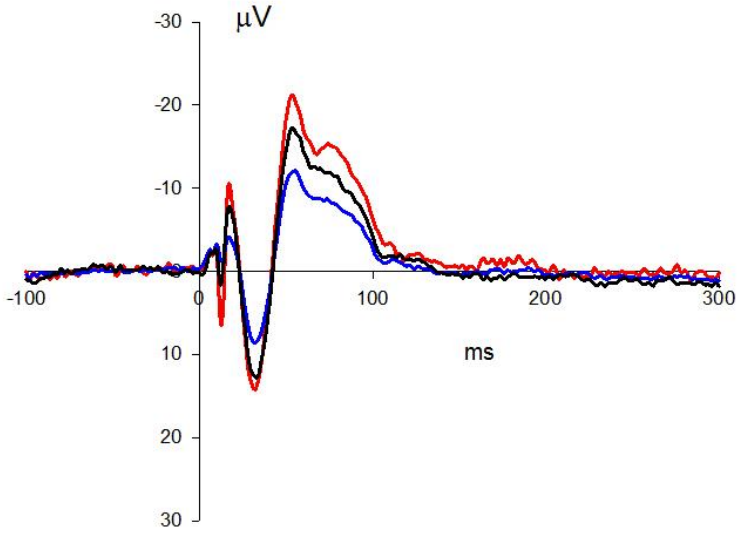
GD10_Control



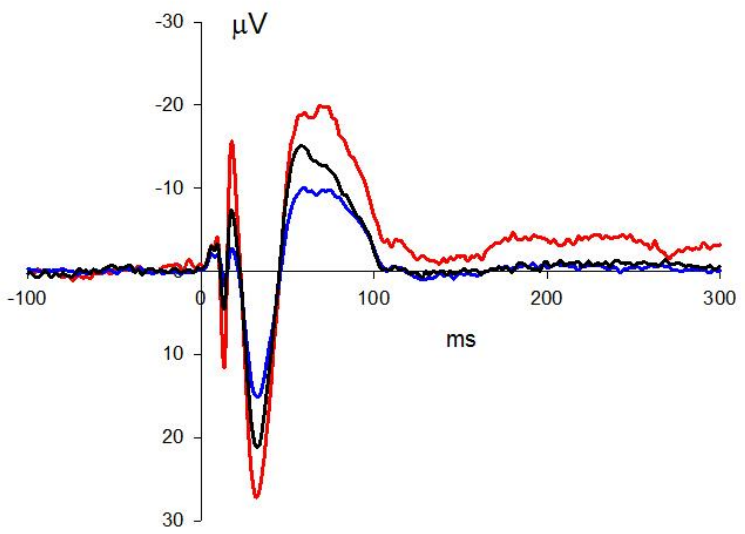
GD10_MIA



GD19_Control

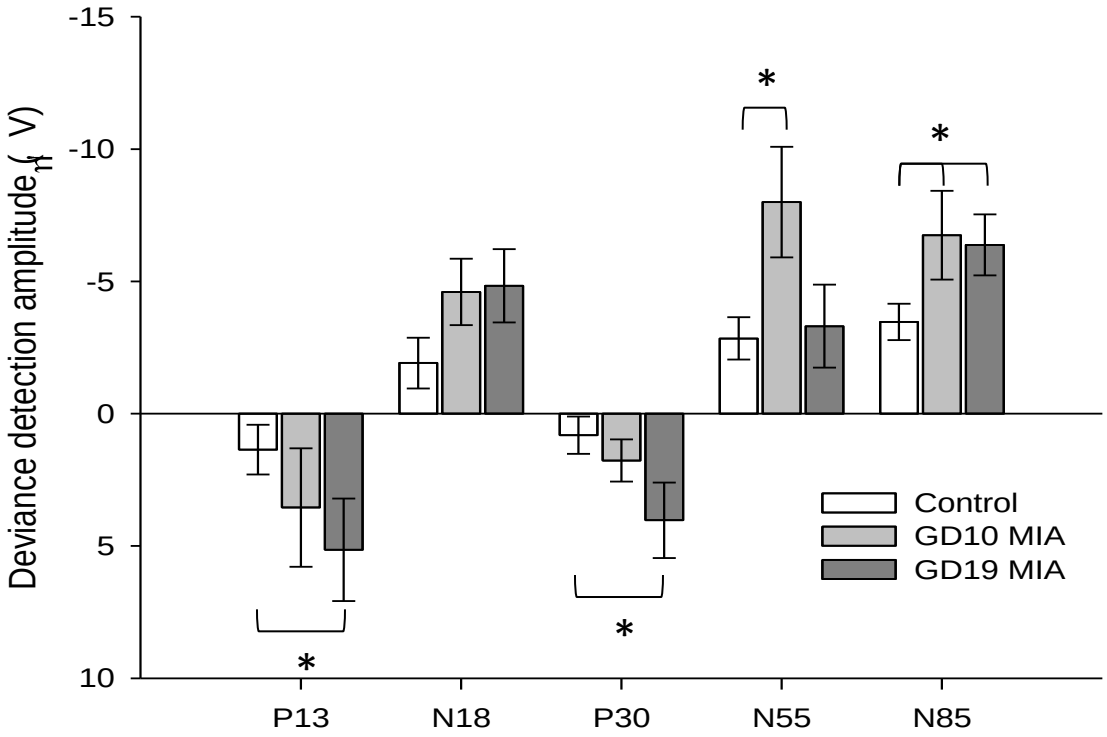


GD19_MIA



Left Frontal Cortex

Effect of MIA



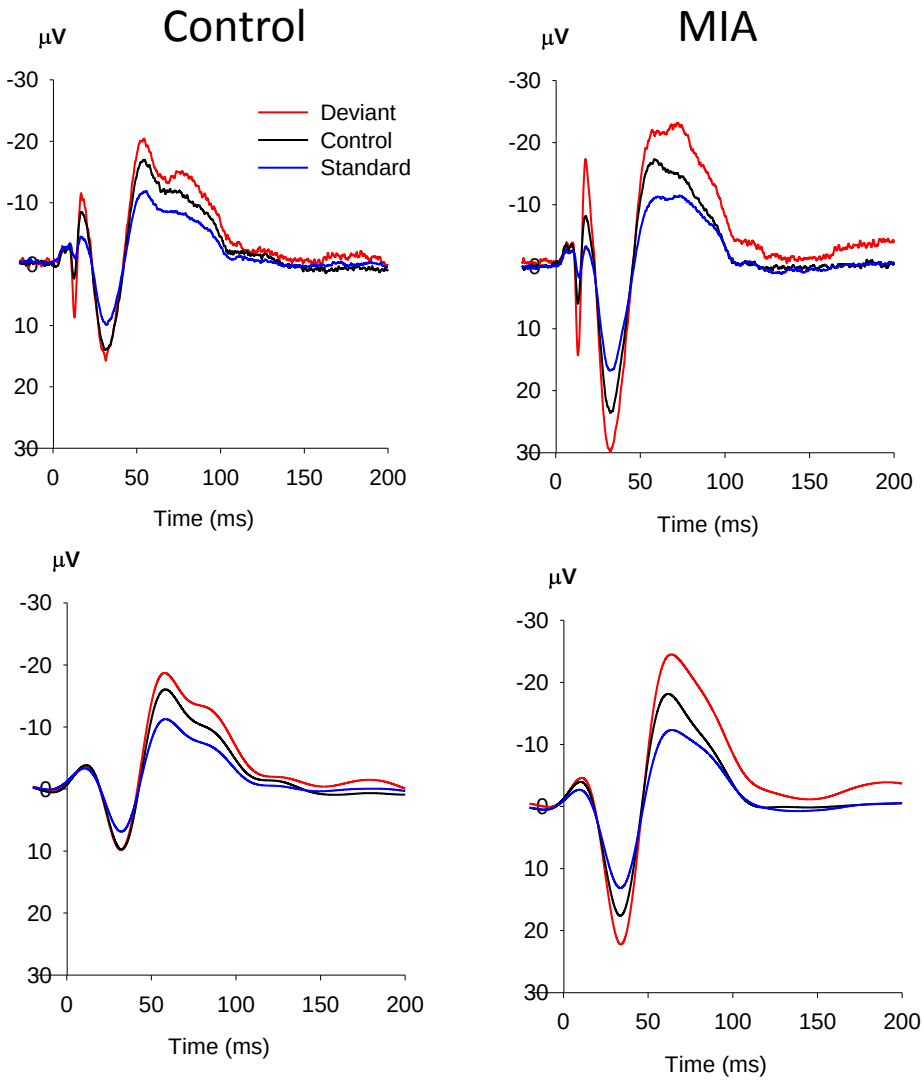
Effect of MIA on Deviance Detection:	
P13	Increased (GD19)
N18	No effect
P30	Increased (GD19)
N55	Increased (GD10)
N85	Increased (both)

Deviance detection = Response to deviant – Response to control

Early effects only evident with high low-pass filter

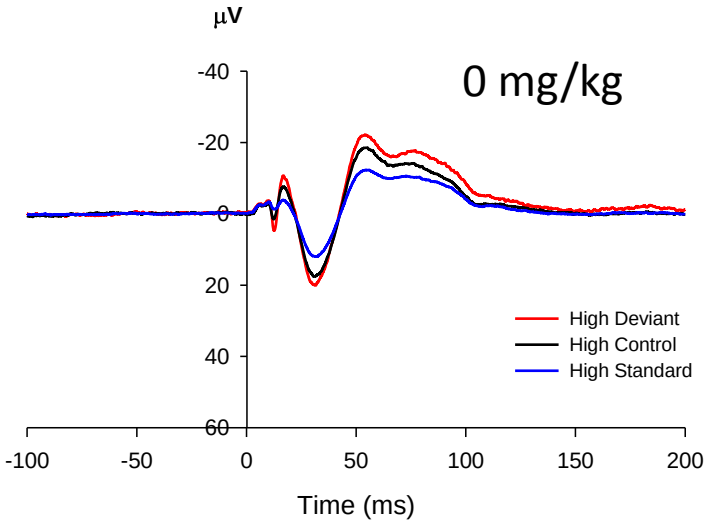
Unfiltered

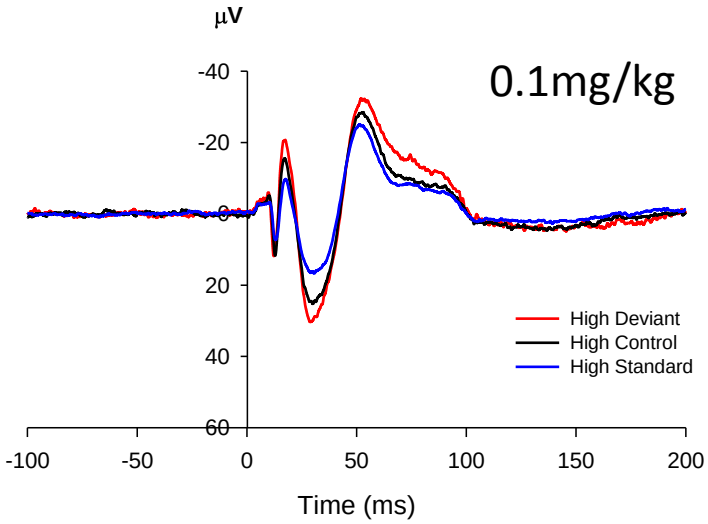
Low-pass 30Hz filter

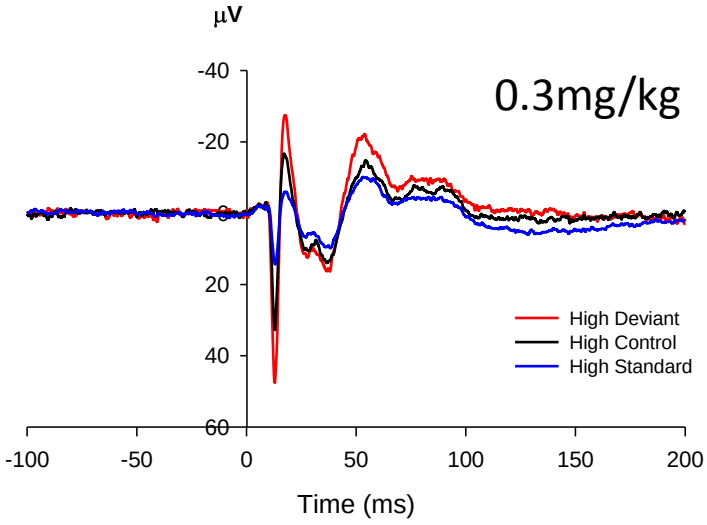


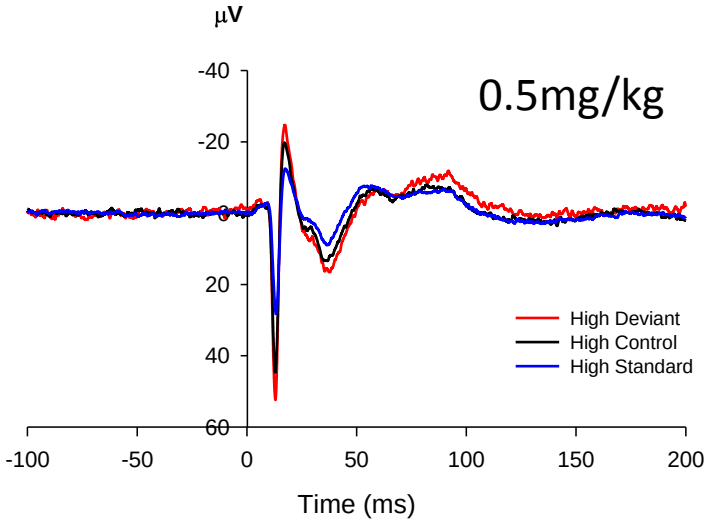
Effect of MK-801 (Controls)

MK-801 – NMDAR antagonist

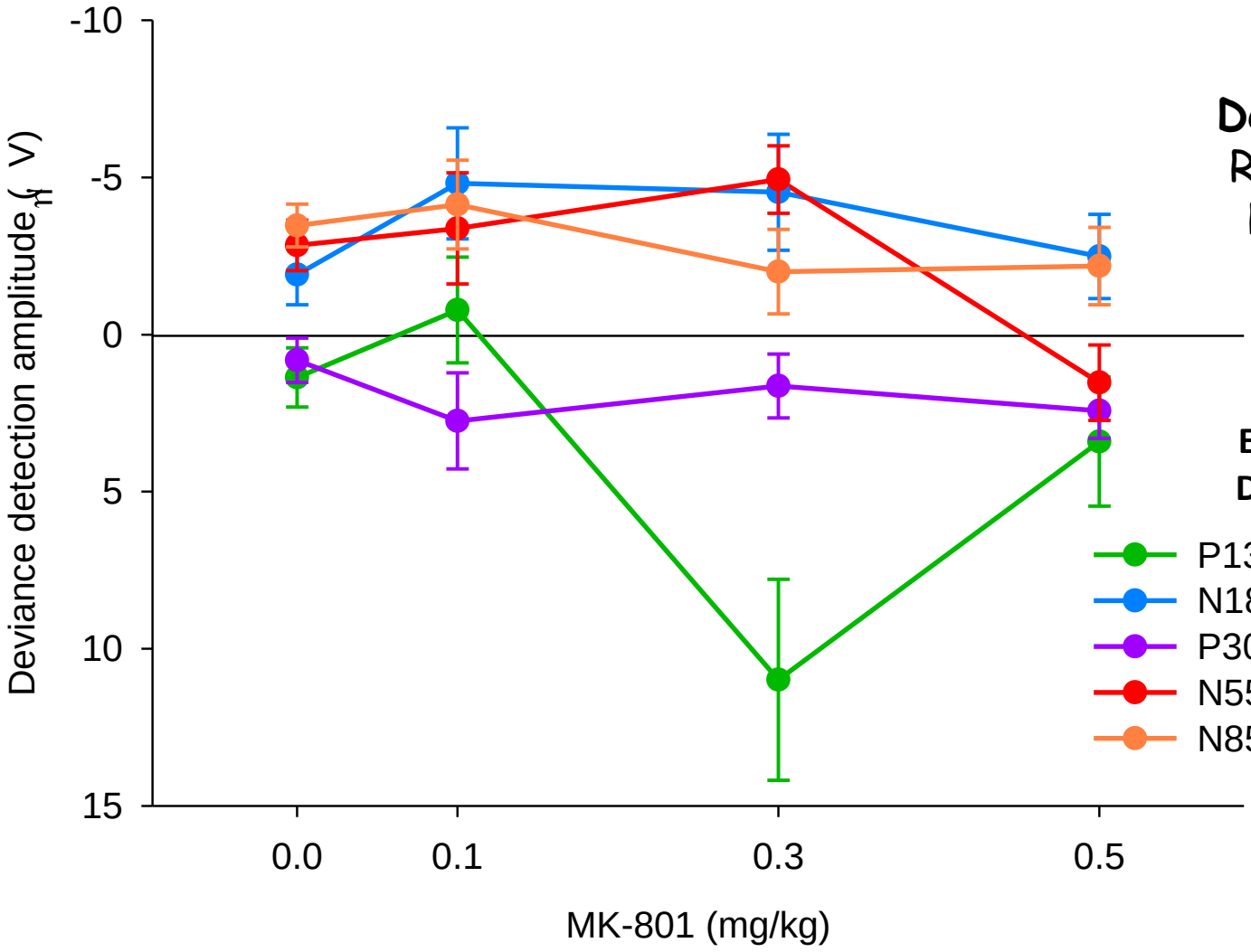








Effect of MK-801 (Controls)



Deviance detection = Response to deviant – Response to control

Effect of MK-801 on Deviance Detection:

P13	Increased (mid-range dose)
N18	Increased (low dose)
P30	Increased (low dose)
N55	Reduced (high dose)
N85	Reduced (high dose)

Summary - Effects of MIA and MK-801 on Deviance detection

Deviance detection					
	Effect of MIA		Effect of MK-801		Effect of MIA x MK-801
P13	↑ (GD19)	P13	↑ (mid-dose)	P13	MIA ↑ effect of MK-801
N18		N18	↑ (low dose)	N18	
P30	↑ (GD19)	P30	↑ (low dose)	P30	
N55	↑ (GD10)	N55	↓ (high dose)	N55	
N85	↑ (both)	N85	↓ (high dose)	N85	MK801 ↓ effect of MIA

In summary:

YES – the rodent brain does produce MMN-like responses!

- Evidence of both early and late deviance detection effects in awake unrestrained rodents
- Possible equivalents to MLR and MMN deviance detection in humans
- In awake animal, late deviance detection effect is a slow negativity → MMN-like
- In anaesthetised animals – the late effect is reversed in polarity (positive) and no early effects

Summary

- MMN-like (late) component is not reduced in the MIA animal model of schizophrenia but is reduced by high doses of NMDAR antagonist
- Deviance detection at both early and late latencies is increased by both MIA and low-mid range dose of NMDAR antagonist
- MIA perturbs inhibitory/excitatory balance →disinhibition effect on early and late components
- May need to add a second hit (eg chronic stressor in adolescence) for full effect of MIA to be expressed

Has the move into animal models got us any closer to being able to examine the molecular and cellular basis of reduced MMN in schizophrenia?

Has the move into animal models got us any closer to being able to examine the molecular and cellular basis of reduced MMN in schizophrenia?

Still a work-in-progress - Ongoing:
Behavioural and cognitive phenotyping
Oscillatory activity
Glutamate receptor densities and expression in brain tissue

WATCH THIS SPACE!

Acknowledgements

Funding sources for animal models:

University of Newcastle – Near Miss Grant
PRC in Translational Neuroscience and Mental Health
Schizophrenia Research Institute (SRI)
Hunter Medical Research Institute (HMRI)
NHMRC project grant: APP102607

Faculty of Science & IT 2012 Visiting Fellow award to Dr. Markku Penttonen.

Rodent project

Lauren Harms
Tamo Nakamura
Deborah Hodgson
Ross Fulham
Aaron Wong
Juanita Todd
Ulrich Schall
Crystal Meehan
Katerina Zavitsanou
Cyndi Shannon Weickert

MinT project

Ulrich Schall
Rebbekah Atkinson
Philip Ward
Juanita Todd
Paul Rasser
Tim Ehlkes
Helen Stain
Tom Weickert
Robyn Langdon

Schizophrenia projects

Sydney

Philip Ward
Stan Catts
Neil McConaghy
Sally Andrews
Anne-Marie Shelley
Alison Fox

Perth

Assen Jablensky
Bill Budd
Juanita Todd
Hamish Innes-Brown
Jo Badcock
Greg Price

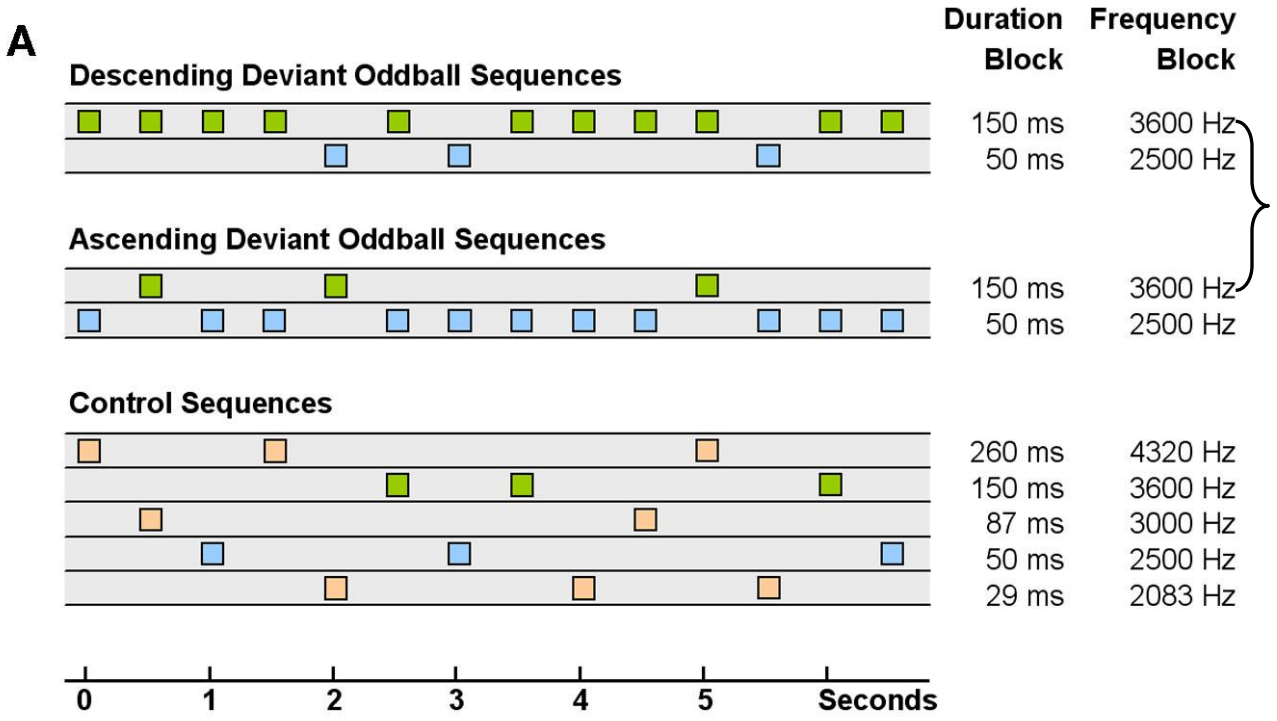
Newcastle

Ulrich Schall
Juanita Todd
Ross Fulham
Paul Rasser
Gavin Cooper
Natasha Matthews
Frini Karayanidis
Patrick Johnston

International

Markku Penttonen
Risto Naatanen
Hirooke Yabe

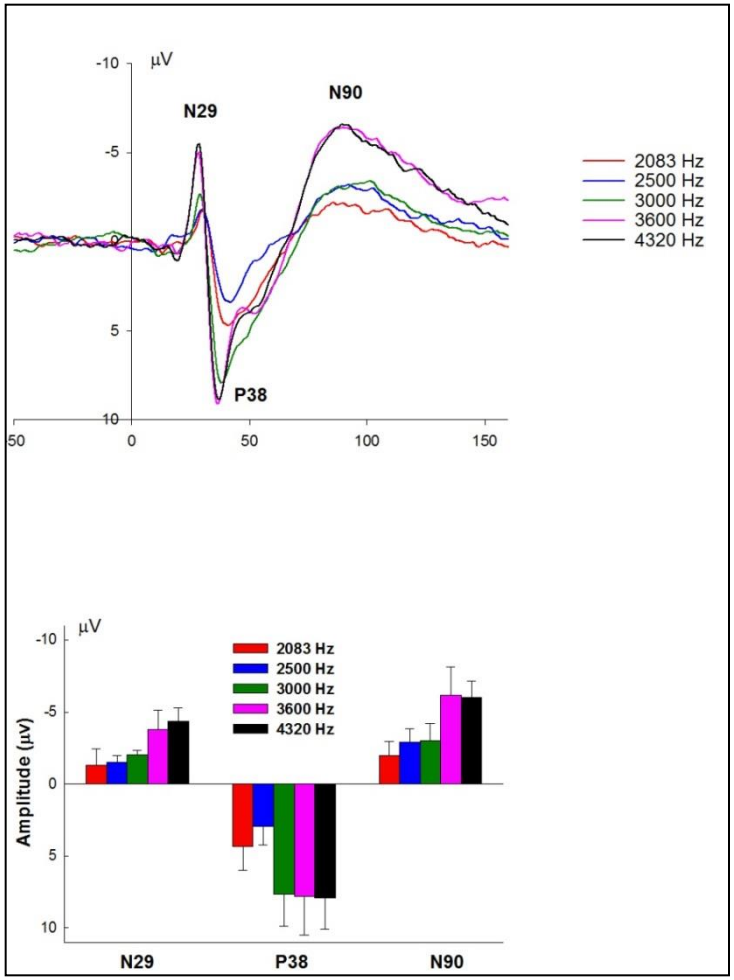
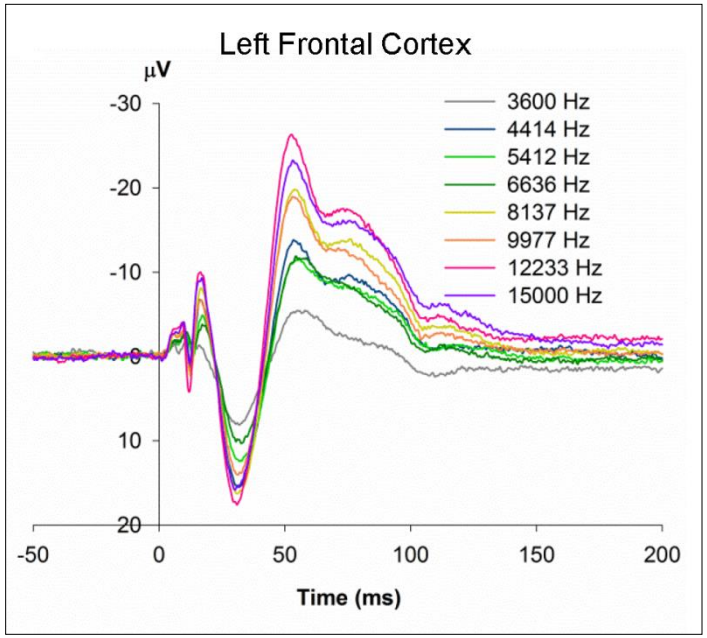
Nakamura et al. 2011 design.



Flip flop design: Allows control of stimulus attributes but not adaptation effects

Why are we concerned about stimulus differences?

Nakamura et al 2011



Harms et al. in revision