

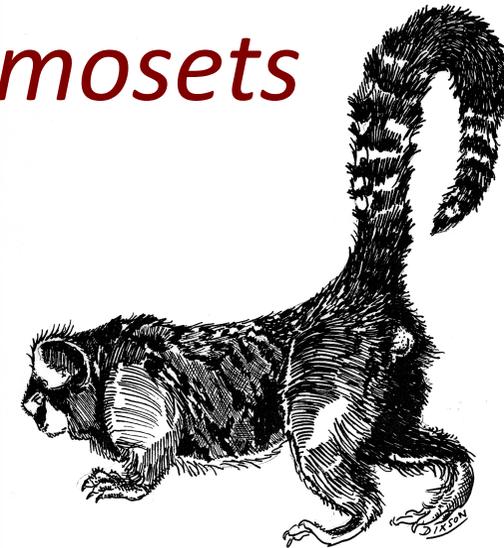
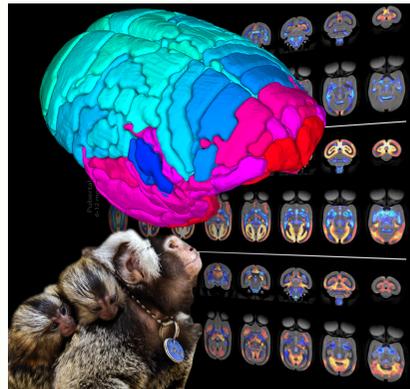


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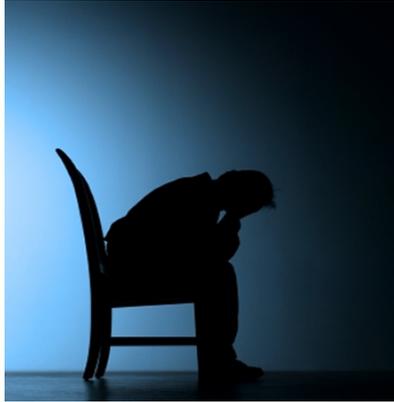
Transgenic and Chimeric Neuroscience Research: Exploring the Scientific Opportunities Afforded by New Nonhuman Primate Models- A Workshop

Session 1: Modelling symptoms of neuropsychiatric disorders in marmosets

Angela Roberts



The Multiple Faces of Psychiatric Diagnosis



Two patients can be diagnosed with the same disorder, e.g. depression, but have no overlapping symptoms.

Even if two patients have the same symptom it is very likely that the psychological and neurobiological causes are not the same, since clinical symptoms e.g. compulsivity, anxiety, anhedonia are poorly characterised.

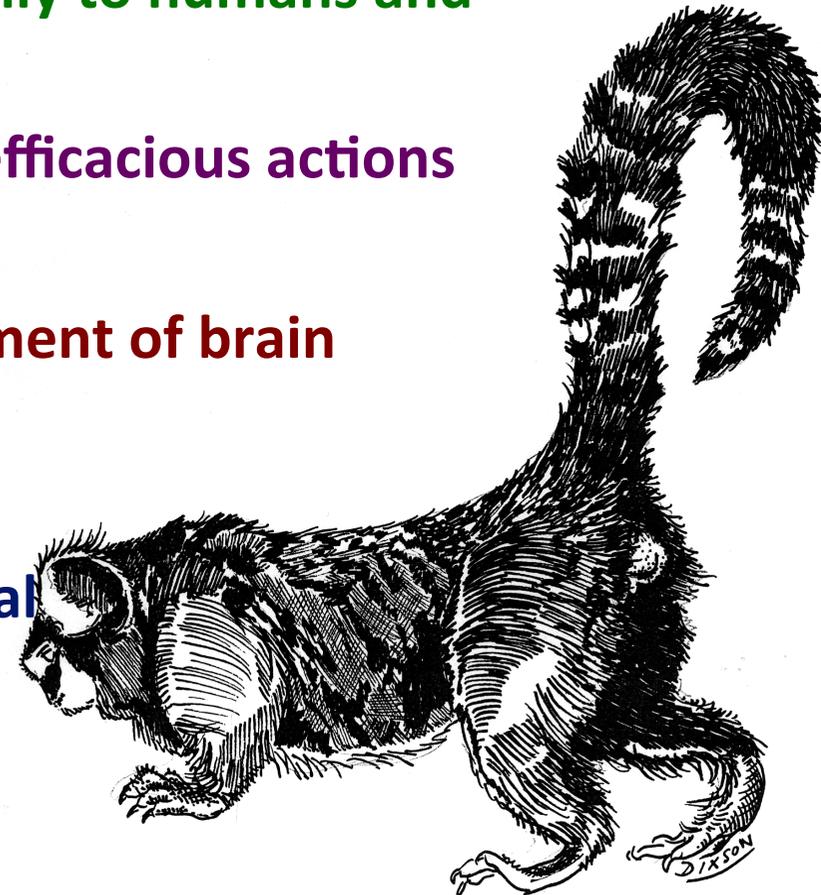
Even when treatments do work, we don't know how?

We can't predict which treatment will work best in any given patient.

Better stratification of psychiatric disorders and development of personalised treatment strategies.

How do we tackle this problem?

- Better understanding of the underlying psychological and neurobiological causes of particular symptoms. Need a range of tests to measure different aspects of these symptoms. **One test \neq one symptom**
- **Use of behavioural tests that can translate easily to humans and the clinical condition**
- **Insight into how current therapies have their efficacious actions and on what brain systems**
- **Better understanding of the 'normal' development of brain circuits underlying cognition and emotion**
- **Better understanding of how genes and environmental risk factors such as psychological stress and inflammation impact upon brain development**
- **Better models of psychiatric disorders**



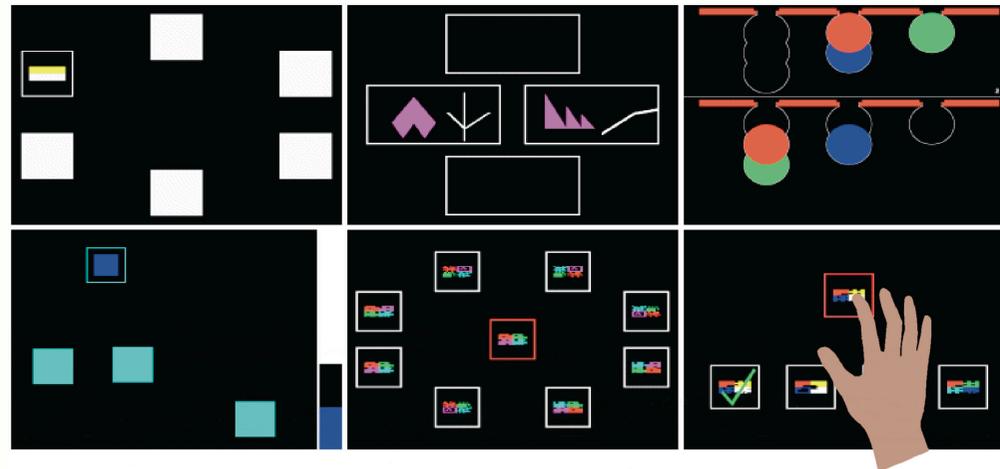
PROCEDURES: Measuring Cognition



Marmoset voluntarily gets into carry box for behavioural testing.

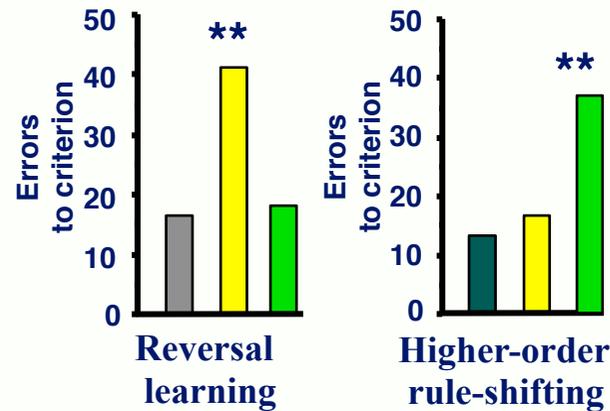
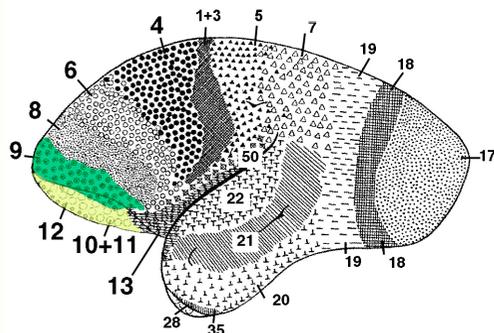
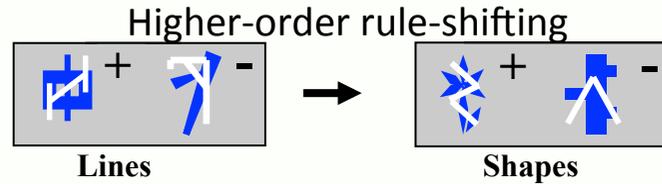
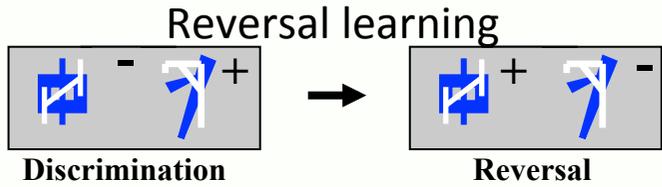


Marmoset performing in the test apparatus for banana milkshake (10-15 min sessions)



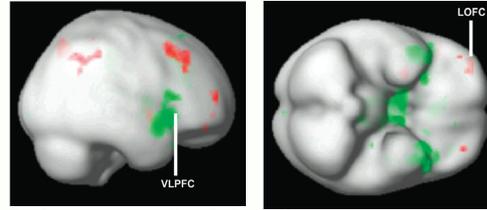
CANTAB Battery of cognitive tests for humans

Cognitive inflexibility: a success story for translation



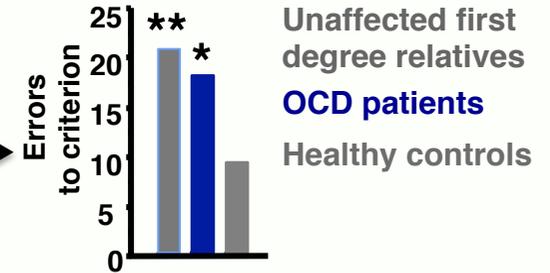
*Dias, Robbins, Roberts (1996)
Nature 380, 69-72.*

Human functional neuroimaging

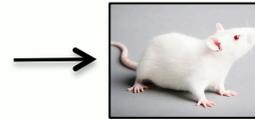


Laboratory of Adrian Owen

Rule shifting: Vulnerability marker for OCD?



Chamberlain et al., Am J Psych, 2006b



Chronic stress: risk factor for neuropsychiatric disease

Laboratory of David Morilak, San Antonio, USA



Transgenic mice models: AD, HD, Schizophrenia

Laboratory of Bussey & Saksida, Cambridge, UK

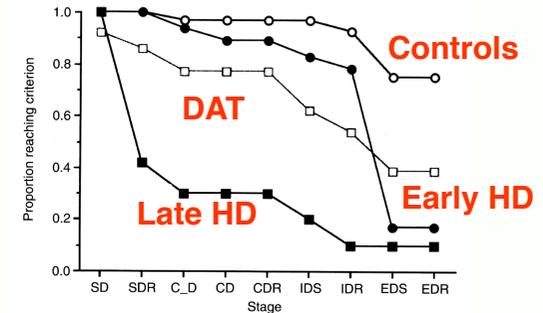


Transgenic sheep

Huntington's disease model

Laboratory of Jenny Morton, Cambridge, UK

Rule shifting: Cognitive marker for early stage HD?



Based on Sahakian et al 1990; Lange et al 1995; Lawrence et al 1996

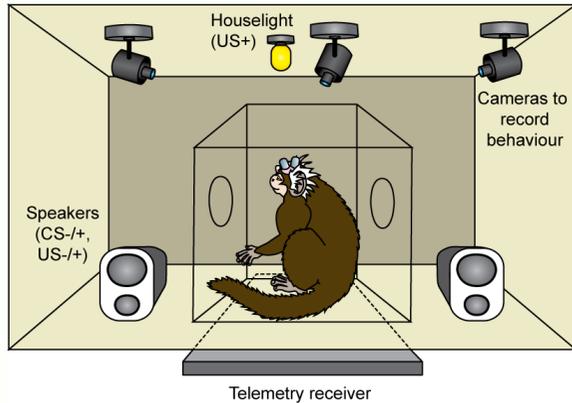
PROCEDURES: Measuring threat-driven behaviours

Relevant to fear and anxiety

Anticipatory negative arousal
Consummatory negative arousal

Uncertainty
Innate threat

Stimuli predicting threat



Aversive loud noise/darkness

Behavioural and cardiovascular responses



Unknown human



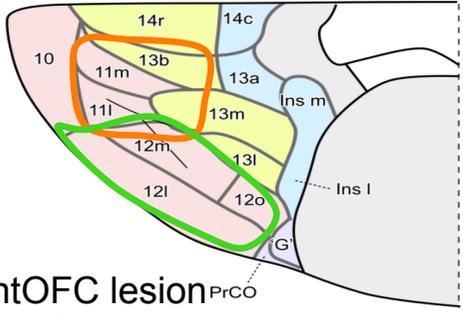
Rubber snake

Pitting +ve stimuli against -ve stimuli

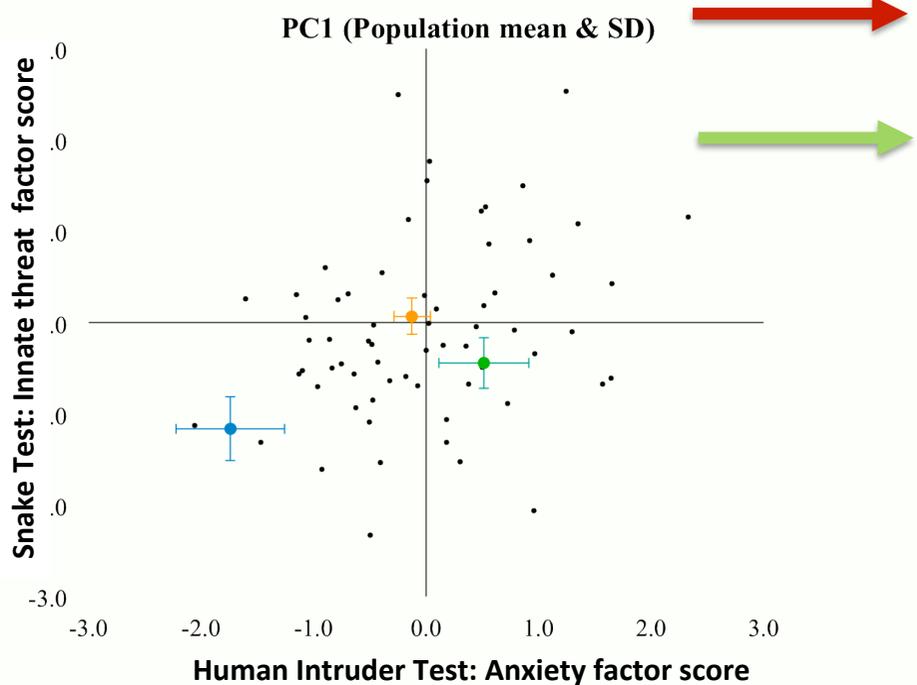


Decision making:
Approach-Avoidance
using mildly aversive
loud noise:
115-120dB (0.3-0.6s)

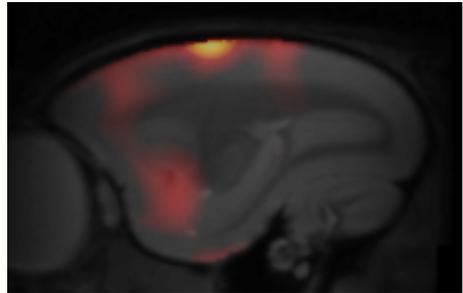
Fractionating out causes of anxiety brings us nearer to individually tailored treatments



▭ antOFC lesion_{PrCO}
▭ VIPFC lesion



FDG PET



Fear – Safety:
Intact



Fear – Safety:
OFC/vIPFC lesion

Anterior OFC damage:

Disrupts updating of value representations of specific outcomes
Schoenbaum et al, ANYAS 2011, 1239:87-99.
Rudebeck & Murray, Neuron 2014, 84:1143-56.

Impaired ability to track punishment in changing environment leading to UNCERTAINTY

Ventrolateral PFC damage:

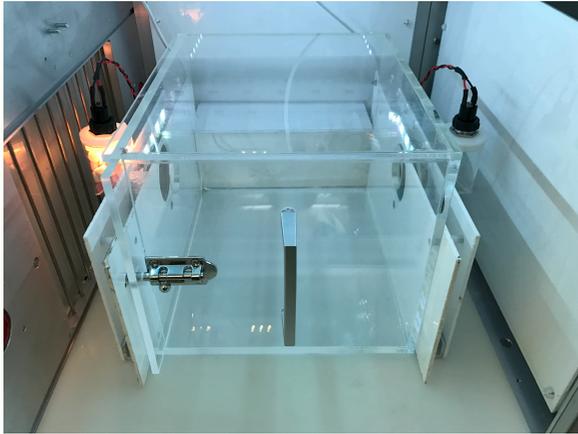
Disrupts attentional control
Dias et al, Nature 1996, 380:69-72.

Enhanced attention towards salient aversive stimuli which increases anxiety.

PROCEDURES: Measuring reward-driven behaviours

Relevant to anhedonia

Stimuli predicting reward

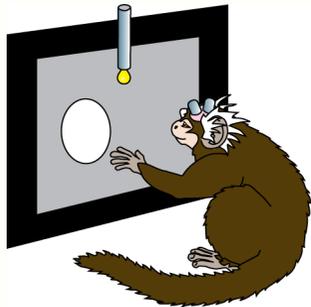


Reward: Marshmallows

Anticipatory positive arousal
Consummatory positive arousal

Willingness to work: Motivation

Pitting +ve stimuli against -ve stimuli



Escalating
schedule of
responses



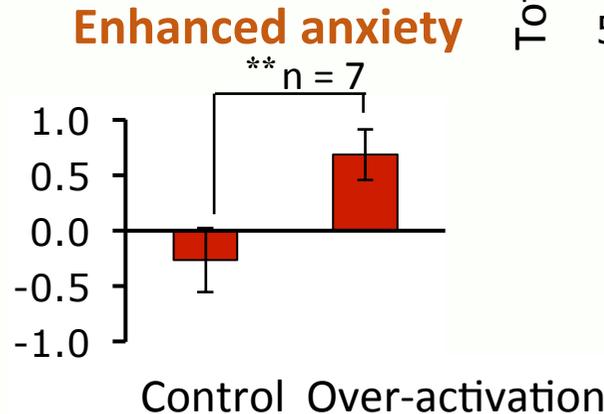
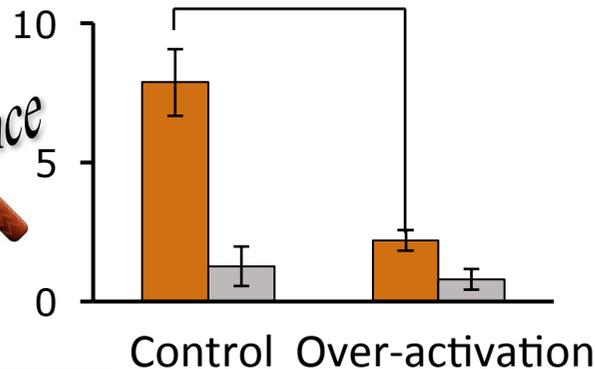
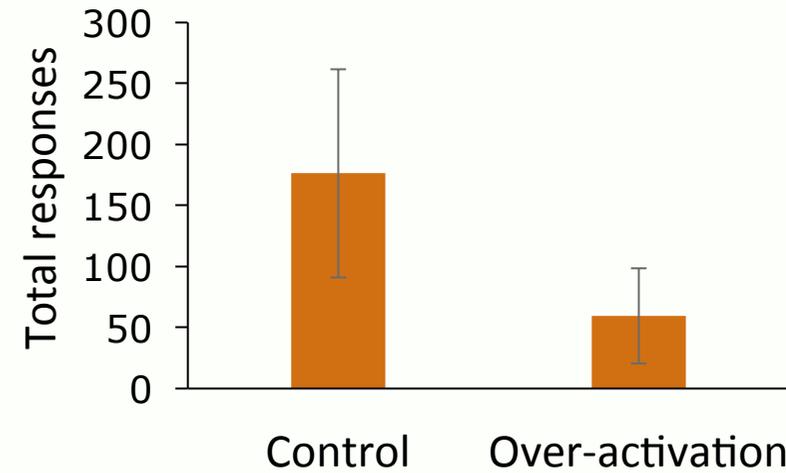
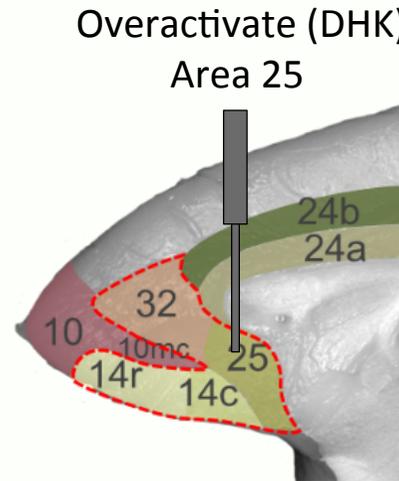
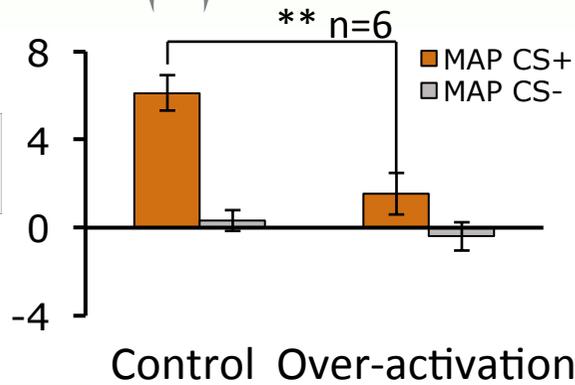
Decision making:
Approach-Avoidance
using mildly aversive
loud noise:
115-120dB (0.3-0.6s)

Over-activity in subgenual cingulate cortex leads to anticipatory and motivational-like anhedonia

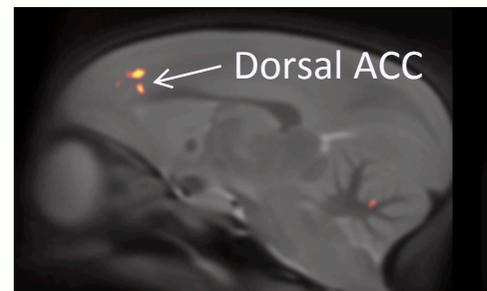
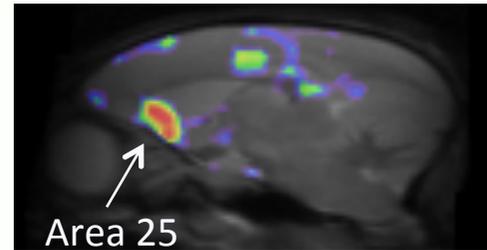
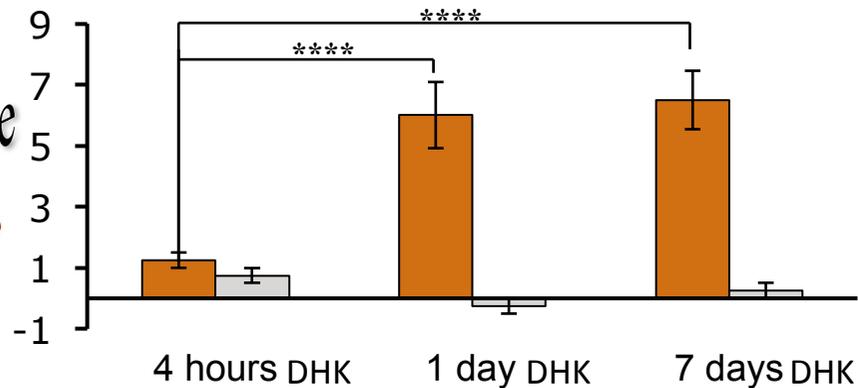
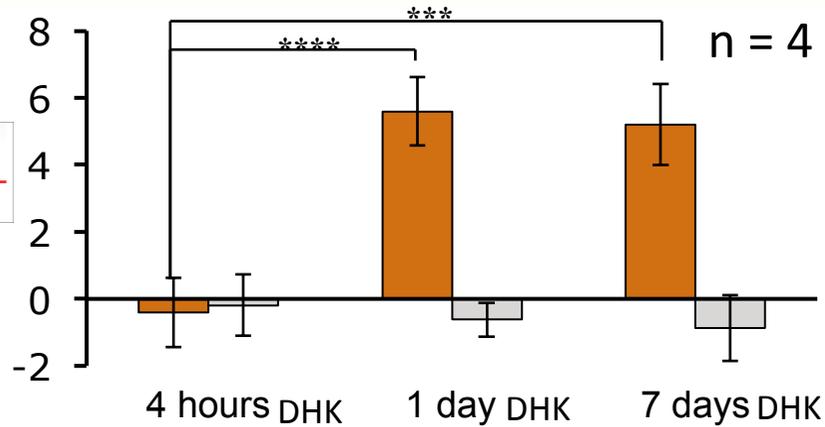
Reduced excitement

← Loss of pleasure →

Reduced motivation



Insight into the actions of the anti-depressant ketamine on anhedonia-related symptoms:

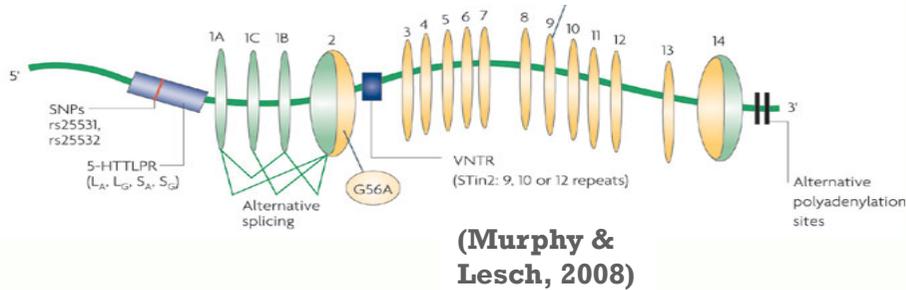


Over-activation increases FDG uptake in: area 25, dorsal ACC, ant. Insula.

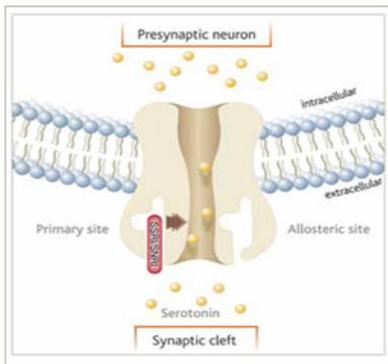
Blocked by Ketamine if given 24 hours earlier

Insights into the action of SSRI's, the first line treatment for depression

Human SLC6A4 gene

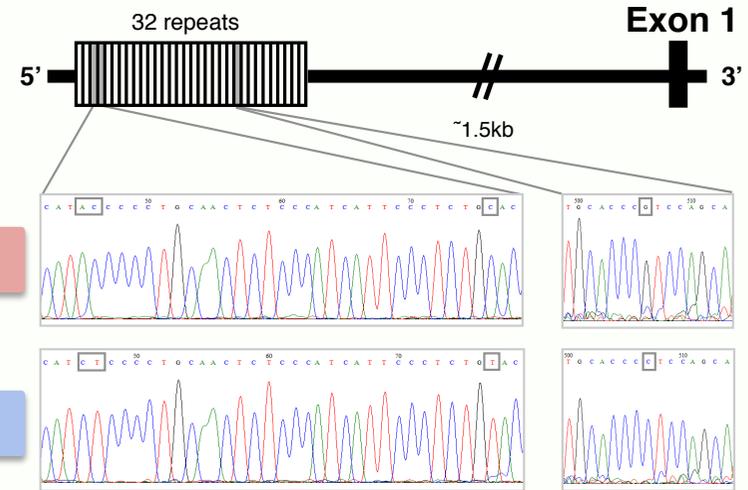


S allele

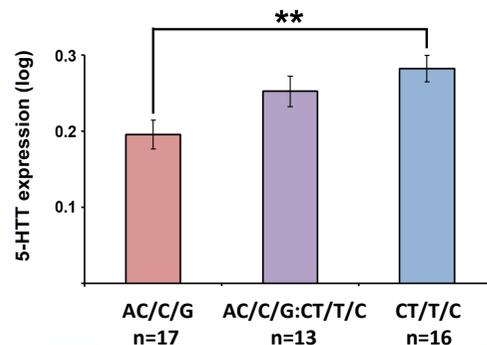


Reduced gene expression and transporter function

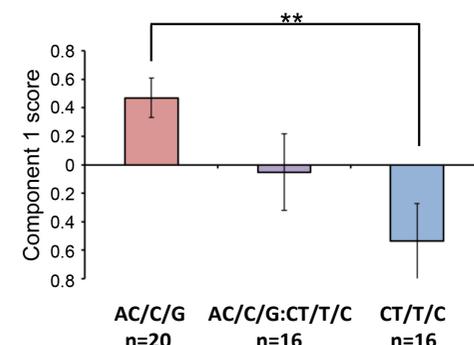
Marmoset SLC6A4 promoter region



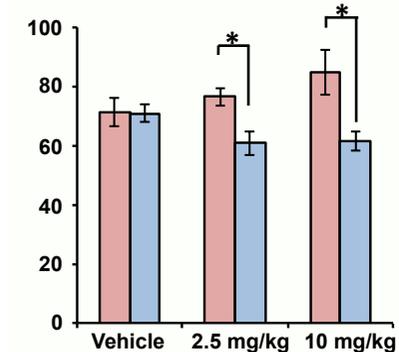
Allele dependent gene expression



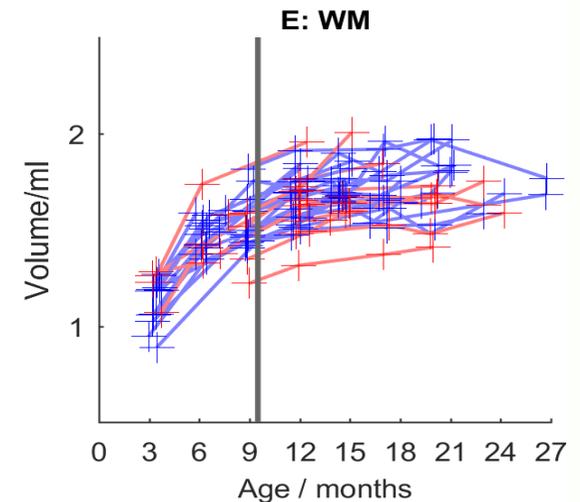
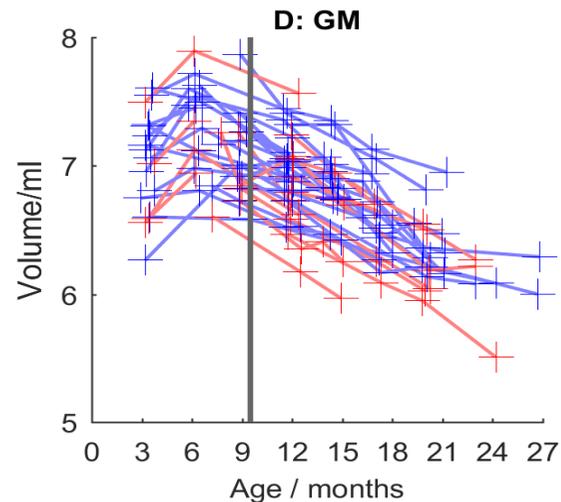
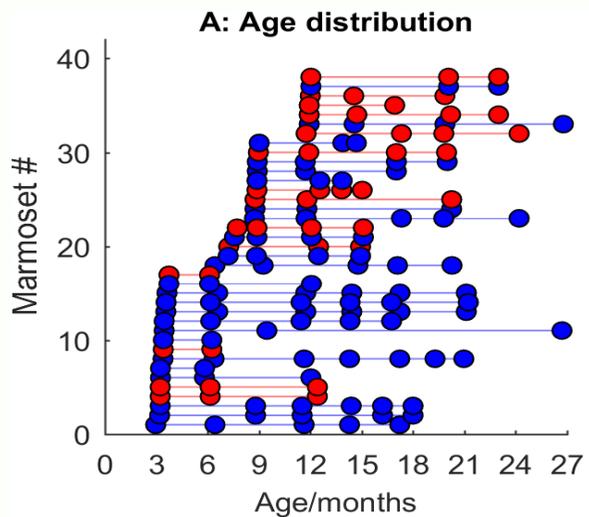
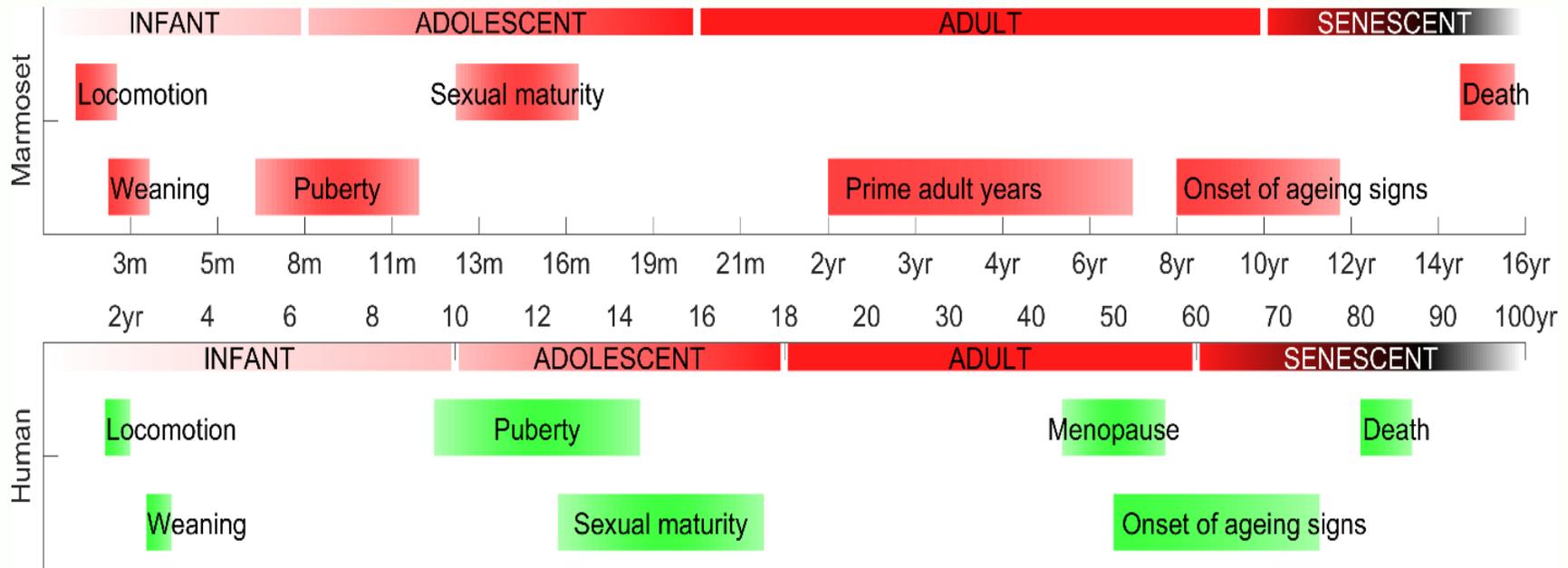
Allele dependent anxious behaviour



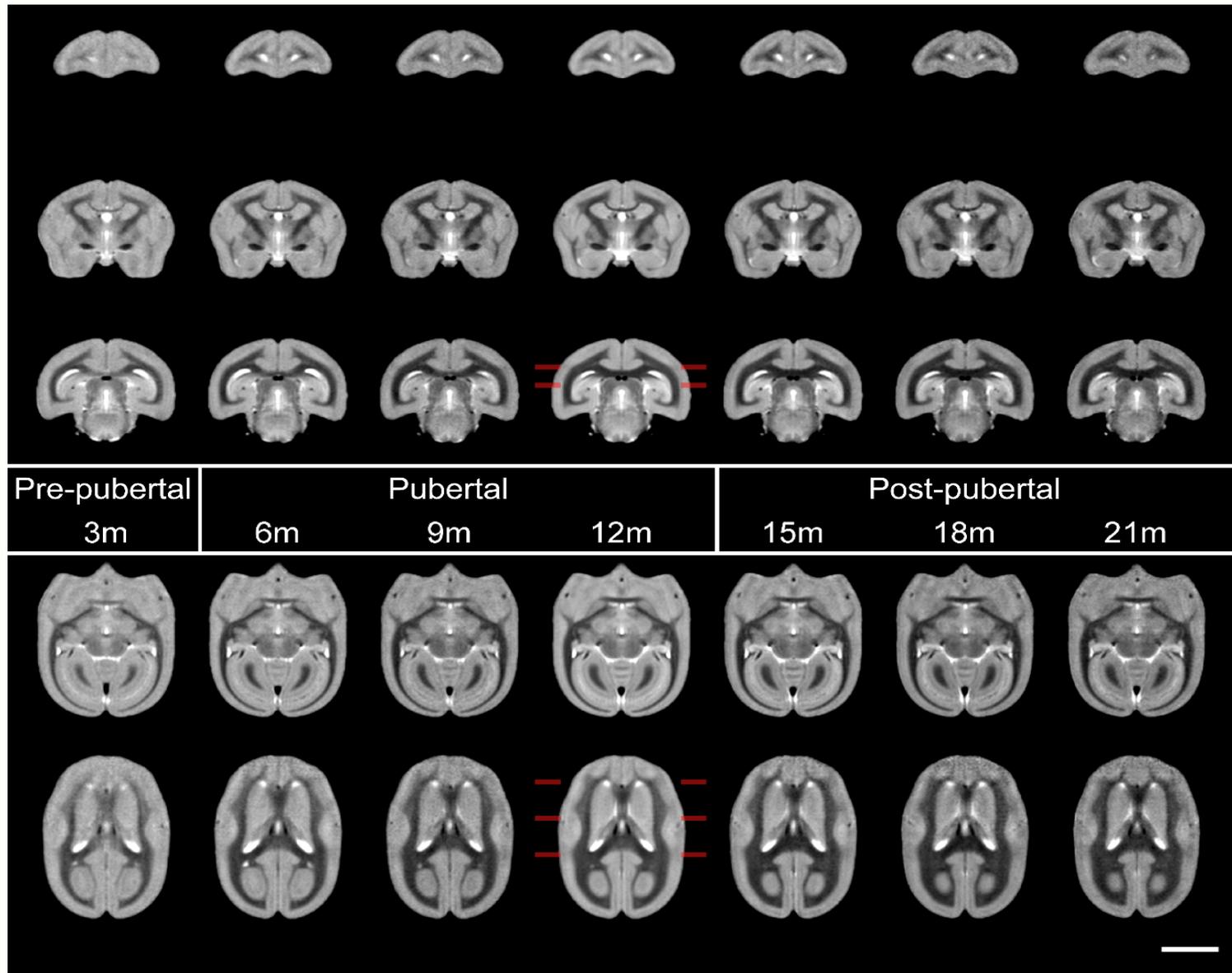
Allele dependent SSRI responsivity



Imaging Brain Development in the Marmoset



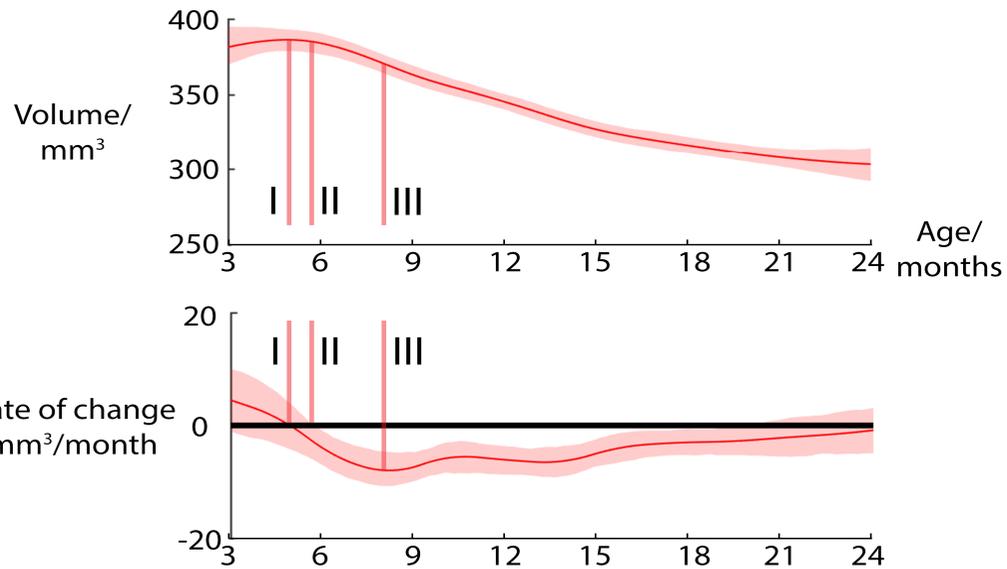
Changes in grey and white matter: 3-21 months



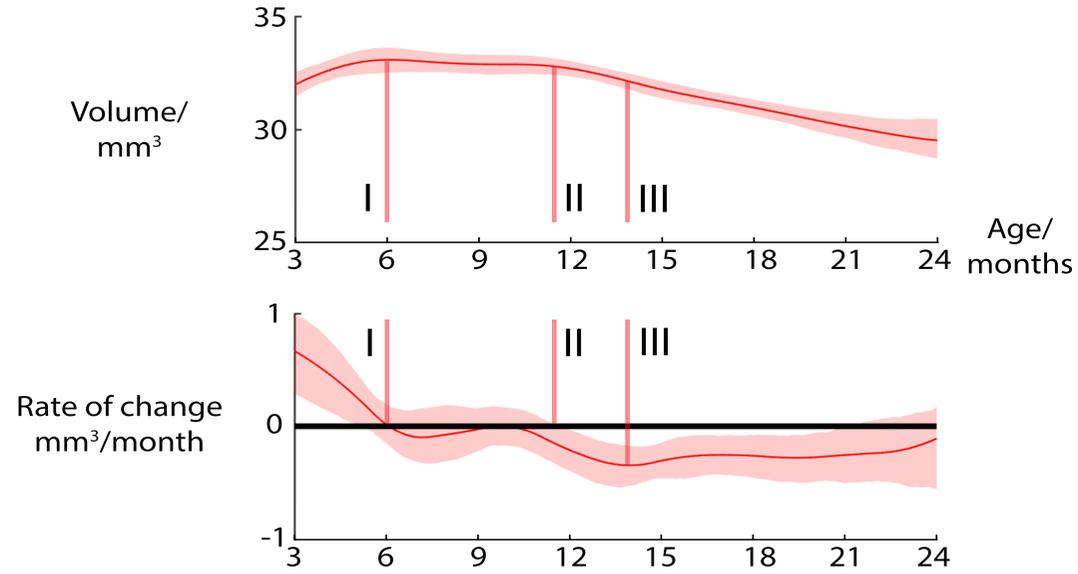
Cortical growth trajectories: 3 months to 2 years

53 cortical regions

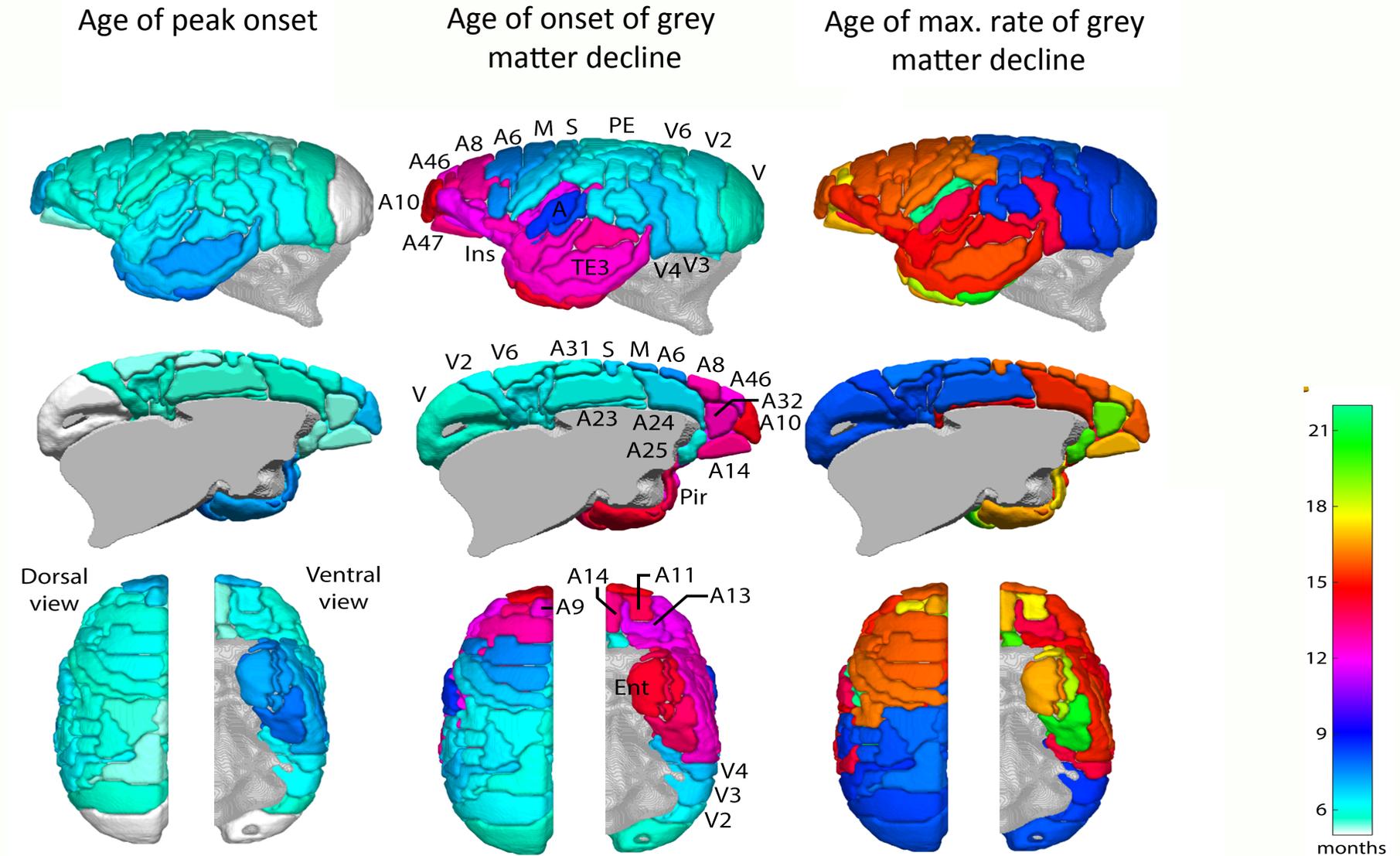
Primary visual cortex



Area 13



Milestones in Cortical Development in Marmosets



The Future

Bipolar mood disorder is a polygenic, highly heritable condition

More heritable than depression.

Polygenic risk score (sum of rare and common variants) for schizophrenia also predicts bipolar disorder

Most variants are in the noncoding, regulatory region

10 genome-wide significant loci

Combine genomic investigation with deeper phenotyping combined with sensitivity to treatments for better stratification

Targeting the switch mechanism in BPD will be important:

shortening and lengthening day length

Chimeric models

incorporating human iPSC-derived neurons into the developing brain



Acknowledgements



Marmoset Research and Translational Neuroimaging Facility

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- Dr Franklin Arborgio***

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- Dr Phil Gaskin***
- Dr Christian Wood***
- Mrs Lauren Anderson***

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