

Possible Mechanisms Mediating the Association between Smoking and Schizophrenia

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Tobacco Smoking in Schizophrenia

Diagnosis

Rate of smoking

Healthy control

30%

Schizophrenia

88%

Mania

70%

Depressive disorder

49%

Anxiety, personality disorder

45-47%

Hughes et al. 1986, Am J Psychiatry

Supported by a recent meta-analysis: de Leon and Diaz, 2005, Schizophr Res

Low Cessation Rates

- 9% vs 14 - 49% in the general population (Meta-analysis, de Leon and Diaz, 2005, Schizophr Res)
12% in a recent study (Culhane et al., 2008, J Clin Psychiatry)
- Poor cessation rate despite high motivation and persistent attempts to quit (Addington et al., 1997, Can J Psychiatry; Lader and Meltzer, 2001, DoH, UK)

Psychosis Proneness and Smoking

- High smoking rate is also found in people with a high level of schizotypal traits/ psychoticism (Eysenck, 1980, *The Causes and Effects of Smoking* many reports including Williams et al., 1996 and Larrison et al., 1999 in *Personality & Individual Differences*).
- With close proximity to schizophrenia but free of medication and illness-related issues, this population may provide insight into smoking – schizophrenia associations.

Temporary Reduction in Symptoms

- Smoking helps to reduce symptoms which some claim may become worse during withdrawal (Dalack & Meador-Woodruff, 1996, Schizophr Res; Glynn and Sussman, 1990, Hosp Comm. Psychiatry)
- Smoking high-nicotine cigarettes, compared to de-nicotinized cigarettes, reduces negative symptoms without affecting positive symptoms (Smith et al., 2002, europsychopharmacol).
- Classic smoking withdrawal symptoms but no worsening of psychotic symptoms (Dalack et al., 1999, Neuropsychopharmacol)
- No difference between placebo and nicotine patches on psychotic symptoms during withdrawal (Yang et al., 2002, Neuropsychopharmacol)

Reduction of Medication Side Effects

- Smoking or nicotine (via patches) can reduce unpleasant side effects of medication

(Goff et al., 1992 , Am. J. Psychiatry; Anfang and Pope, 1997, Psychopharmacology; Yang et al., 2002, Neuropsychopharmacol).

- There is however a report of greater movement abnormalities in patients who smoke than those who do not

(Nilsson et al., 1997, Biol. Psychiatry).

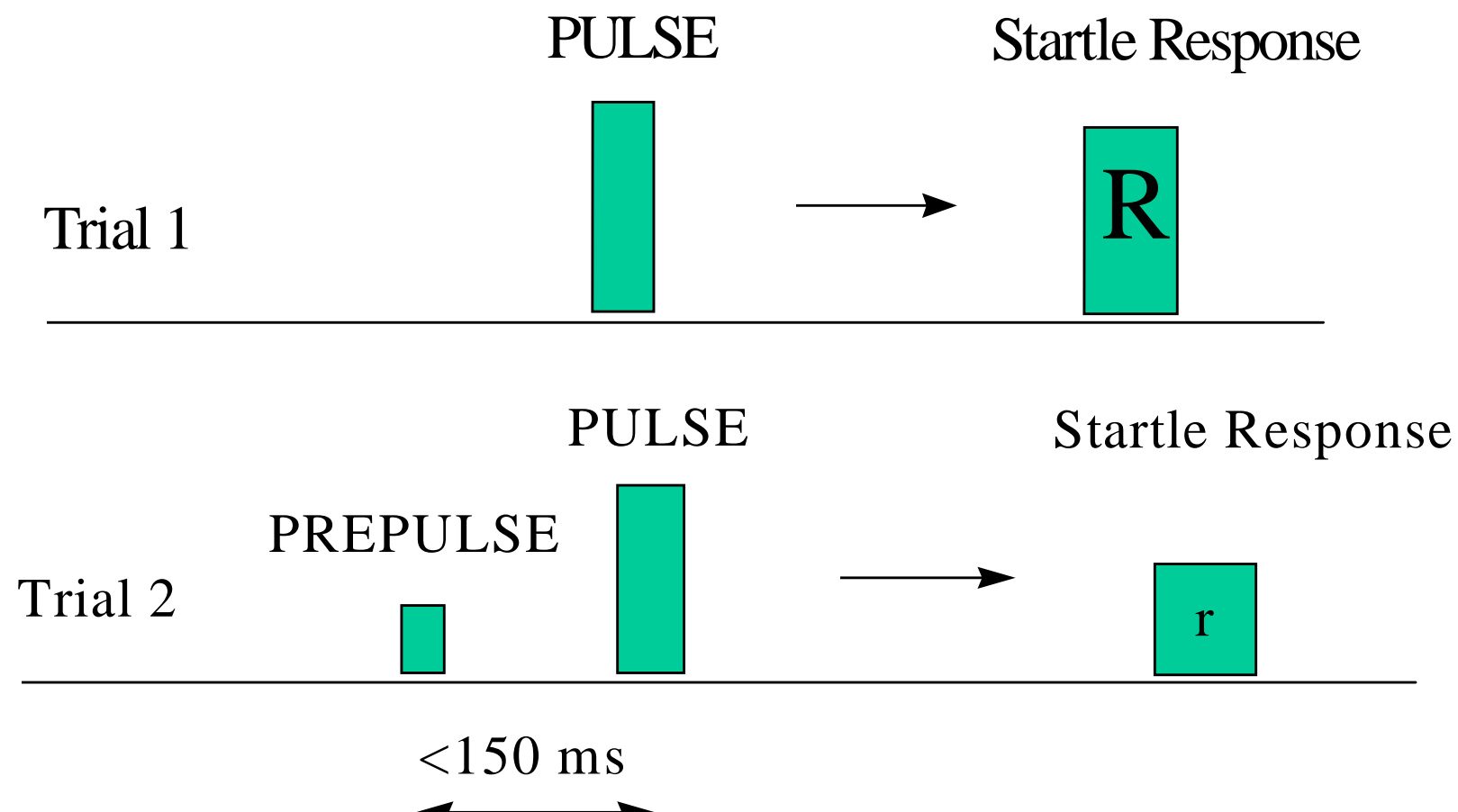
Possible Mechanisms Mediating Schizophrenia-Smoking Associations

- Reduction in psychiatric symptoms
- Reduction of side effects of anti-psychotics
- Improvement in sensorimotor (PPI) / sensory gating (P50 gating) and cognitive deficits

P50 gating studies by Leonard / Freedman Group
(Leonard et al., 1996 Schiz Bull)

Kumari & Postma (2005) Neurosci Biobehav Rev

Prepulse Inhibition of the Startle Response



Patients, on average, show less PPI than controls.

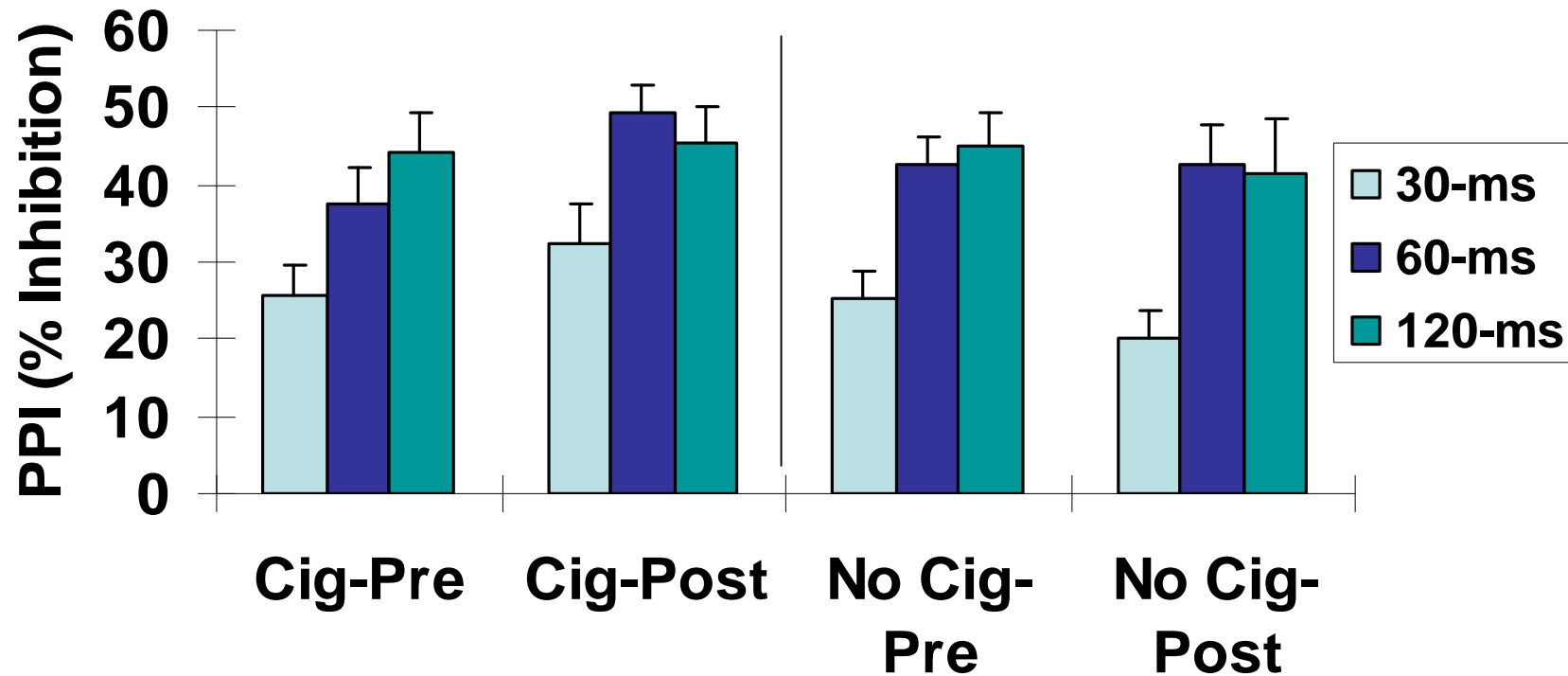
(> 25 studies from Braff and other laboratories across the world)

Nicotine Enhances Prepulse Inhibition in Animals

- Nicotine enhances (strain dependent) and nAChR antagonist mecamylamine reduces PPI (Reviews, Swerdlow & Geyer, 1998, Geyer et al. 2001).
- Reversal of apomorphine-induced disruption of PPI by nicotine - blocked by mecamylamine (Suemaru et al. 2004 Br J Pharmacol).
- Nicotine attenuates disruption of PPI by phencyclidine (PCP) in some strains (Spielewoy and Markou, 1995, Behav Genet; Andreasen et al. 2006, Behav Brain Res; Terry et al. 2005 CNS Drugs Rev).

Human Studies

Cigarette smoking increases PPI in smoking-deprived healthy smokers.

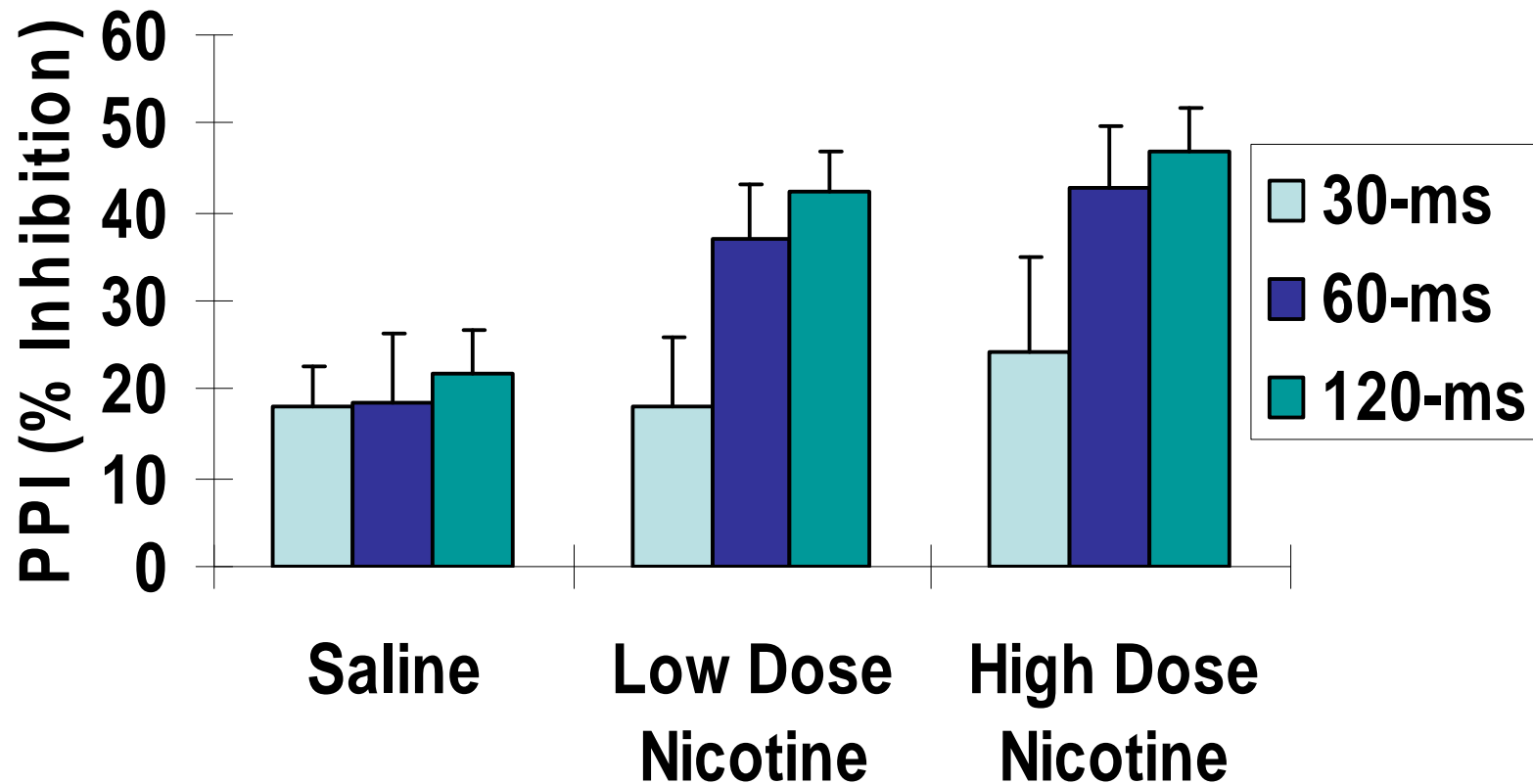


Kumari et al. (1996) Psychopharmacology

Also reported by Della Casa et al. (1998) Psychopharmacology

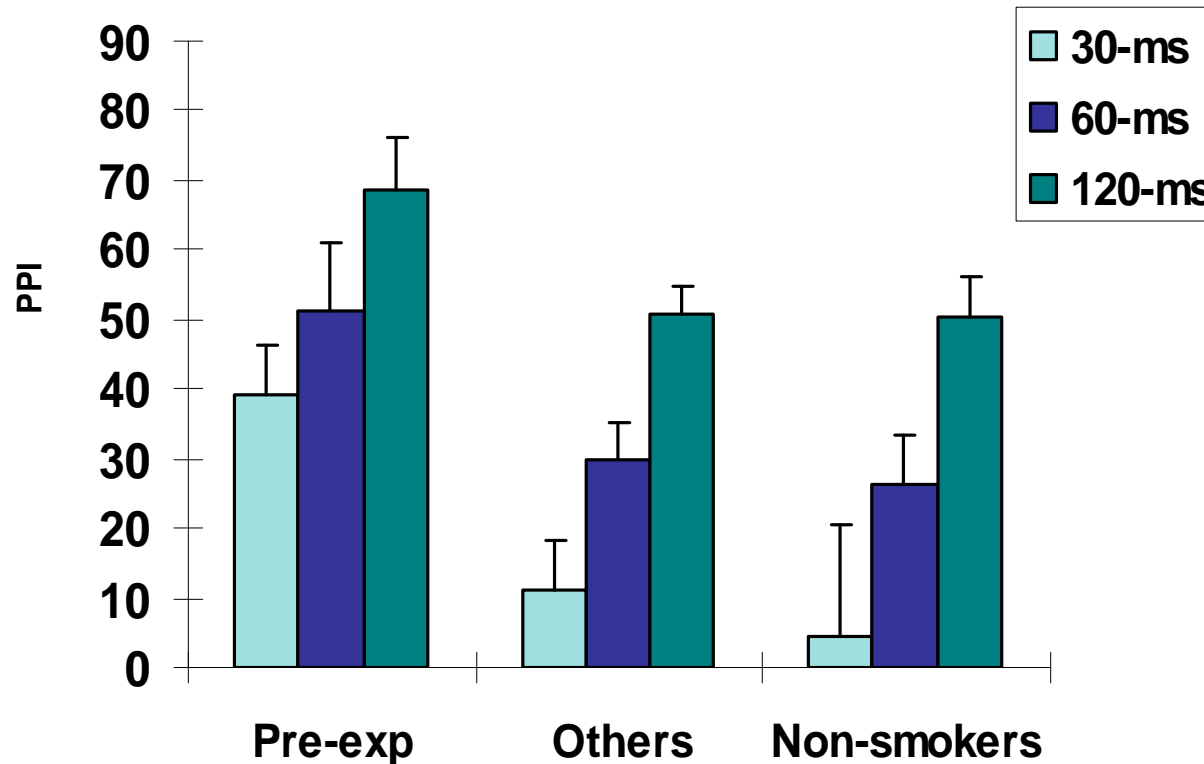
Duncan et al. (2001) Psychopharmacology

Subcutaneous Nicotine and PPI in Healthy Non-smokers.



Kumari et al. (1997) Psychopharmacology

Cigarette Smoking and PPI in Schizophrenia

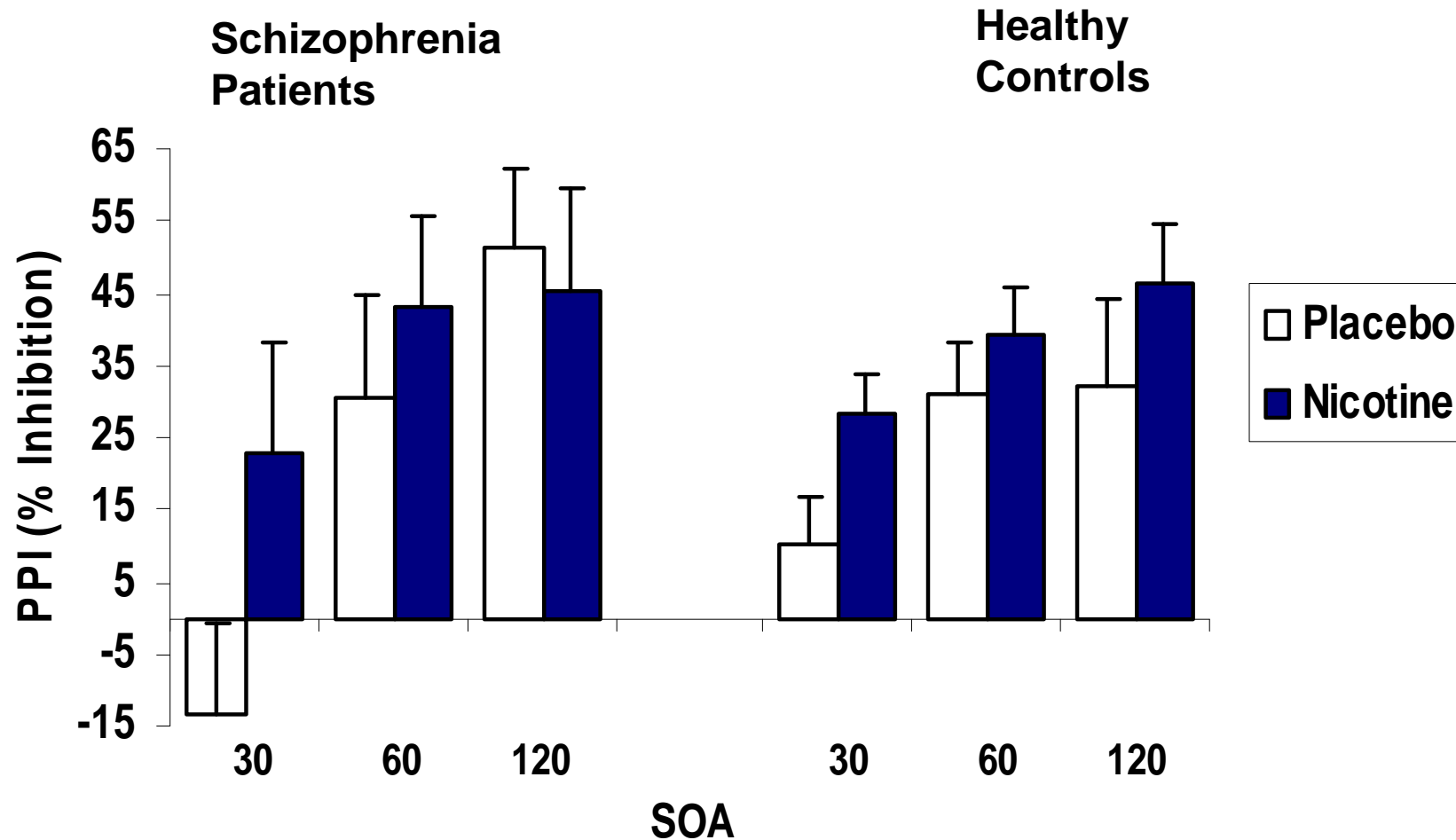


Kumari et al. (2001) *Hun Psychopharmacol Clin Exp*

George et al. (2006) *Schiz Res* smoking-enhanced PPI in patients

Swerdlow et al. (2006) *Arch Gen Psychiatry* - more PPI in smoking than non-smoking patients

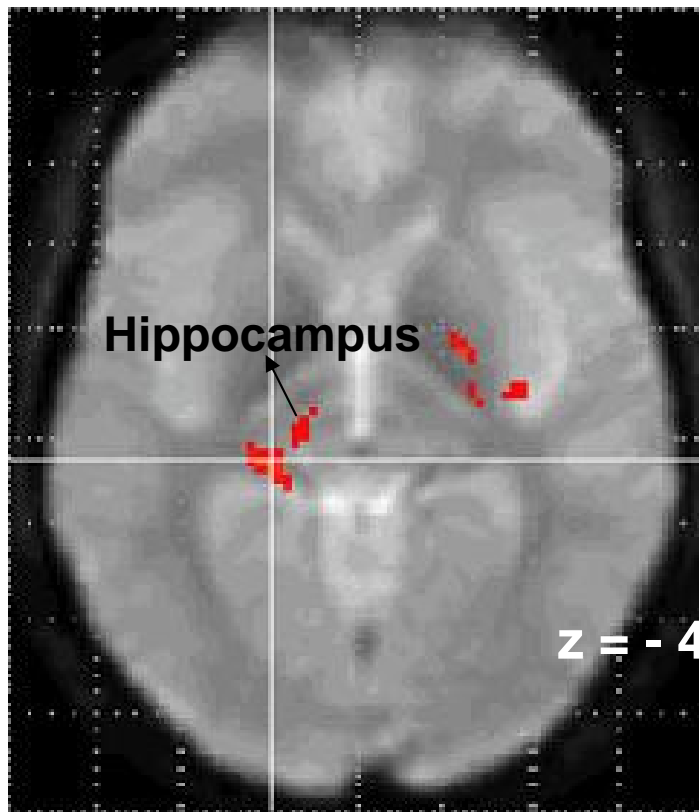
Nicotine and Tactile PPI in Schizophrenia and Healthy Controls



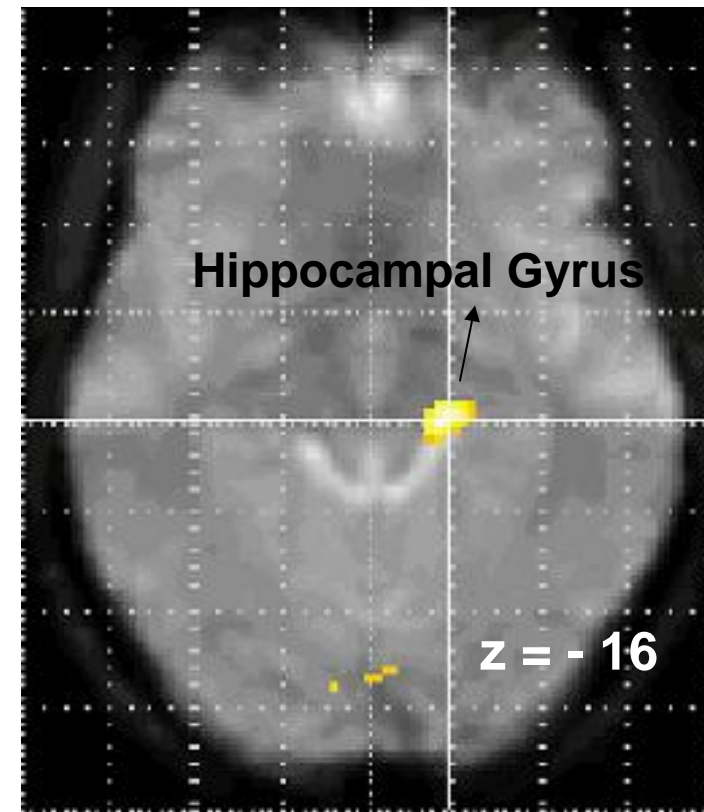
Postma et al. (2006) Psychopharmacology

fMRI Observations

Greater activation after
nicotine than placebo in
controls



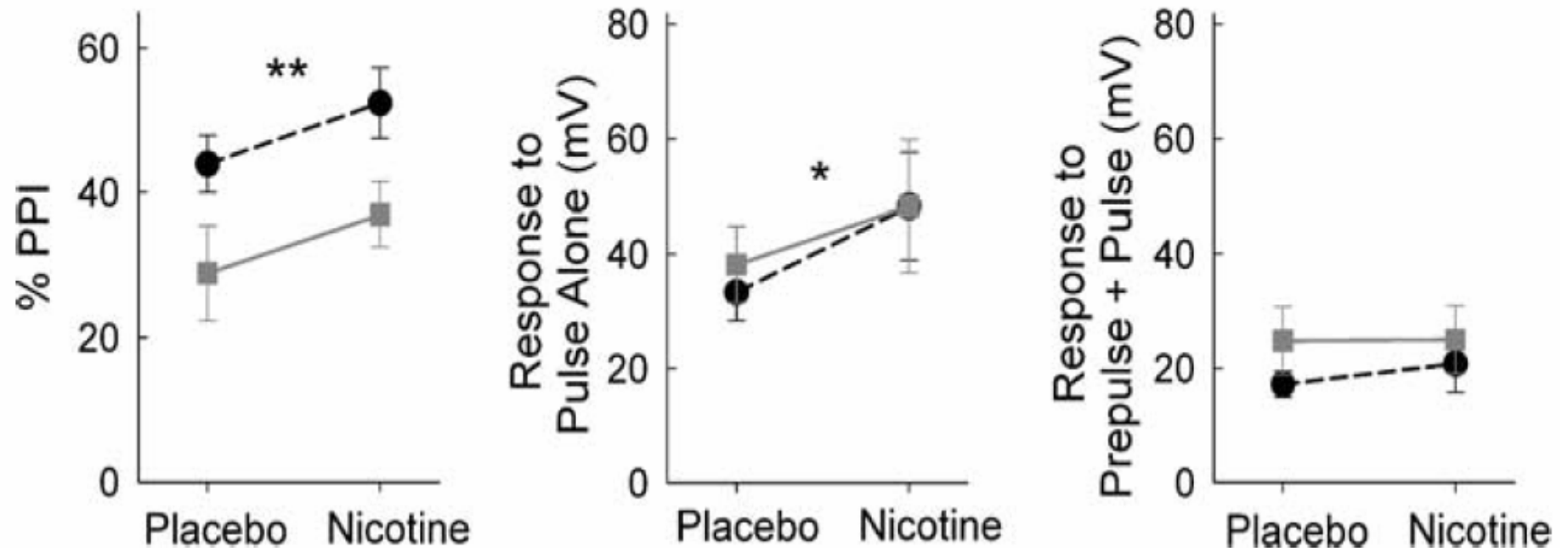
Greater activation in
schizophrenia patients
compared to controls under
nicotine



Postma et al. (2006) Psychopharmacology

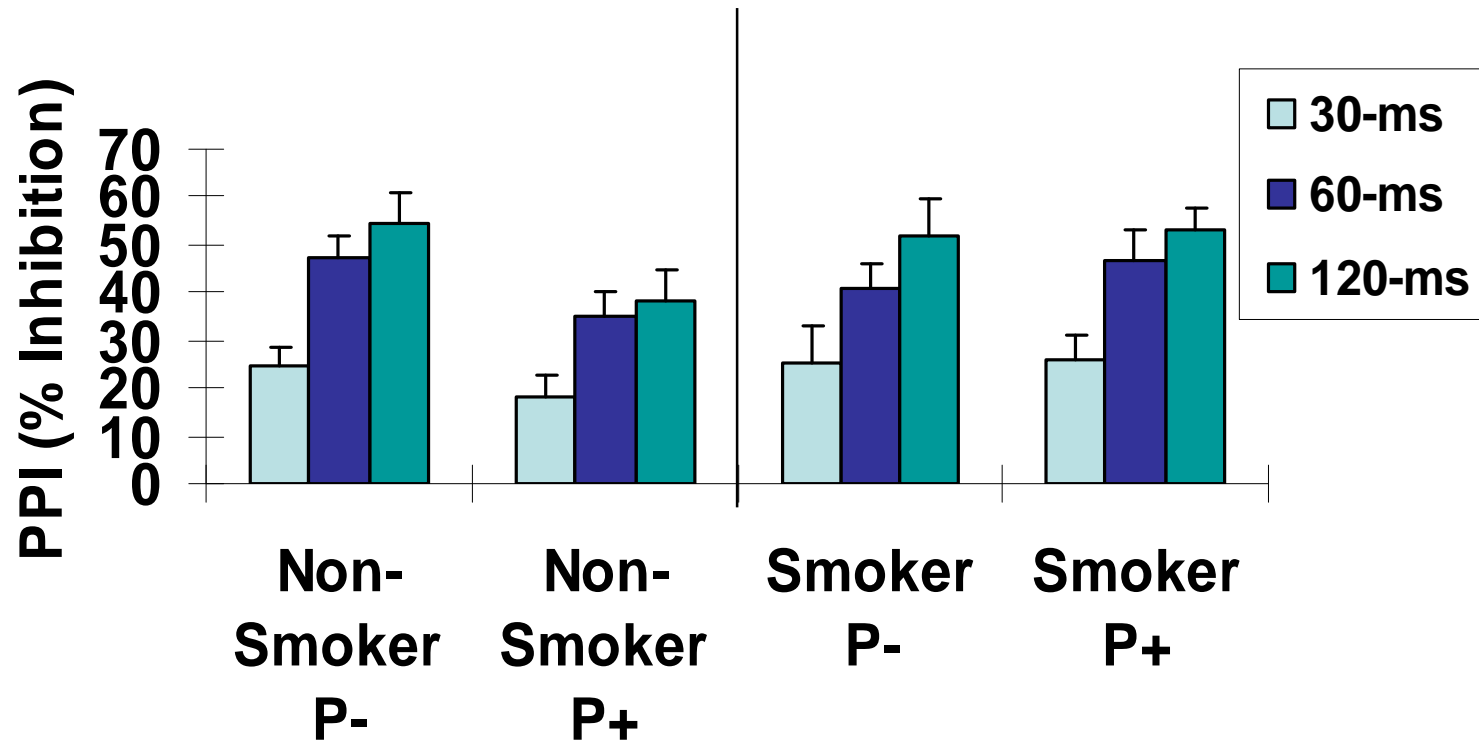
Nicotine Effect on PPI in Schizophrenia Patients and Healthy Controls

---●--- Healthy Controls (n=12)
---■--- Schizophrenia Patients (n=18)



Hong et al. (2007) Neuropsychopharmacology

Psychosis Proneness x Smoking Status



Kumari et al. (1997) Personality & Individual Differences

Replicated by Evans et al. (2005) Psychophysiology

Duration of Smoking Deprivation and PPI Disruption in Regular Smokers

- Comparable PPI in the 13-h and 1-h deprived smokers (Khan et al., in preparation).

The finding may suggest that if smokers can bear the initial disruption in PPI (and possibly relevant gating and cognitive functions), they may not experience further substantial disruption during subsequent hours of abstinence.

Smoking Reduction / Early Abstinence in Schizophrenia

- Clozapine reduces *ad lib* smoking.
(George et al., 1995, J Clin Psychiatry; McEvoy et al., 1995, Biol. Psychiatry; Procyshyn et al., 2001, Int. Clin. Psychopharmacol; 2002, Eur Neuropsychopharmacol)
- Clozapine also improves PPI.
(Kumari et al., 1999, Am J Psychiatry; Vollenweider et al., 2006, Biol Psychiatry)
- Later age at smoking initiation and attention performance predict early abstinence (Culhane et al., 2008, J Clin Psychiatry)
- Smoking motivation and triggers of relapse?

Smoking Motivation

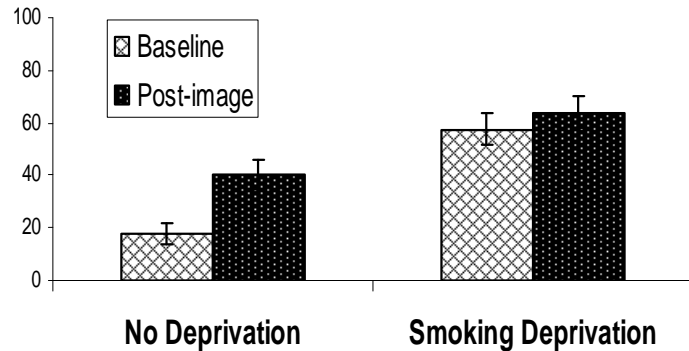
Different for Depression and Schizophrenia?

- Smokers with high scores on measures of depression report smoking for 'negative affect control'.
- Those with schizotypal traits report smoking for 'sensory and intellectual stimulation'

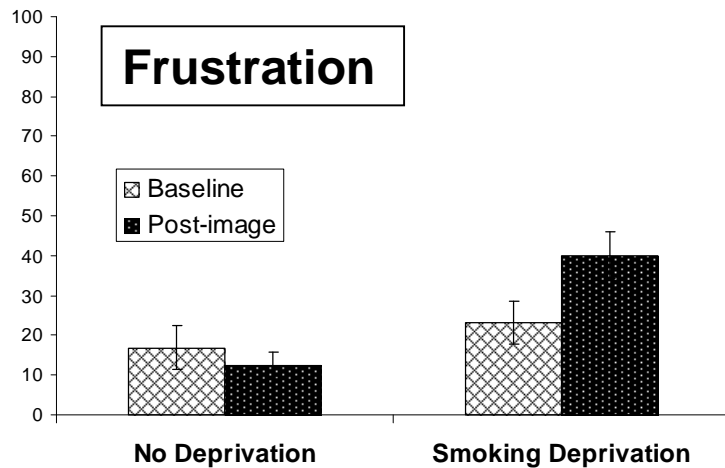
(Joseph et al., 2003, Personality and Individual Differences)

Smoking cue exposure typically increases self-reported craving and autonomic reactivity in regular smokers.

Desire to Smoke



Frustration



In the U.K - plans to ban the display of tobacco products in all retail outlets from 2013.

PRE-SMOKE



ACTIVE-SMOKE



POST-SMOKE



Khan et al., in preparation

Outlook

- Important to develop nicotinic agonist (other) treatments capable of improving gating and attention.
- Open-ended trials and longer support.
- Consideration of patients' reasons for continued smoking / relapse and perhaps non-nicotinic therapies to deal with them.

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Thank you for your attention

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