

# Development of Translational Biomarkers of Attention Function

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## Translational goal: Objective measure of treatment effect on attention mechanisms

### Target Validation

- A significant proportion of Wyeth portfolio targets cognition, in schizophrenia as well as in neurodegenerative disorders

### Target/Compound Interaction

- Attention is a central feature of cognitive processes

### Pharmacodynamic Activity

- There are multiple attention mechanisms that can be distinguished by psychophysical tests (error rates, speed of processing); anatomy (lesion studies, functional imaging, electrical activity) & pharmacology

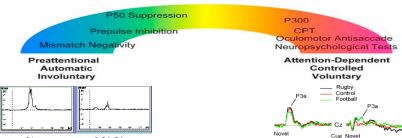
### Disease Biomarker & Disease Modification

- Wyeth compounds may selectively affect only certain components of attention systems

### Patient Stratification

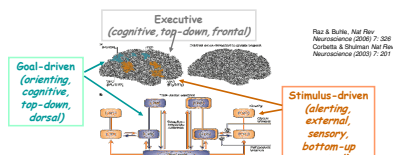
- Rational development ideally involves accurate measurement of effects on each separate component
- Clinical electrophysiology is much cheaper than functional imaging, can be performed by hospital personnel and has exquisite time resolution

## Strategy: Compare established Pre-Attentive Biomarker with new Attention-Dependent Biomarker



It is assumed that automatic, low level, control is involved in PrePulse inhibition (PPI) of EMG (illustrated on the left). Possibly analogous ERP P3a 'inhibition effects' (illustrated on the right) are seen in tasks using novel distractors in a Continuous number Decision Task (CDT). The large centrally distributed 'Novel' P3a may mark activation of the goal-driven system of the attention network (see below) and the small right-lateralised 'Cue Novel' P3a may mark activation of the stimulus-driven system. Contact sports players appear unable to inhibit the small P3a response. These ERP 'inhibition effects' may mark the influence of the goal-driven system on the stimulus-driven system and may serve as a 'cognitive' biomarker for treatments of psychosis, anxiety or depression or the effects of cognition enhancers.

### Three attention system networks (alerting, orienting, executive)



It is assumed that the goal-driven and stimulus-driven systems compete for control of attention orientation

## Methods

Participants: Patients with schizophrenia (N=10; Age 39; IQ 108), Controls (N=16; Age 40; IQ 115). Patients with Schizophrenia: Obesity 70%; Hypertension 20%; Smoker 70%; Head Injury 30%; Past Heavy Drink 40%; Past Hallucinogen 70%; Past Stimulants 70%.

EEG/ERP: 32 channel Biosemi active electrode system (2048 Hz sample rate). Brain Vision Analyzer software. Independent Component Analysis for blink artifact removal. Artifact rejection +/- 70 µV. Complex Morlet wavelet analysis 3-60 Hz, normalised and baseline corrected. Averages are of single trial wavelet analyses.

EMG: Data recorded from pairs of electrodes below the right and left eyes, rectified and then averages generated for each condition.

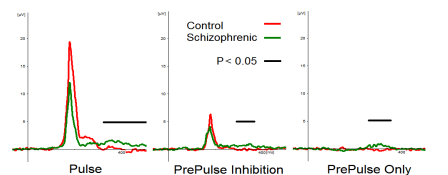
Procedure: Biographical Questionnaire, Spielberger State and Trait Anxiety Inventory, EEG Preparation, Visual Alertness Scale (VAS), Continuous number Decision Task (CDT), VAS, PrePulse Inhibition Task (PPI), VAS.

Data Analysis: Unrelated paired t-tests comparisons at each channel, time and frequency data point.

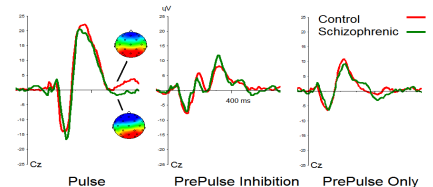
## Pre Pulse Inhibition (PPI) Task

PPI task: 70dB white noise background, 85dB white noise PrePulse, 105 dB white noise Pulse. PrePulse Pulse ISI 120 ms, ITI 9-15 seconds mean 12 seconds. Sequence: 6 Pulse stimuli, then 32 each of Pulse, PrePulse-Pulse or PrePulse (pseudo random distribution) then 6 Pulse stimuli to finish. Total duration 23 minutes.

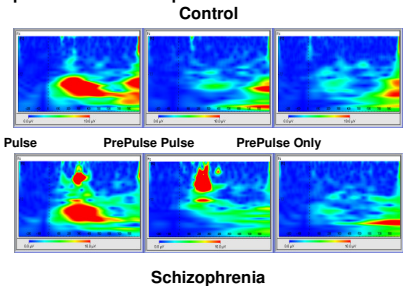
## PPI EMG: Atypical antipsychotics normalise PPI in patients with schizophrenia but they still exhibit greater late residual EMG activity



## PPI Event Related Potentials: ReOrienting Negativity (RON) is significantly larger over left frontal regions in patients with Schizophrenia



## PPI Wavelet EEG frequency: Pulse stimuli evoke normal theta activity and suppression of theta but more high frequency EEG responses in patients with schizophrenia than in controls

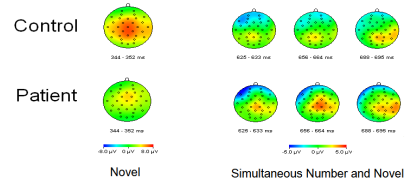


## Continuous number Decision Task (CDT)

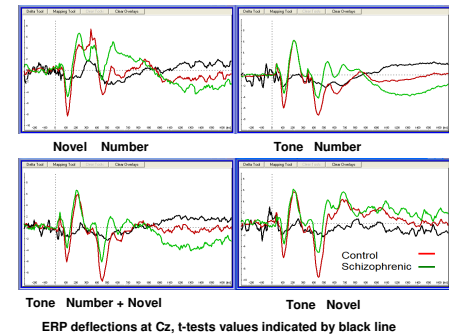
Standard stimulus pair consists of tone followed by spoken number (ISI 300 ms, ITI 2300 ms). Forced choice odd or even number decision (between 2 and 9). No response required on trials in which number is replaced by novel sound. Total duration 20 minutes.

Task Performance	Schiz	Control
RT Tone Number	690	660
RT Tone Number + Novel	693	677
RT Novel Number	731	713
Err Total	5%	3%

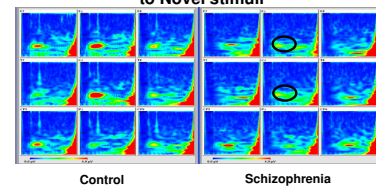
## CDT Event Related Potentials: Patients with Schizophrenia exhibit reduced P3b responses to uncued Novel stimuli but larger right lateralised P3a responses to cued Novel or Number stimuli



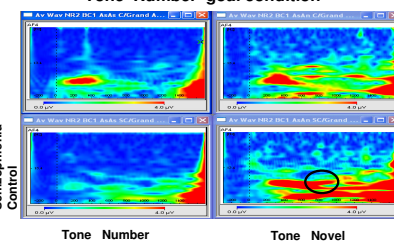
## CDT Event Related Potentials:



## CDT Wavelet EEG Frequency Analysis: Reduced theta to goal stimuli but increased theta to Novel stimuli



## Tone Number 'goal condition'



## These procedures may be suitable for quantitative assessment of distinct aspects of attention in schizophrenia

Recent advances in EEG signal decomposition techniques mean better artifact reduction and more comprehensive assessment of function than available previously

- Portable: can be performed in EEG laboratory
- Transparent analysis procedures
- Low cost compared to functional imaging

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