



Motivation – Why Imaging Genetics?

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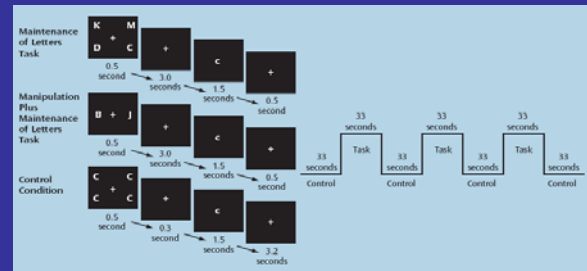
Why imaging genetics?

1. To translate candidate brain mechanisms of cognition and disease from **basic neurobiology** to the **live working human brain**
2. To link imaging strategies with human genetics/genomics towards potential rational treatment development.
3. Discovery of new genes and brain mechanisms to guide hypothesis-generation

Genetic dissection of dopaminergic (DA) mechanisms in human prefrontal-striatal circuits and its relationship with schizophrenia

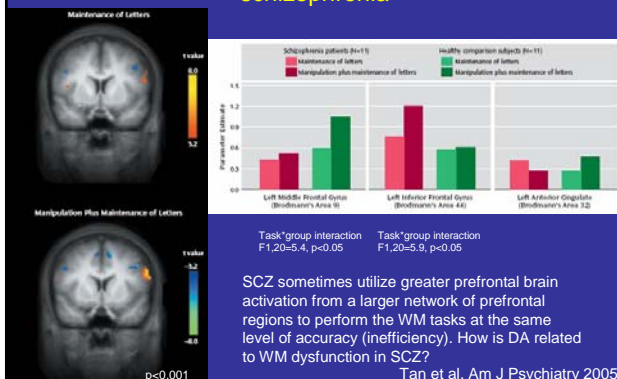
1. Working memory (WM) dysfunction in schizophrenia
2. Examine predictions from neurobiology of DA function and their links with human working memory processes via interacting DA-related gene effects on prefrontal brain systems: COMT, GRM3, AKT1.

Working memory component processes



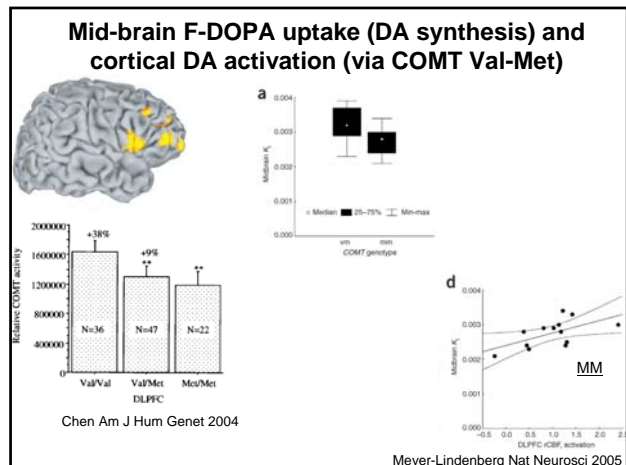
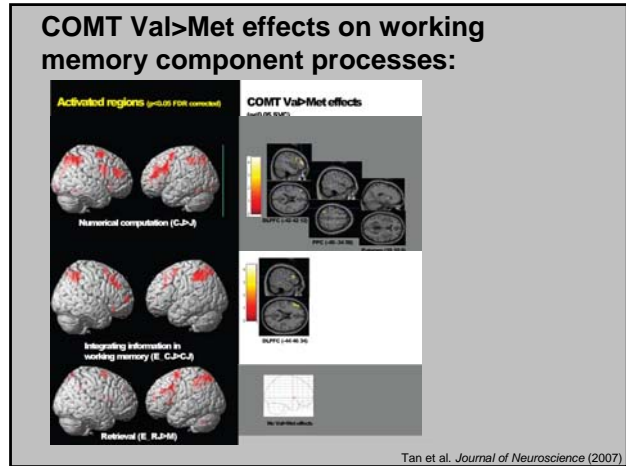
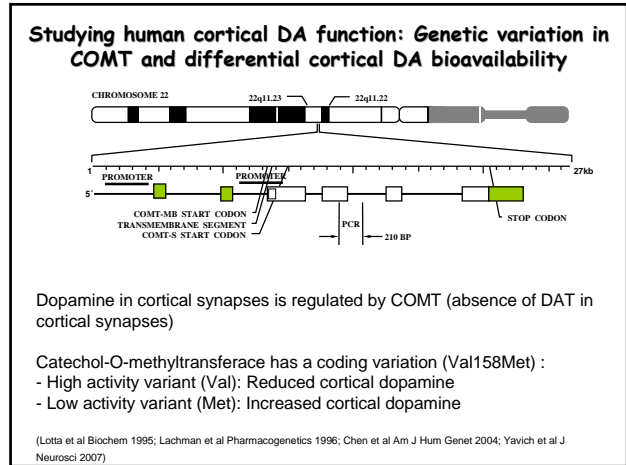
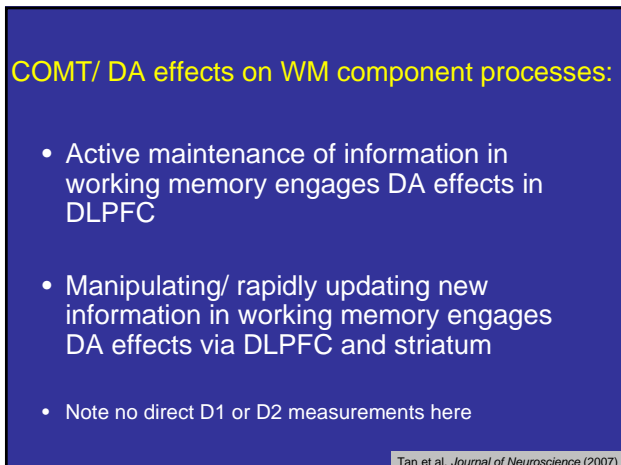
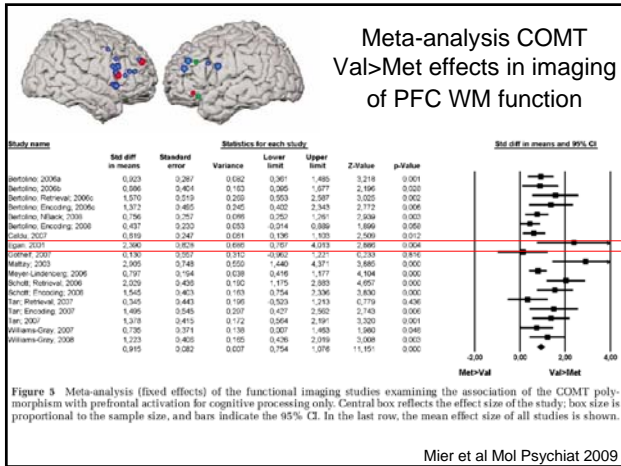
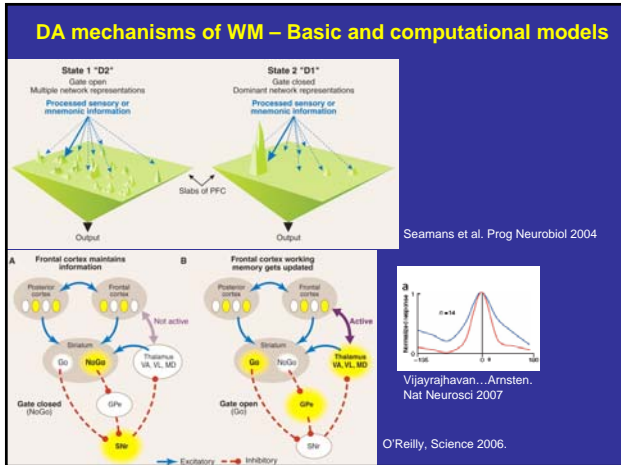
Chee & Choo, J Neurosci 2004
Tan et al, Am J Psychiat 2005

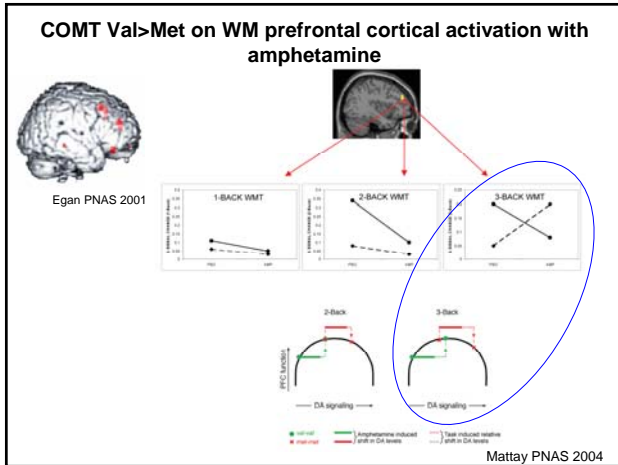
Neuroimaging of working memory components in schizophrenia



Working memory, DA and genetics of schizophrenia

- WM is critically implicated in cognitive deficits of SCZ ; DA is implicated in WM and SCZ
- Twin studies: WM performance is genetically heritable (Toulopoulou et al. Arch Gen Psychiat 2007), as are WM brain activation patterns (Koten et al. Science 2009)
- WM brain activation is also inefficient in unaffected siblings of SCZ – brain activity is a potential intermediate phenotype representing genetic risk of SCZ (Callicott et al Am J Psychiat 2003).

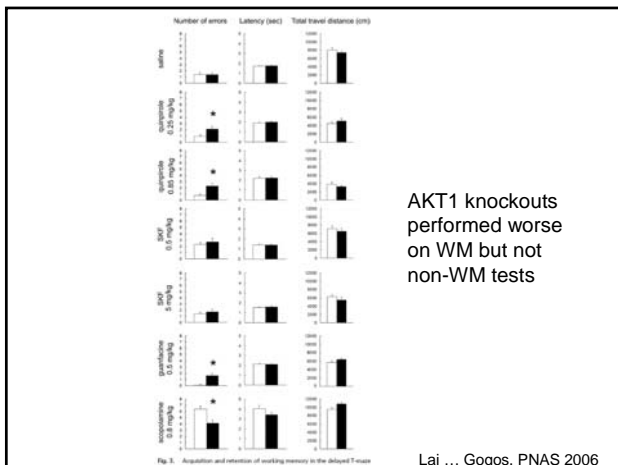
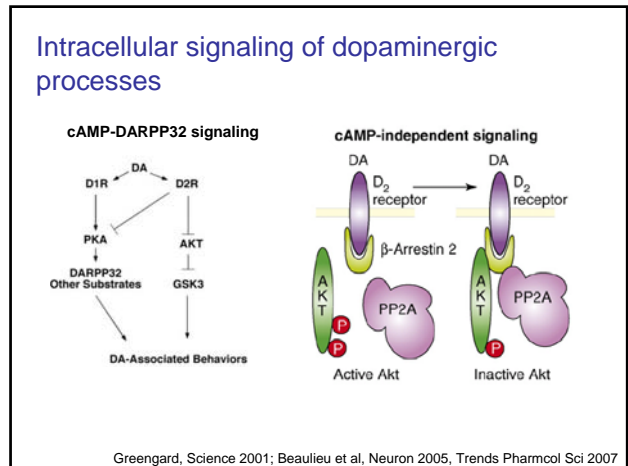
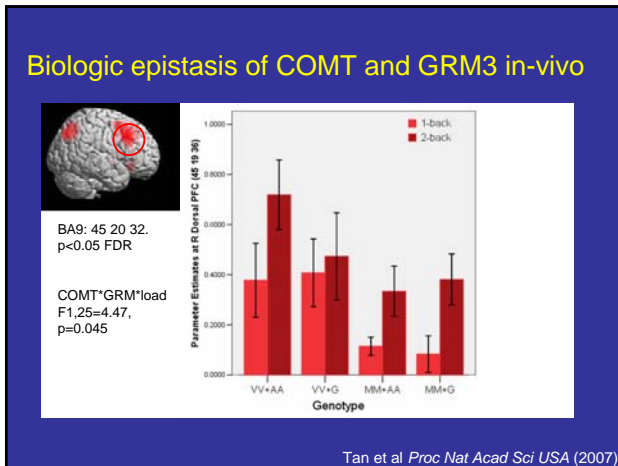




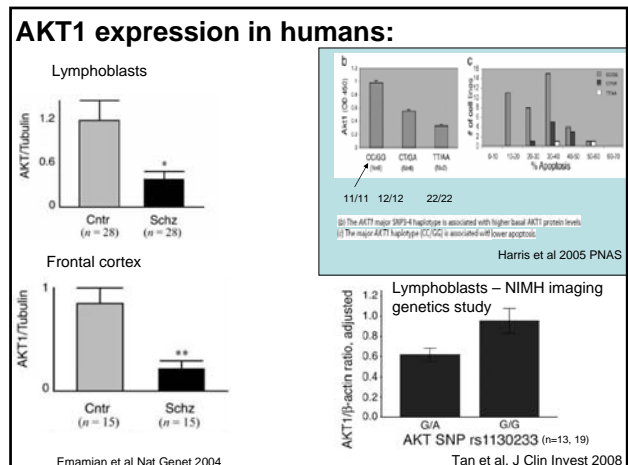
What about other genes that impact dopaminergic human brain function?

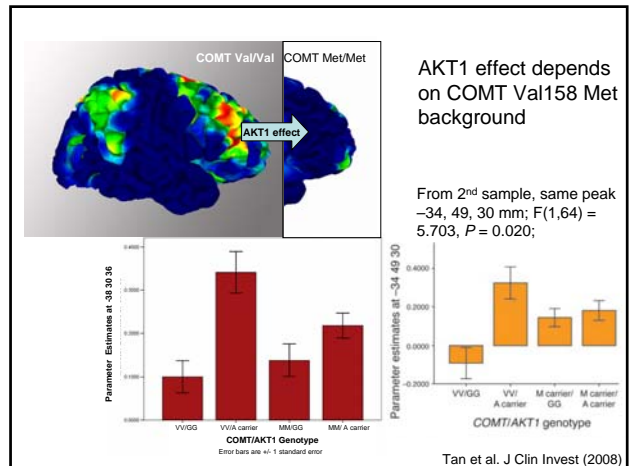
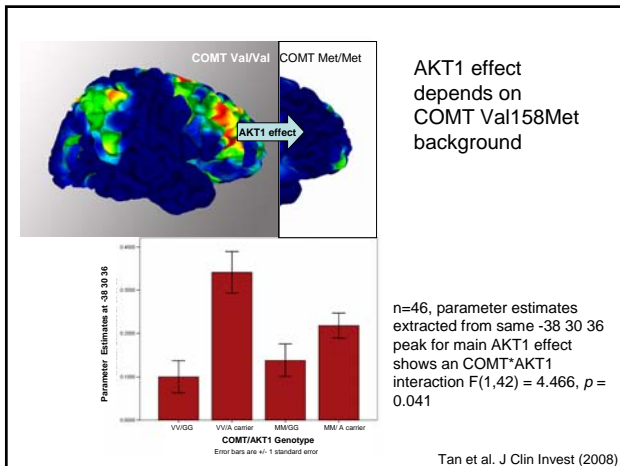
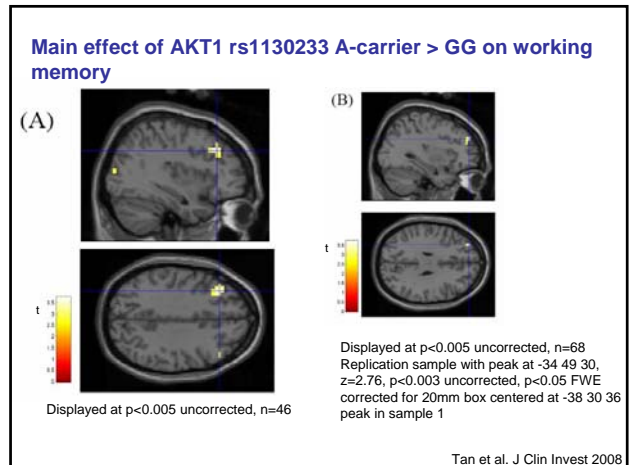
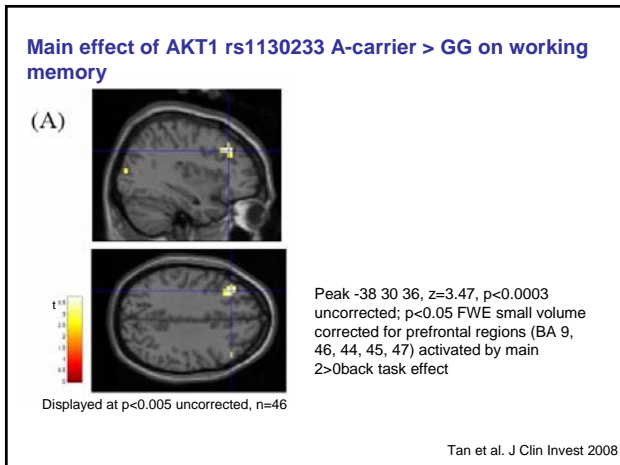
- DA system acts in concert with NMDA/ glutamatergic (and GABAergic) brain systems
- GRM3 variation impacts SCZ risk, glial glut transporter expression, PFC processing efficiency (Egan et al PNAS 2003)
- Combined deleterious COMT & GRM3 variation?

Shen et al Science 2008



AKT1 knockouts performed worse on WM but not non-WM tests





A primate-specific, brain isoform of *KCNH2* affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia

Stephen J Huffaker^{1,2}, Jingshan Chen^{1,2}, Kristin K Nicodemus^{1,2}, Fabio Sambataro^{1,2}, Feng Yang³, Venkata Mattay^{1,2}, Barbara K Lipska^{1,2}, Thomas M Hyde^{1,2}, Jian Song^{1,2}, Dan Rujescu⁴, Ina Giegling⁵, Karine Mayilyan⁶, Morgan J Proust¹, Armen Soghoyan⁵, Grazia Caforio⁶, Joseph H Callcott¹, Alessandro Bertolino⁶, Andreas Meyer-Lindenberg^{1,2,7}, Jay Chang^{2,8}, Yuanyuan Ji⁹, Michael F Egan¹, Terry E Goldberg^{1,2}, Joel E Kleinman^{1,2}, Bai Lu^{2,3} & Daniel R Weinberger^{1,2}

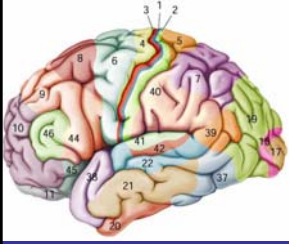
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- Integrating multiple samples for genetic association, imaging genetics, cell biology experiments to elucidate the genetic brain mechanisms relevant to cognition in scz

Conclusions:

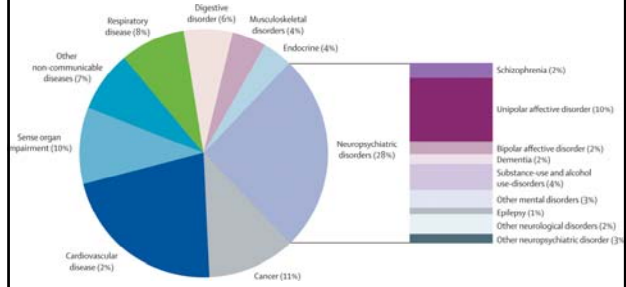
1. Active maintenance and manipulation processes in working memory are critically implicated in schizophrenia and heritable
2. Dopaminergic genes influence differing levels of human working memory brain processes. Cortical DA processes are engaged in active maintenance of information, while striatal-cortical DA processes in the rapid updating and manipulation of information.

Conclusions



3. Imaging genetics can begin to elucidate predictable interactions between dopaminergic, glutamatergic and intracellular signaling genes, thus integrate basic and human studies
4. Systematic imaging studies of genes together with biologic evidence also provides tractable paths to novel treatment hypotheses for cognitive dysfunction in schizophrenia eg COMT, GRM3, AKT1, BDNF, KCNH2 have existing/pipeline drugs that could be relevant to such imaging pharmacogenetic experiments in the future

Global burden of disease and cognitive deficits



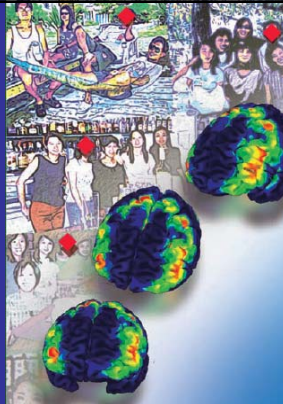
C.J.L. Murray and AD Lopez, Editors, *The global burden of disease and injury series, volume 1: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*, Harvard University Press, Cambridge, MA, USA (1996).

CBDB, CCAP, NIMH

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