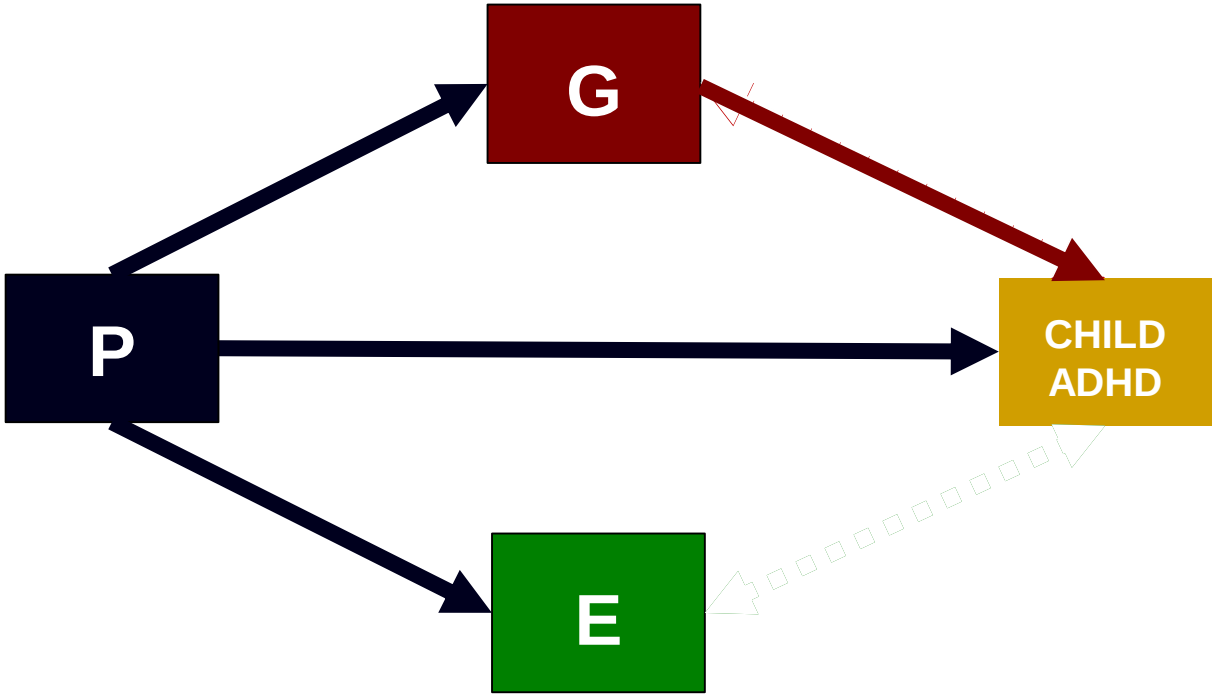
What have we learnt about the causes of ADHD?

Edmund Sonuga-Barke FBA FMedSci

RUNNING ORDER

- The translational imperative in ADHD science
- What have learnt about the aetiology of ADHD?
  - *Genes*
  - *Environments*
  - *GE interplay*
- What have we learnt about ADHD pathophysiology?
  - *Heterogeneity*
  - *Causation*
  - *Complexity*

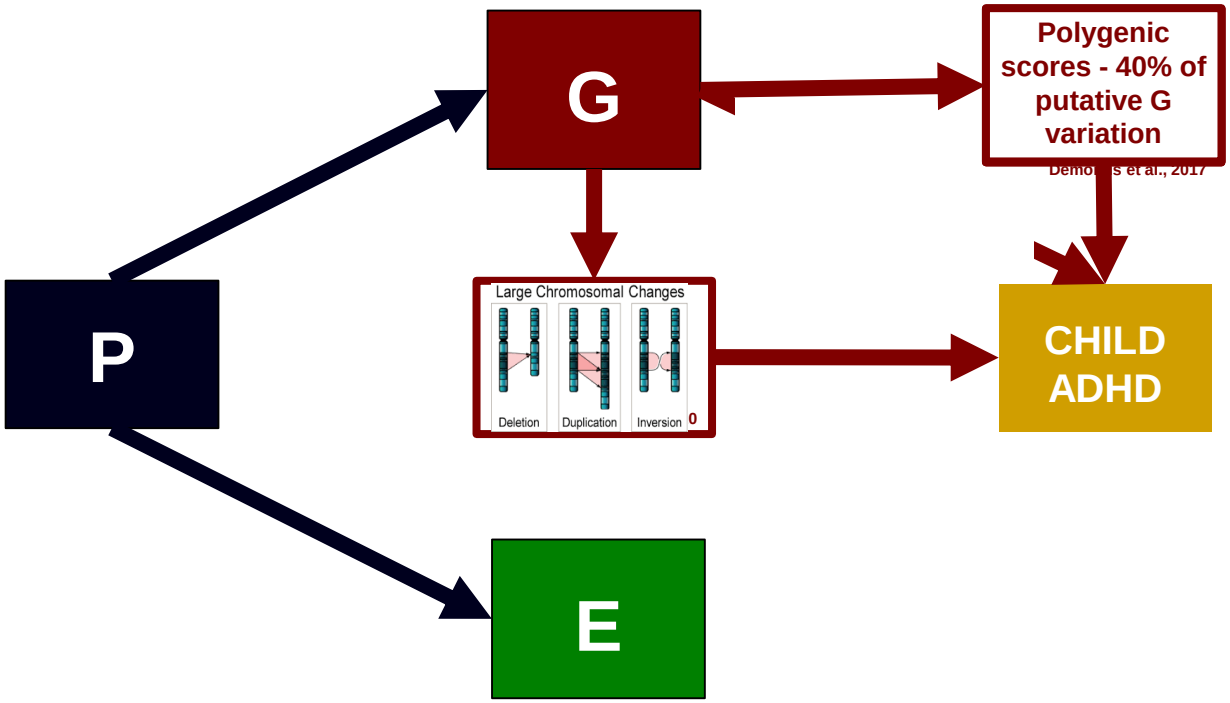
PARENTS PASS ON GENES (G) AND CREATE ENVIRONMENTS (E)



Twin studies suggest 70% is due to shared genes - 0% to shared environment

Burt (2009) Psychol Bull. 135, 608-37.

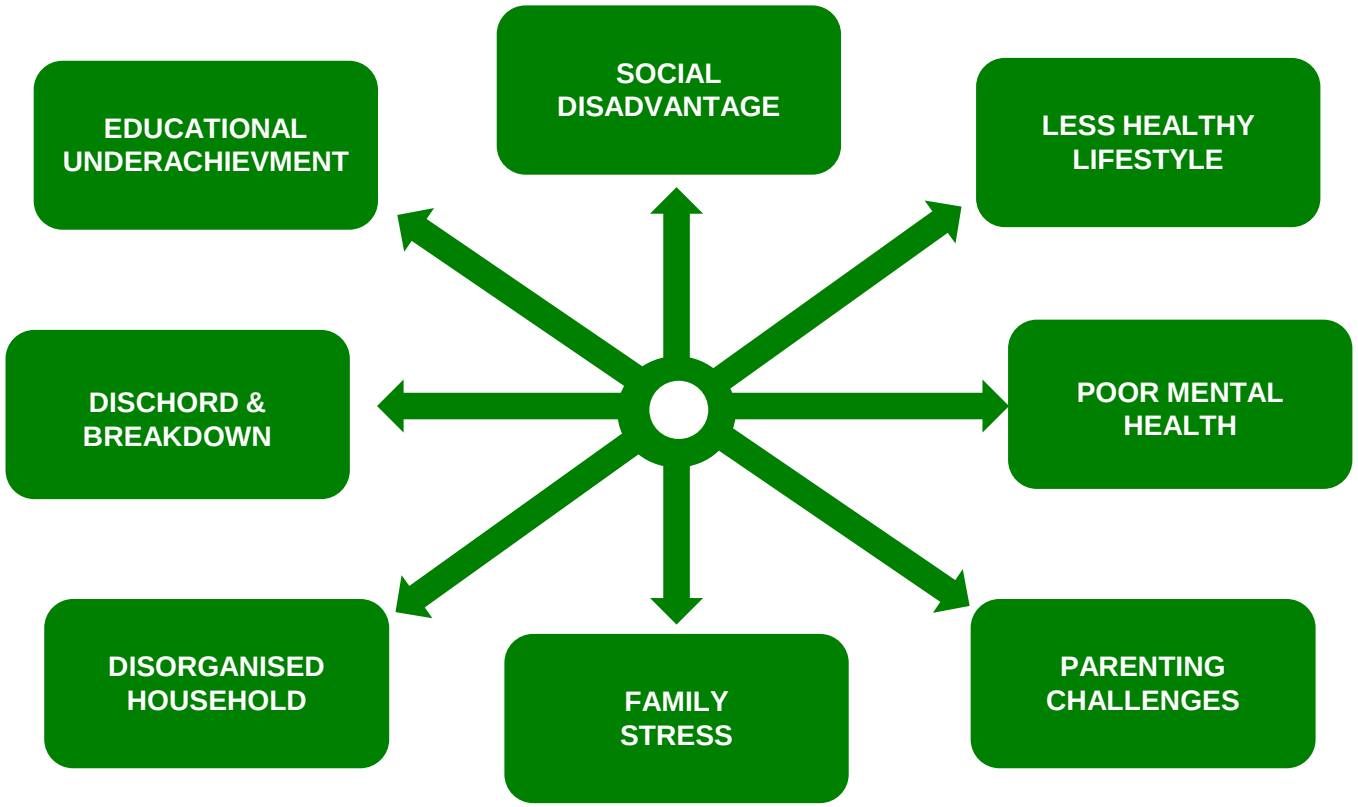
CAN STUDYING GE INTERPLAY HELP US FIND THE MISSING GENES?



"dark heritability"

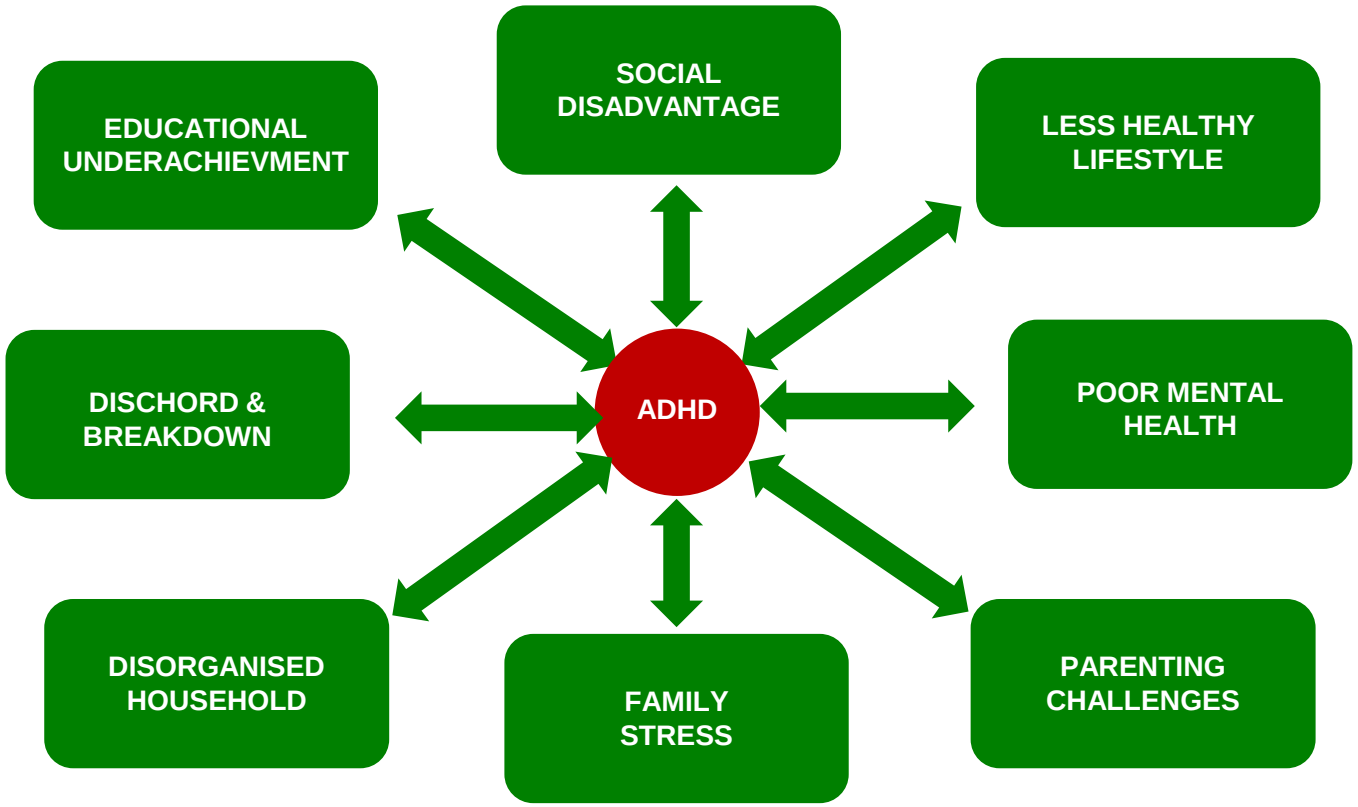
Lesch (2014) JCPP, 55, 201-203

ADHD IS MORE PREVALENT IN THOSE FAMILIES



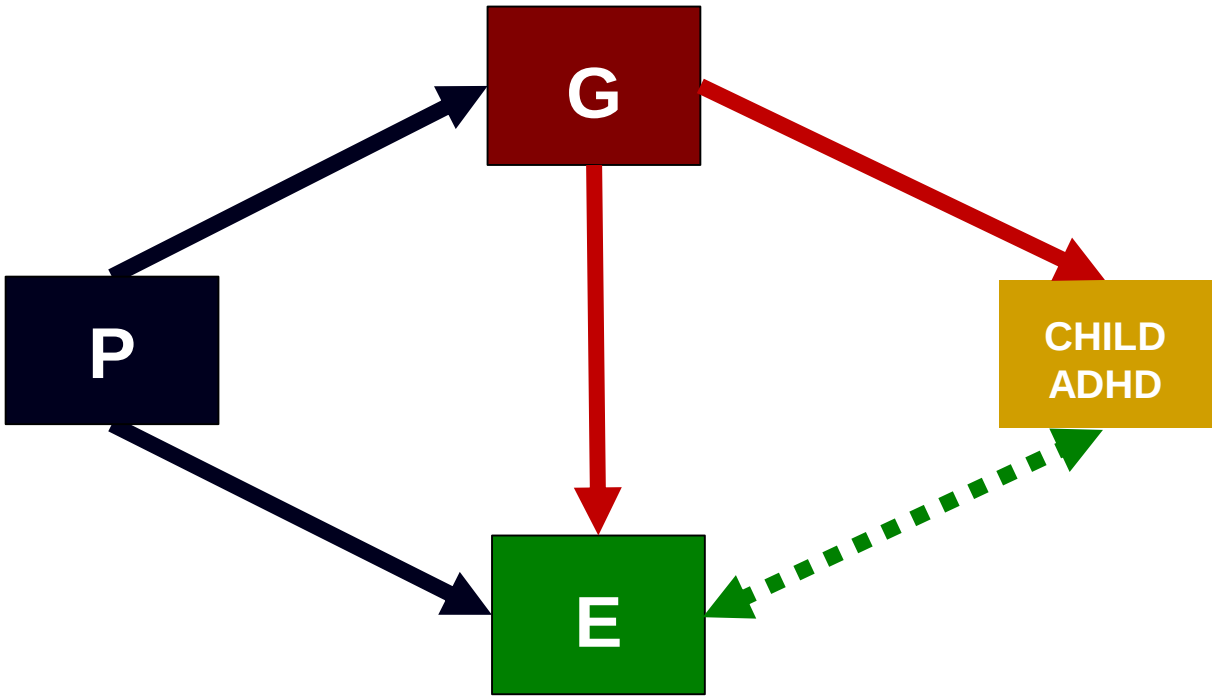
There is no simple story about what drives what?

ADHD IS MORE PREVALENT IN THOSE FAMILIES



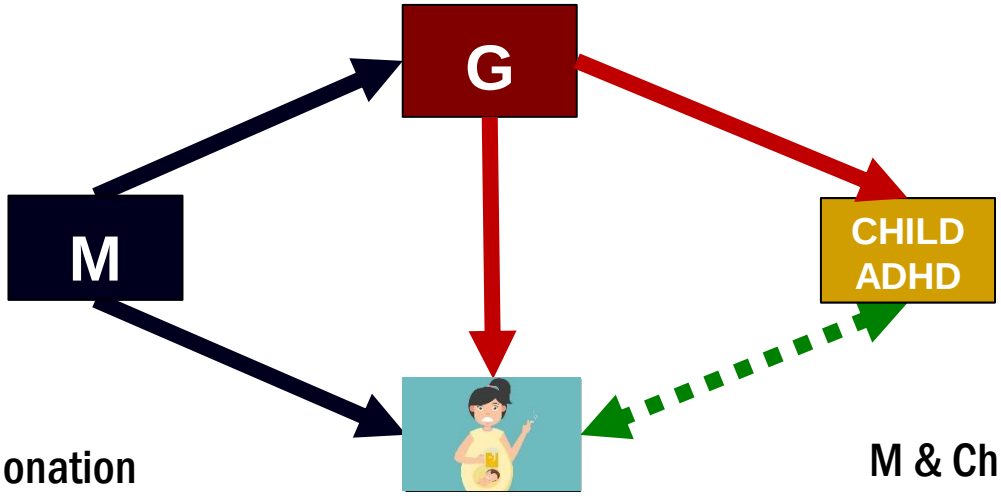
Small and non-deterministic and reciprocal associations.

BOTH E AND ADHD CAUSED BY THE SAME GENES



If real, the correlation between E and ADHD should be present whatever the genetic relationship between child and mother.

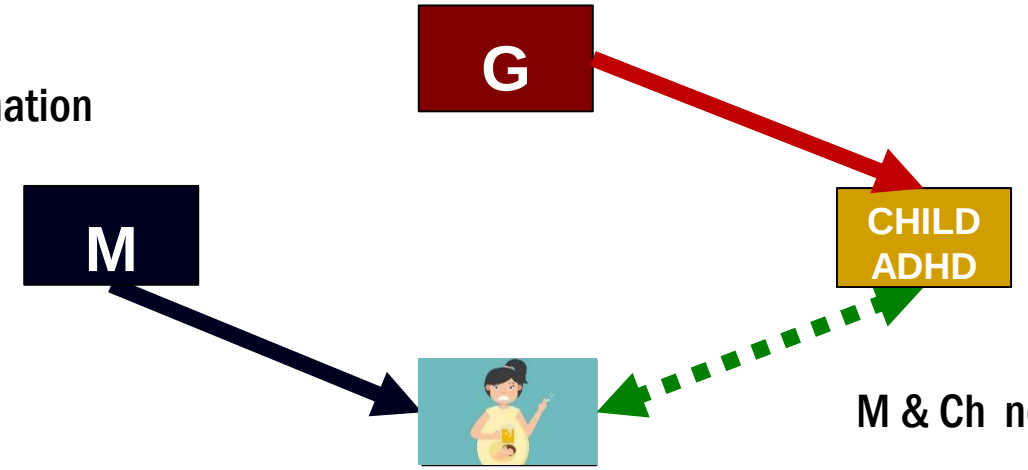
COMPARE IVF BY SPERM V EGG DONATION
CARDIFF IVF STUDY



IVF through sperm donation

M & Ch genetically related

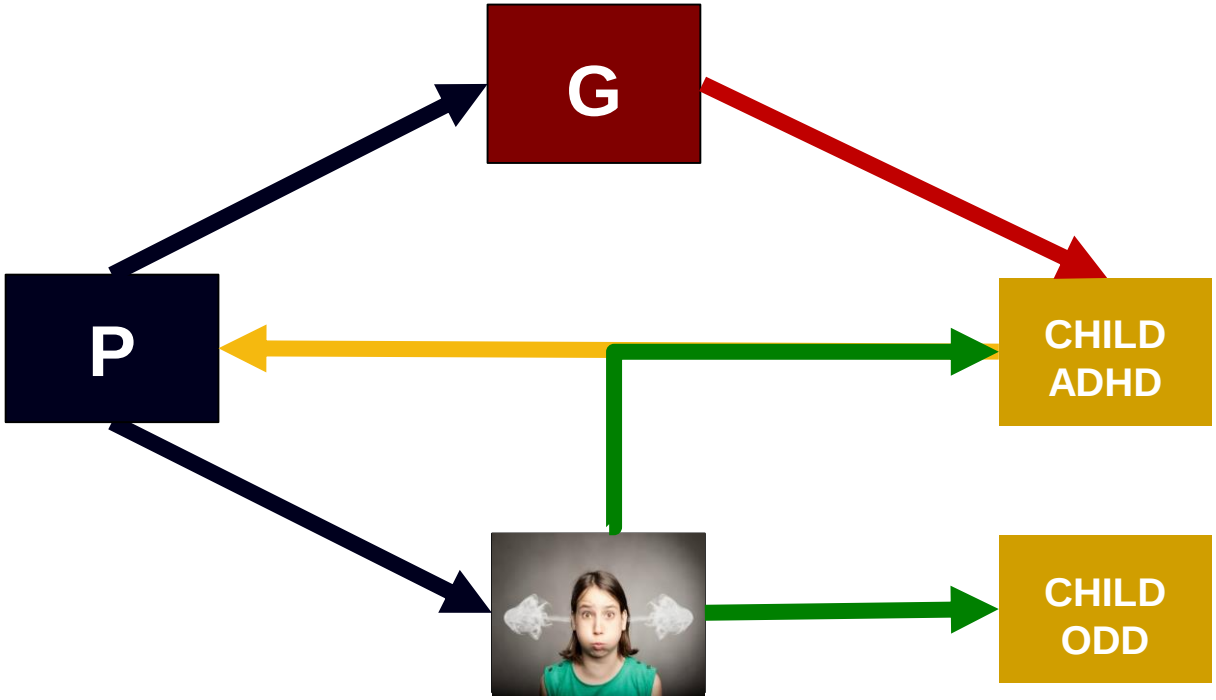
IVF through egg donation



M & Ch not genetically related

Smoking and ADHD was only correlated where the M & Ch were genetically related.

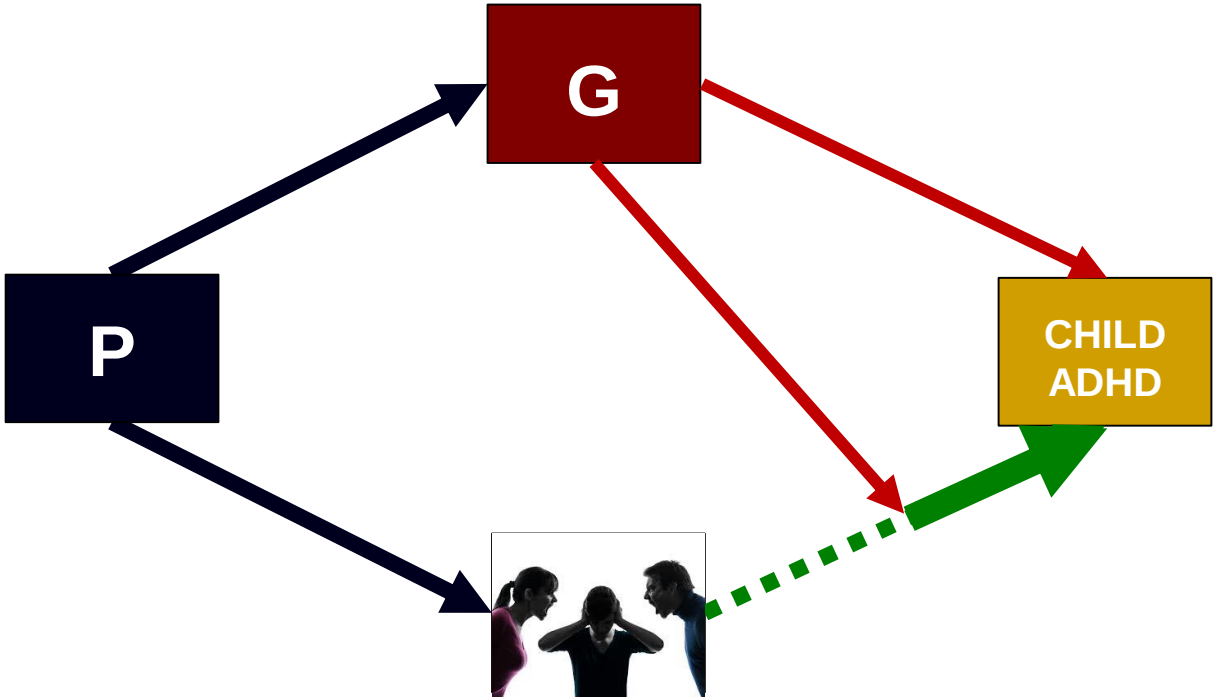
EVOCATIVE GE CORRELATIONS



Adoption studies support that this is not the result of passive GE

Harold et al. (2012)

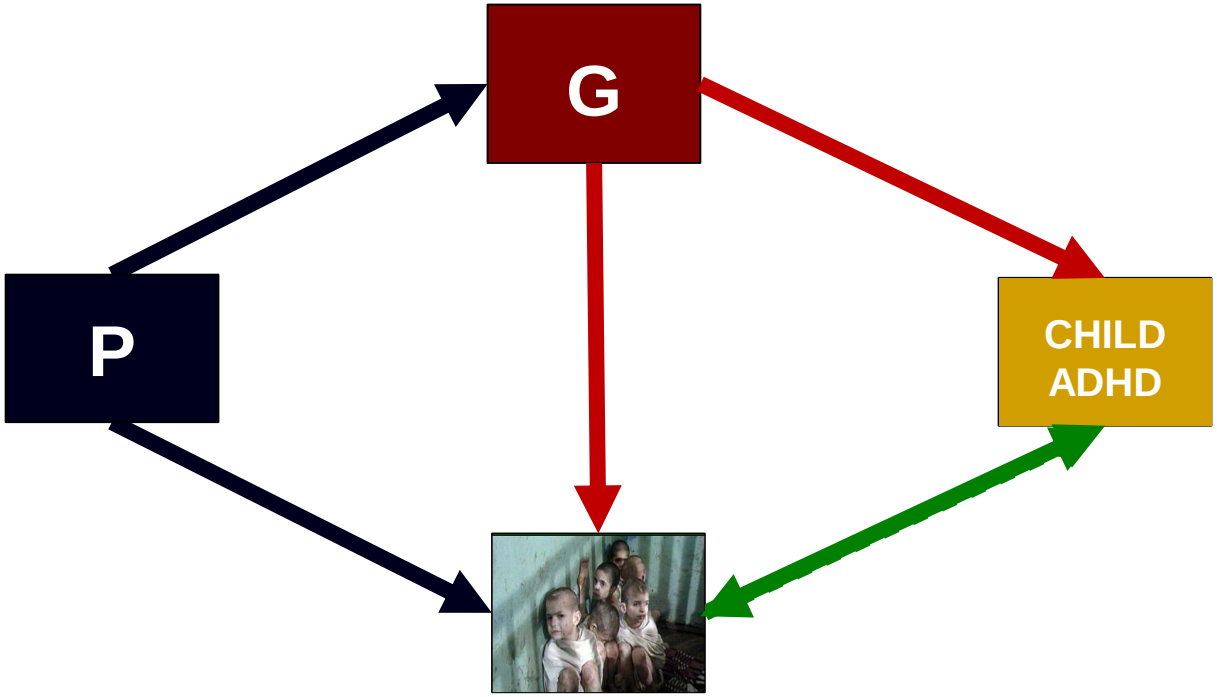
ARE E EFFECTS MISSED BECAUSE THEY ARE CONDITIONED BY G?



Now: Many reported but unreplicated GxE effects implicating a range of Gs and Es

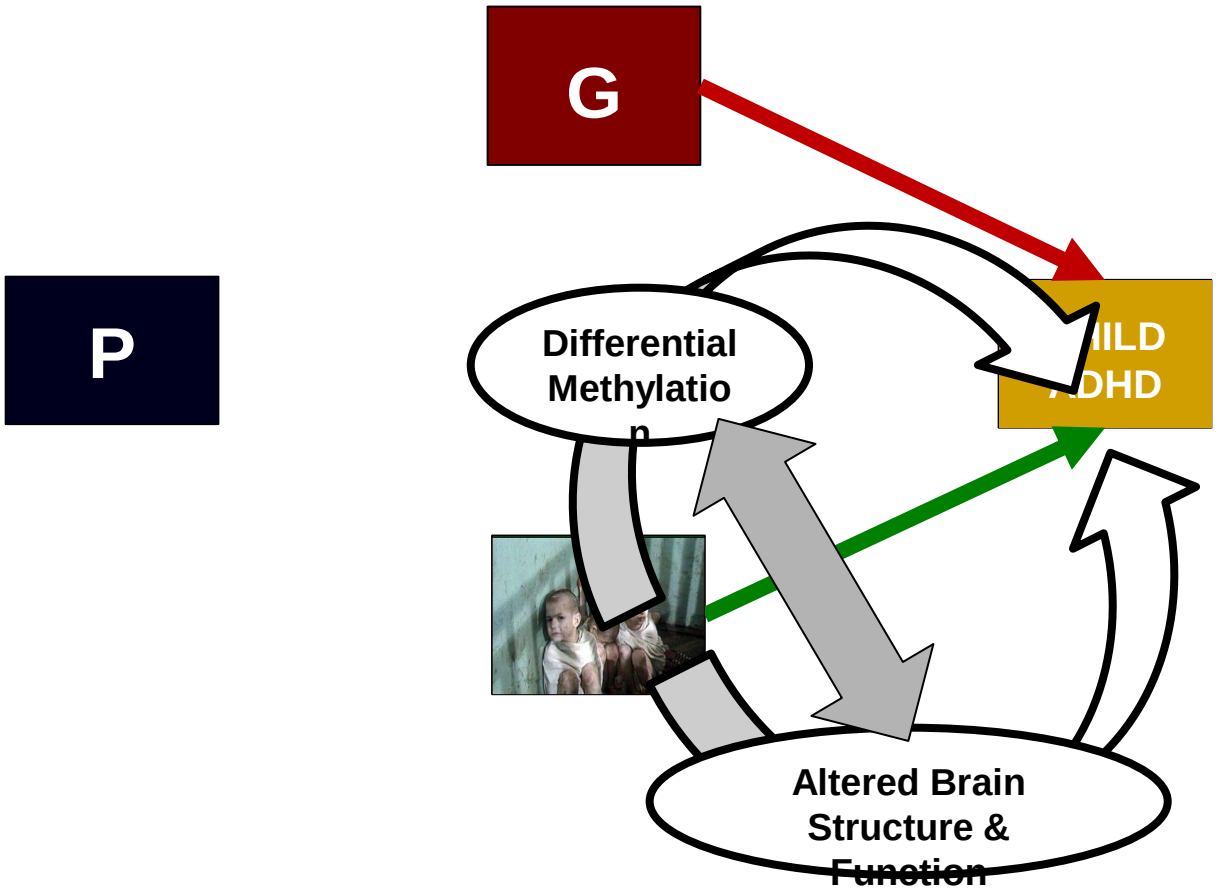
Nigg et al. (2010) JAACAP, 49, 863–873

COULD SEVERE ADVERSITY INDUCE EXTREME BRAIN PLASTICITY TO OVERRIDE G?



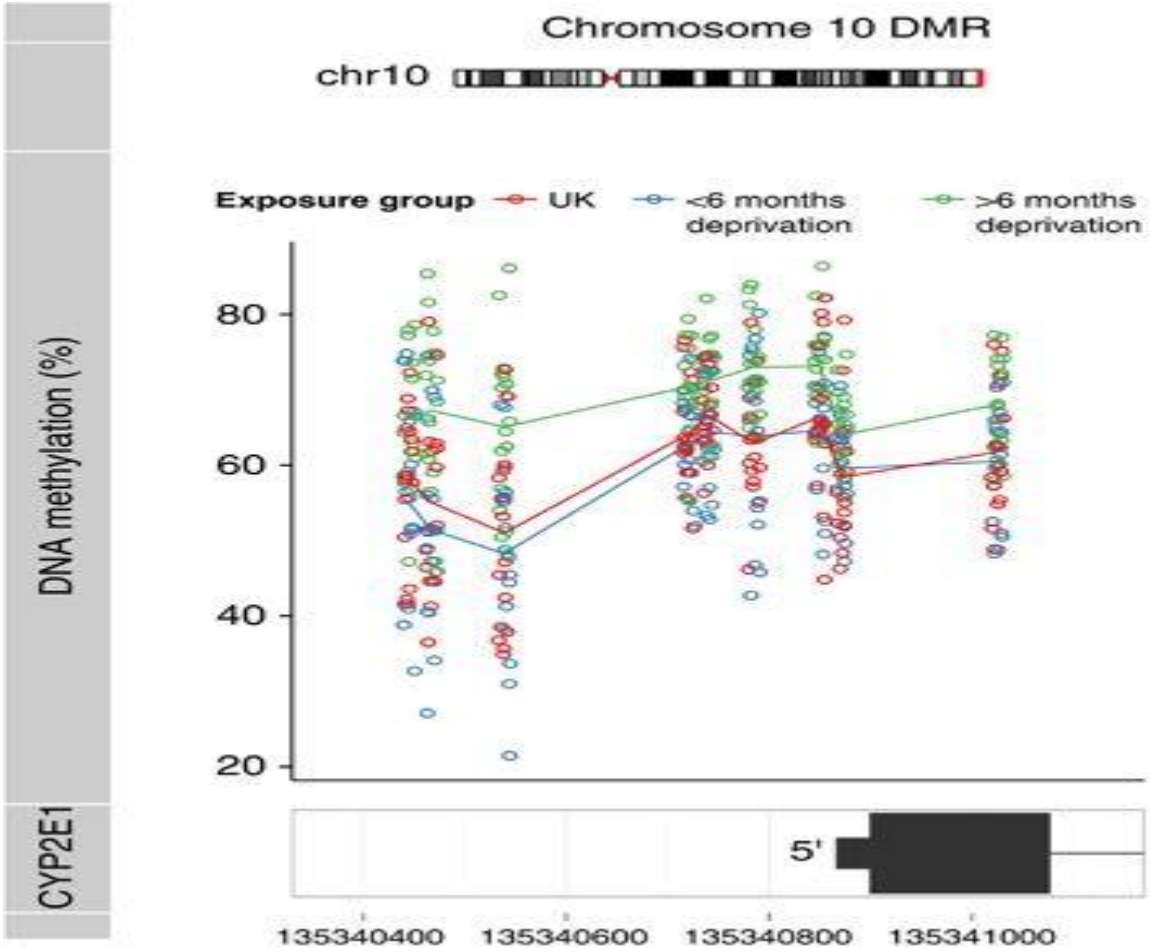
These effects are unlikely to be the result of common G or prenatal risks

WHAT MIGHT MEDIATE THESE EFFECTS?



NEURAL PROGRAMMING

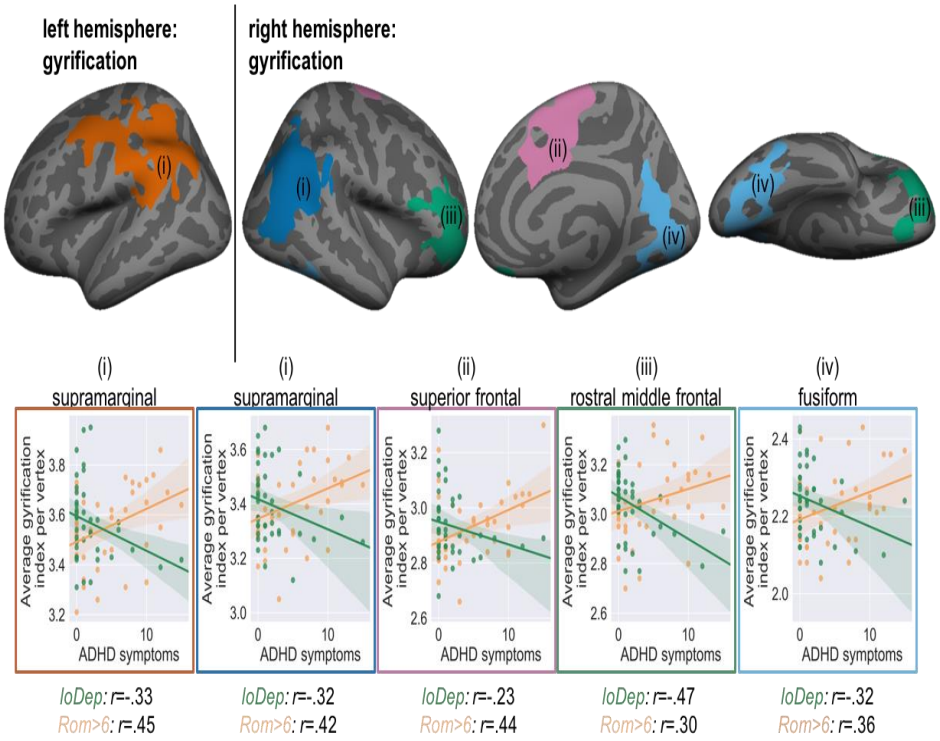
INITIAL EVIDENCE OF THE ENDURING EFFECTS OF DEPRIVATION ON METHYLATION



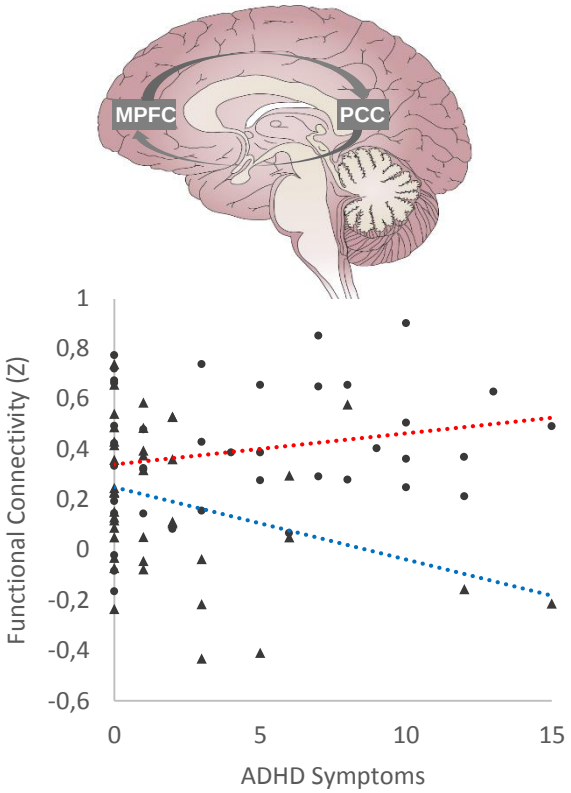
Differentially methylated CYP2E1 gene region – widely expressed in brain - lipid synthesis

Kumsta et al. 2016

INITIAL EVIDENCE THAT DEPRIVATION-DRIVEN ADHD HAS A DIFFERENT NEURAL SIGNATURE



STRUCTURE

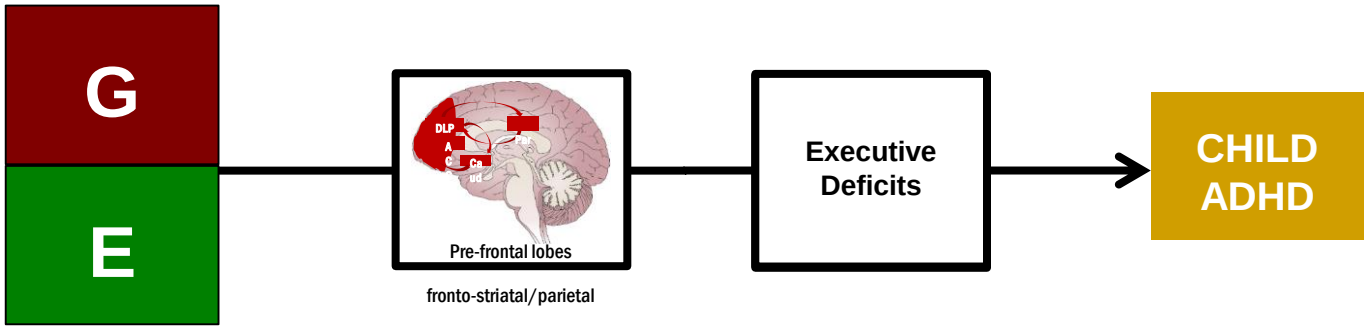


FUNCTION

Deprivation-driven ADHD marked by increased DMN connectivity

Broulidakis in prep

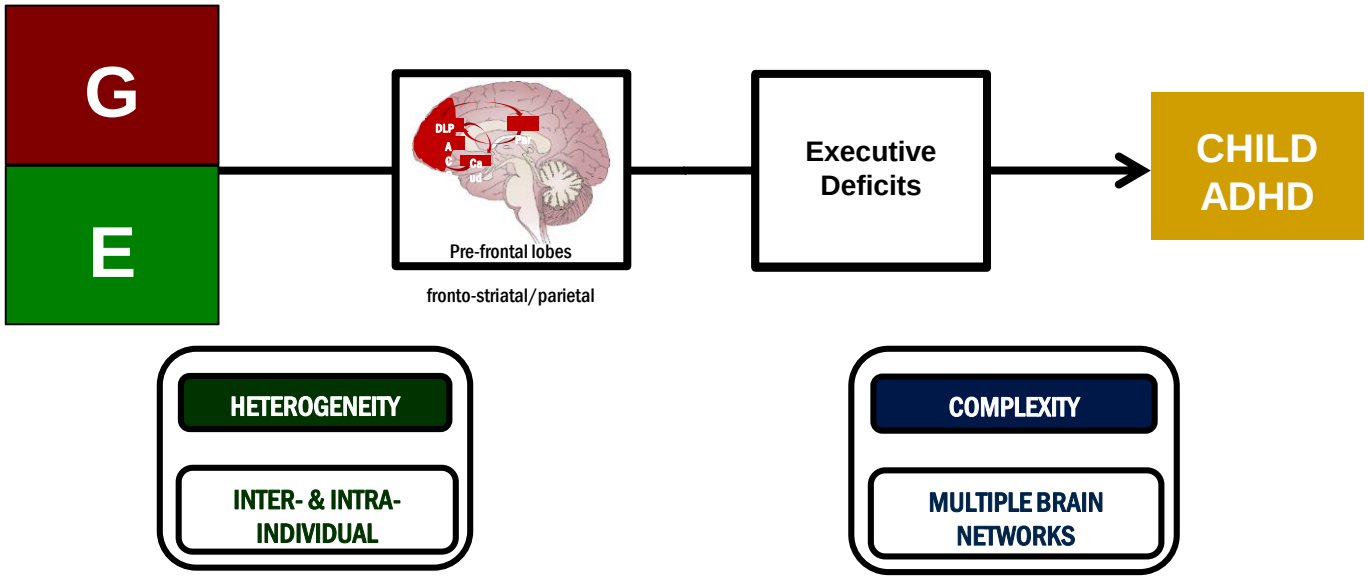
WE ALSO KNOW MUCH MORE ABOUT ADHD PATHOPHYSIOLOGY



Now – Alterations in regional communication through disconnectivity within circuits

Posner et al (2014) Neuropsychol Rev 24, 3–15

WE ALSO KNOW MUCH MORE ABOUT ADHD PATHOPHYSIOLOGY



DISCOVERY OF ADHD COMPLEXITY & HETEROGENEITY HAVE LED TO THE RE-EVALUATION OF THE EF DEFICIT MODEL

HETEROGENEITY
THESIS & ANTI-THESIS

THESIS

ADHD IS AN EXECUTIVE DYSFUNCTION DISORDER – EF DEFICITS ARE UBIQUITOUS, STABLE, NECESSARY AND SUFFICIENT.

ANTI-THESIS

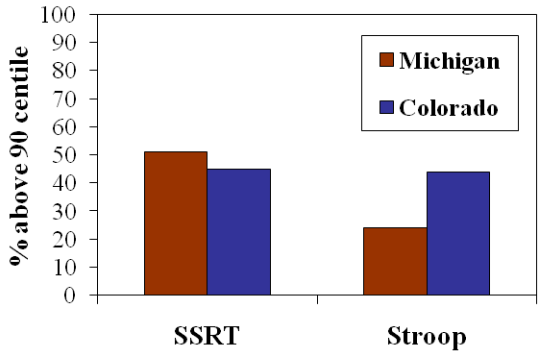
ADHD IS NEUORPSYCHOLOGICALLY HETEROGENEOUS CONDITION WITH VARIATION IN EF BETWEEN PATIENTS.

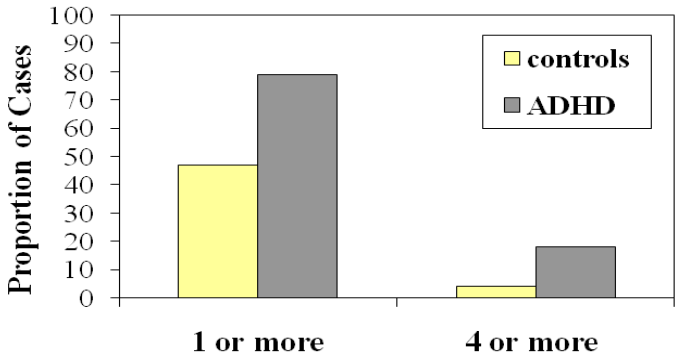
TRAIT HETEROGENEITY IN ADHD EVIDENCE

ADVANCING THE NEUROSCIENCE OF ADHD

Causal Heterogeneity in Attention-Deficit/ Hyperactivity Disorder: Do We Need Neuropsychologically Impaired Subtypes?

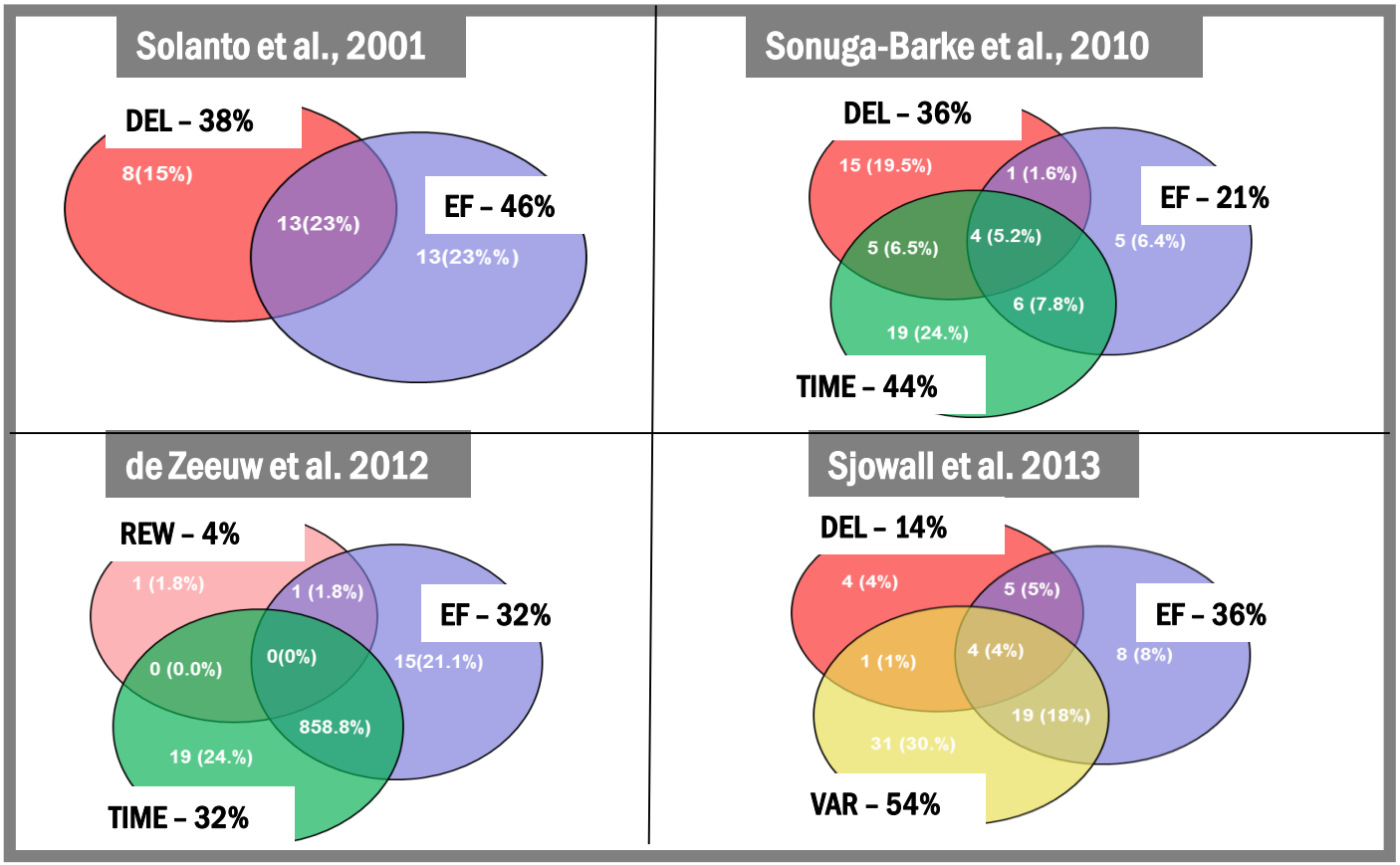
Joel T. Nigg, Erik G. Willcutt, Alysa E. Doyle, and Edmund J.S. Sonuga-Barke



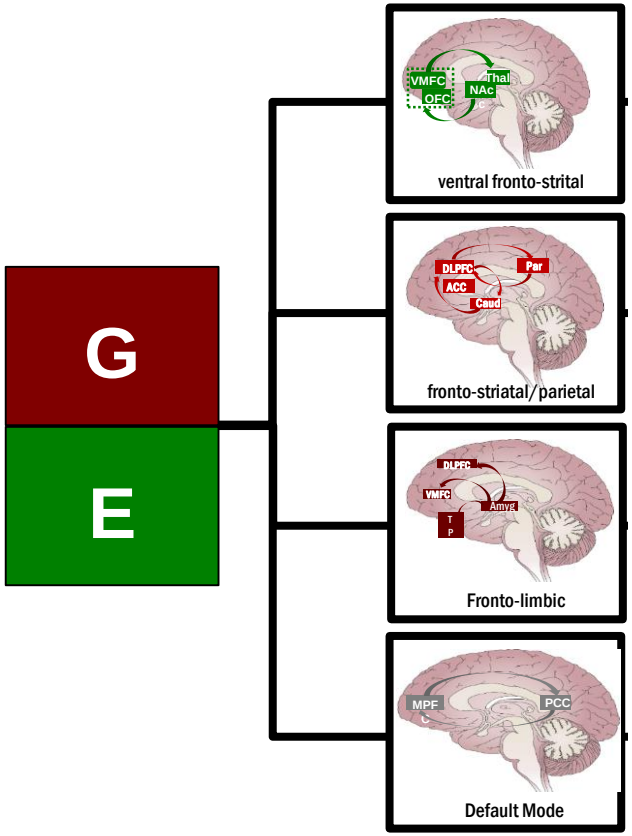


AT MOST ONLY 50% OF ADHD PARTICIPANTS HAD AN EF DEFICIT

THEN THERE WERE TWO....ER NO I MEAN THREE...



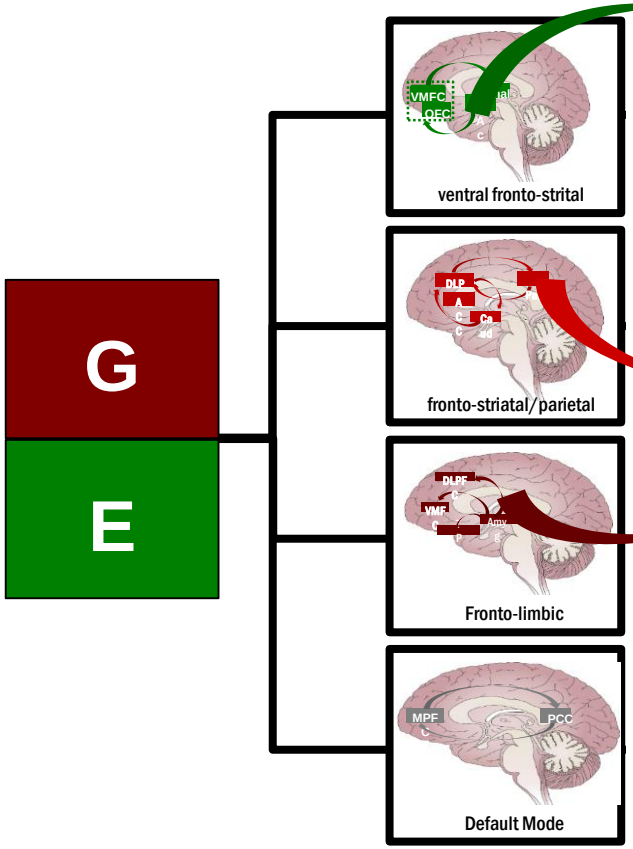
MULTIPLE PATHOPHYSIOLOGICAL PATHWAYS



Which may cleave into dissociable neuropsychological clusters of individuals

Fair et al. (2012) PNAS109, 6769-74

MULTIPLE PATHOPHYSIOLOGICAL PATHWAYS



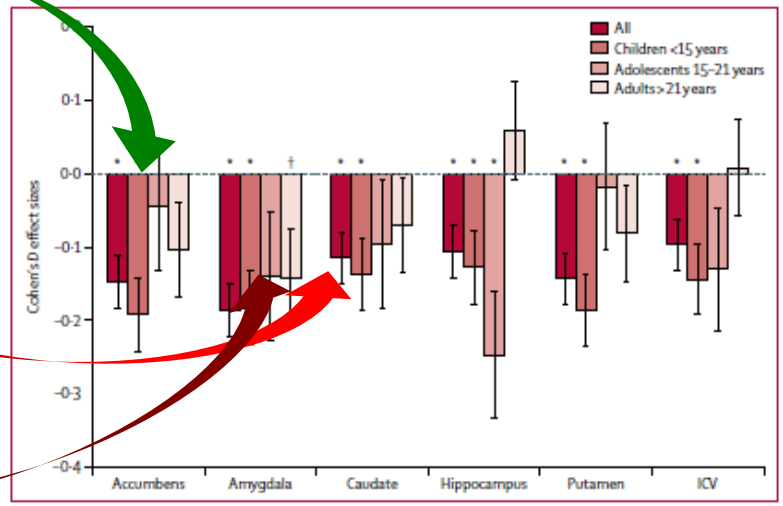


Figure 1: **Cohen's d effect sizes of differences between patients with ADHD and healthy controls for subcortical volumes and intracranial volume, for all patients, children only (<15 years), adolescents only (15–21 years), and adults only (>21 years)**
Error bars denote standard error. *Significant after false discovery rate correction. †Nominally significant at p<0·05. ICV=intracranial volume.

Structural alterations map onto these different pathways

Hoogman et al (2017), Lancet 44,1087-1099

COMPLEXITY
THESIS & ANTI-THESIS

THESIS

ADHD IS PATHOPHYSIOLOGICALLY SIMPLE - DRIVEN PRIMARILY BY DYSFUNCTION IN ONE SYSTEM.

ANTI-THESIS

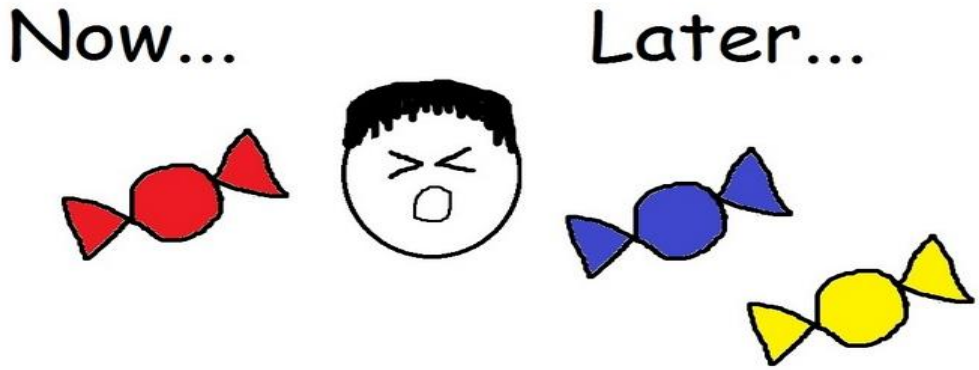
EVEN WITHIN SPECIFIC SUB-GROUPS OF PATIENTS ADHD INVOLVES THE INTERACTION BETWEEN MULTIPLE BRAIN SYSTEMS AND COGNITIVE PROCESSES.

IMPULSIVE CHOICE IN ADHD

A SIMPLE BEHAVIOUR WITH A COMPLEX NEURAL ARCHITECTURE

IMPULSIVE CHOICE

- In every day life, where our resources are finite, we have often to choose between lager later (LL) over smaller sooner (SS) rewards to act effectively.



CHILDREN WITH ADHD WAIT LESS THAN THEIR PEERS

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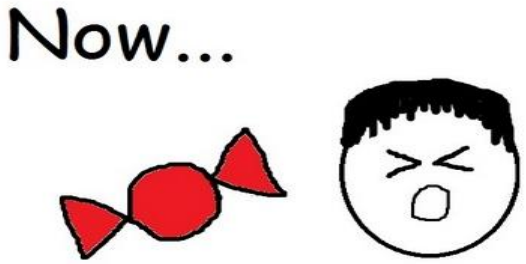

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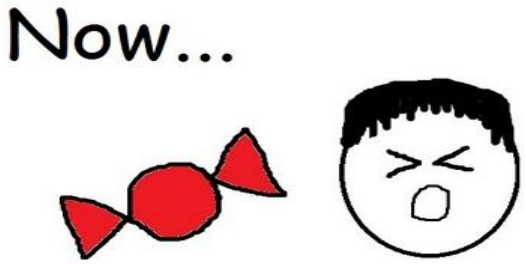
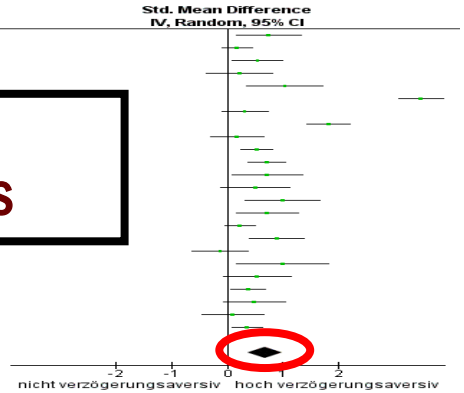


Study or Subgroup	Control Mean	Control SD	Control Total	ADHD Mean	ADHD SD	ADHD Total	Weight	Std. Mean Difference IV, Random, 95% CI
Antrop et al. (2006)	75,6	27,09	25	52,8	33,01	25	4,0%	0,74 [0,17, 1,32]
Bidwell et al. (2007)	32,7	5,5	109	31,7	5,6	106	4,5%	0,18 [-0,09, 0,45]
Bitsakou et al. (2009a)	77,61	31,43	29	60,87	29,91	54	4,2%	0,54 [0,09, 1,00]
Bitsakou et al. (2009b)	87,32	26,49	21	81,34	24,85	23	4,0%	0,23 [-0,36, 0,82]
Dalen et al. (2004)	55	22,5	18	32,5	20	18	3,8%	1,03 [0,35, 1,72]
Solanto et al. (2007)	40,25	20,5	20	43,58	28,84	60	4,2%	-0,12 [-0,63, 0,38]
Sonuga-Barke et al (1992)	48	34	16	18	20	11	3,5%	1,00 [0,18, 1,82]
Vloet et al. (2010)	68,85	37,55	25	49,75	31,16	20	4,0%	0,54 [-0,06, 1,14]
Wahlstedt et al. (2009)	47,6	29,5	62	37,08	26,42	120	4,5%	0,38 [0,07, 0,69]
Wilhelm et al. (2011a)	63,9	39,23	27	45,45	35,72	24	4,1%	0,48 [-0,08, 1,04]
Wilhelm et al. (2011b)	62,6	42,62	27	58,35	40,83	24	4,1%	0,10 [-0,45, 0,65]
Yang et al. (2011)	99,49	4,97	100	97,68	5,13	100	4,5%	0,36 [0,08, 0,64]
Total (95% CI)			**1120**			**1495**	**100,0%**	**0,69 [0,38, 1,00]**

Heterogeneity: Tau² = 0,52; Chi² = 280,00, df = 23 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4,40 (P < 0.0001)

Ivo Marx

MIDA/CDT - 1 PT AFTER 2 SECS VERSUS 2 PTS AFTER 30 SECONDS



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THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry 57:3 (2016), pp 321–349 doi:10.1111/jcpp.12496

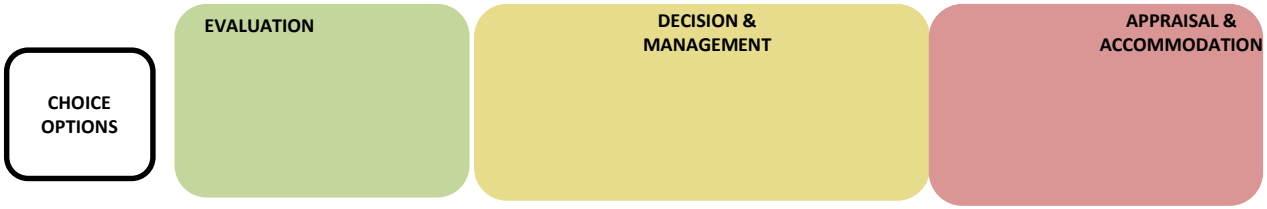
Annual Research Review: Transdiagnostic neuroscience of child and adolescent mental disorders – differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety

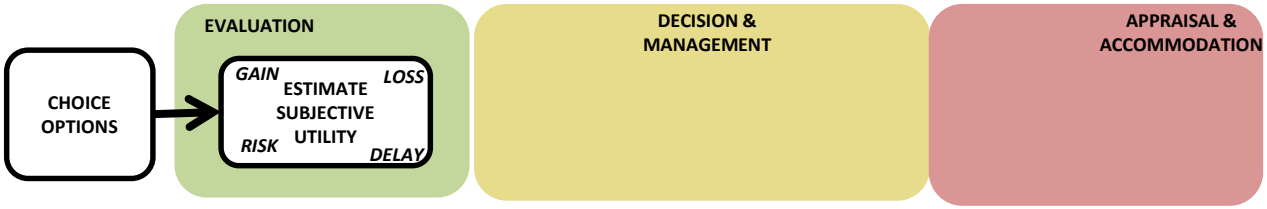
Edmund J. S. Sonuga-Barke,[1] Samuele Cortese,[1,2] Graeme Fairchild,[1] and Argyris Stringaris[3]

[1]Developmental Brain-Behaviour Laboratory, Academic Unit of Psychology, University of Southampton, Southampton, UK; [2]Child Study Center at NYU Langone Medical Center, New York, NY, USA; [3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

INCORPORATING THE USUAL SUSPECTS

EXECUTIVE AND REWARD PROCESSES


CHOICE OPTIONS
EVALUATION
DECISION & MANAGEMENT
APPRAISAL & ACCOMMODATION


CHOICE OPTIONS
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DECISION & MANAGEMENT
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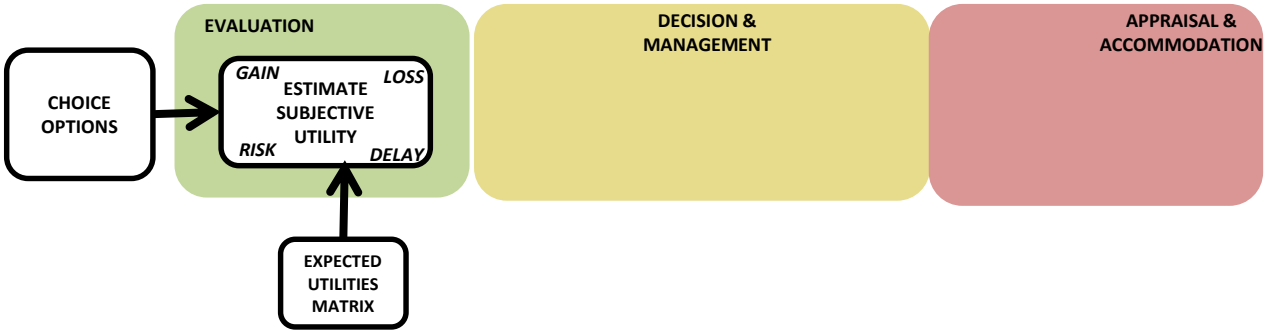
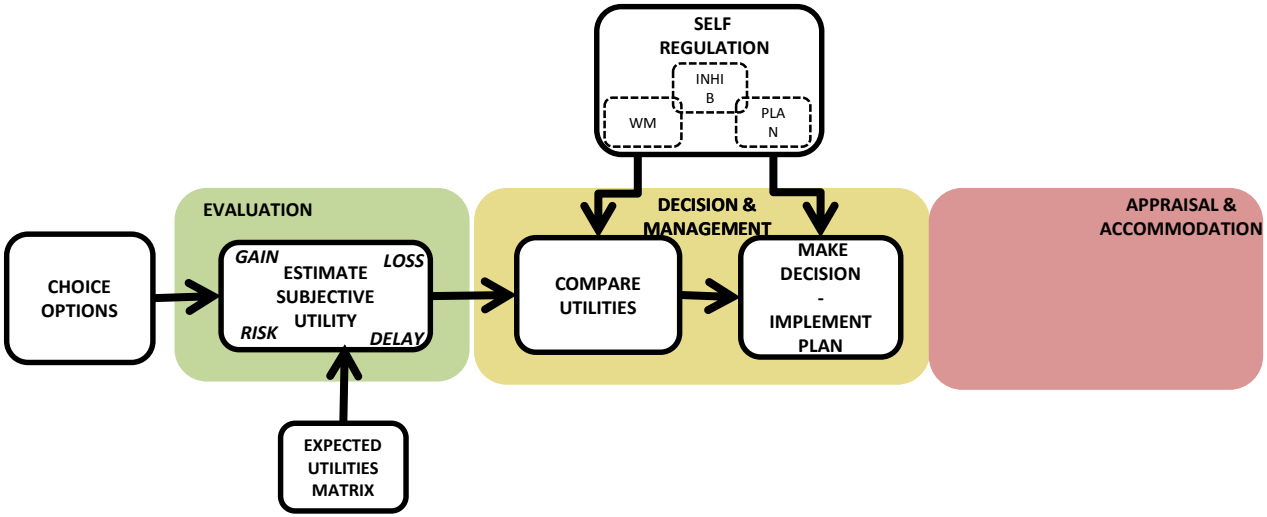
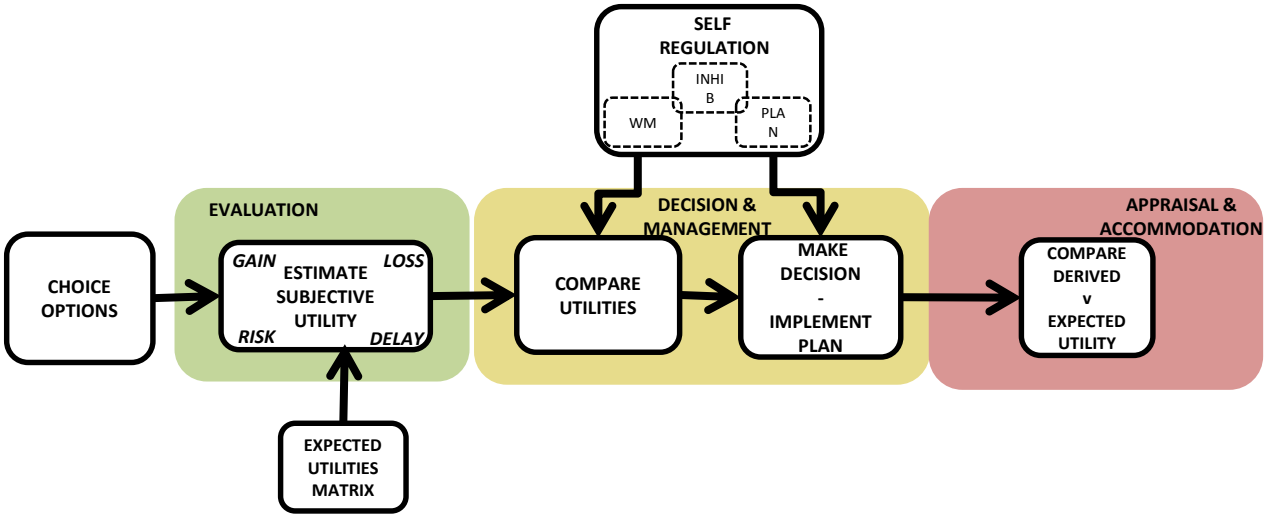


IMPLICIT REINFORCEMENT PROCESSES

HIGHER ORDER EXECUTIVE PROCESSES



IMPLICIT REINFORCEMENT PROCESSES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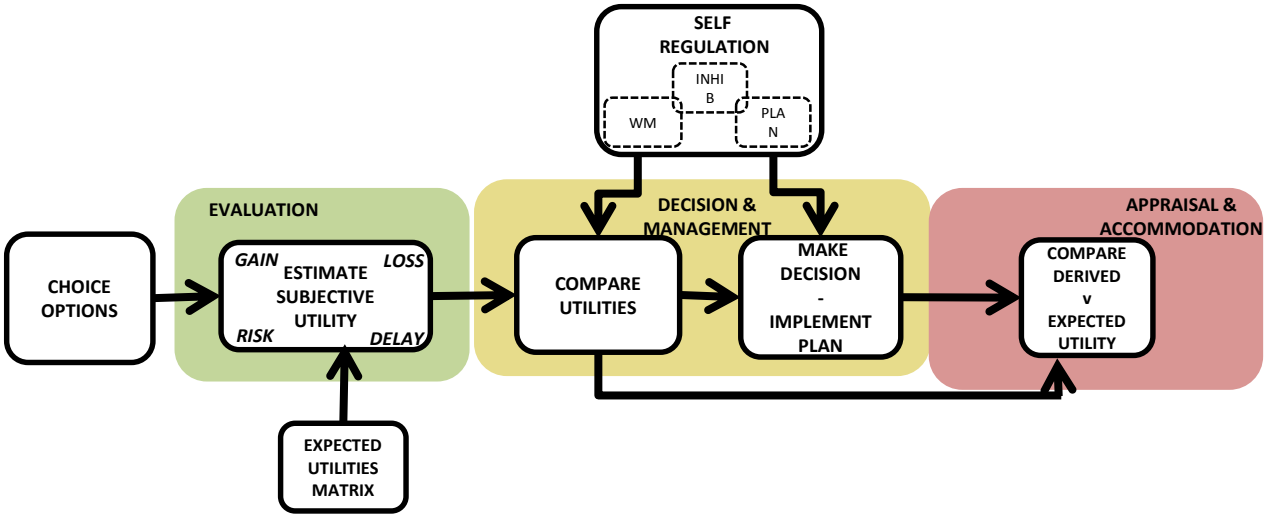
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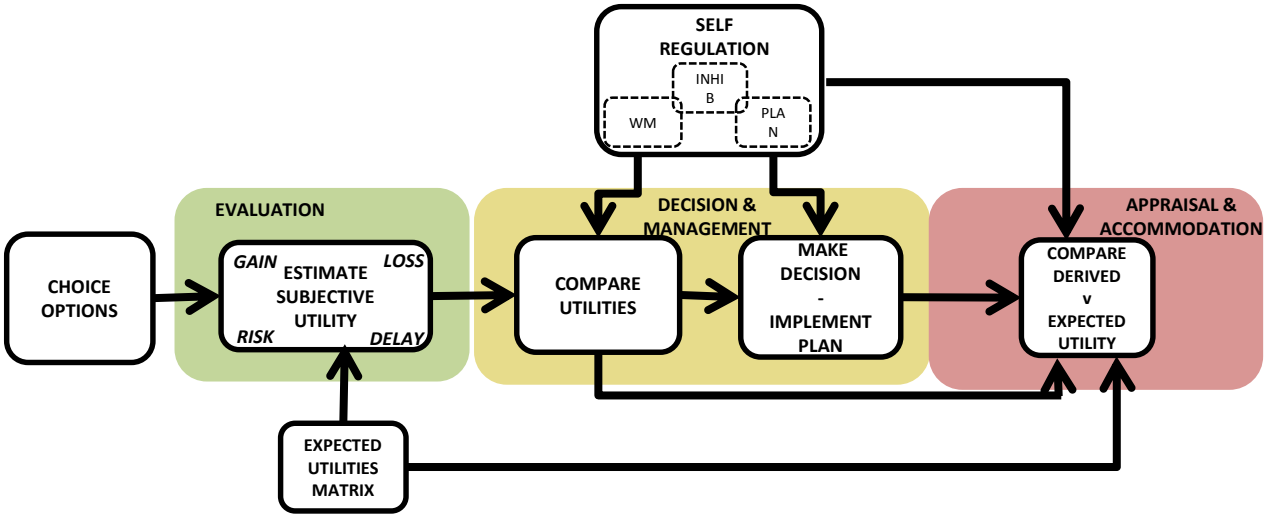
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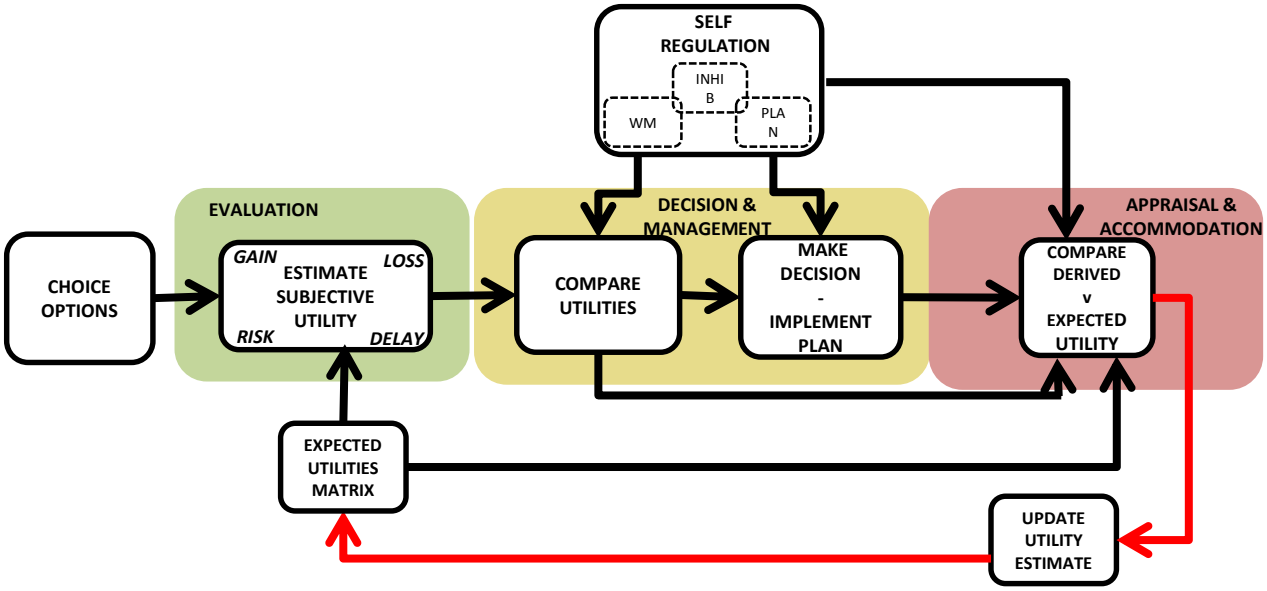
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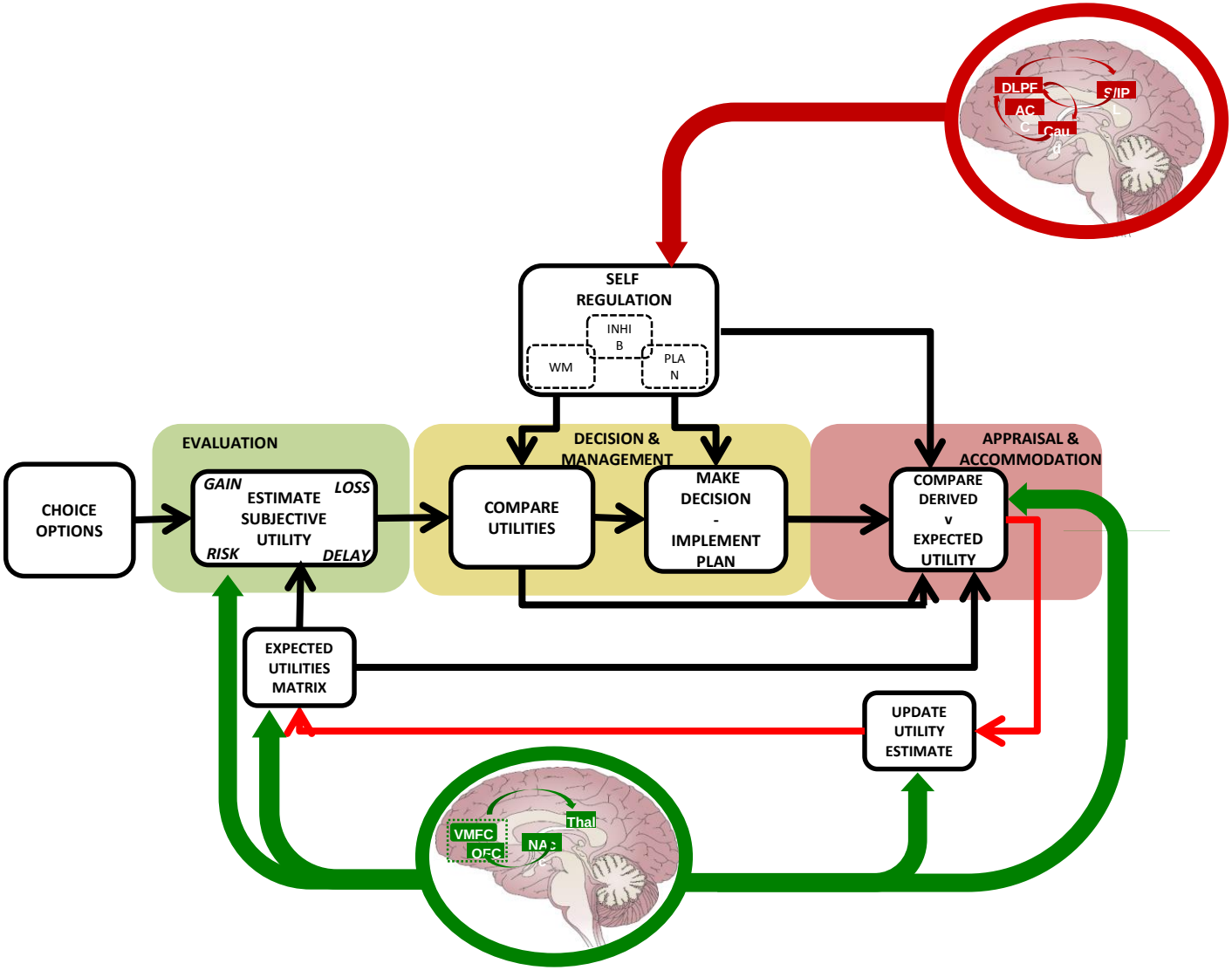
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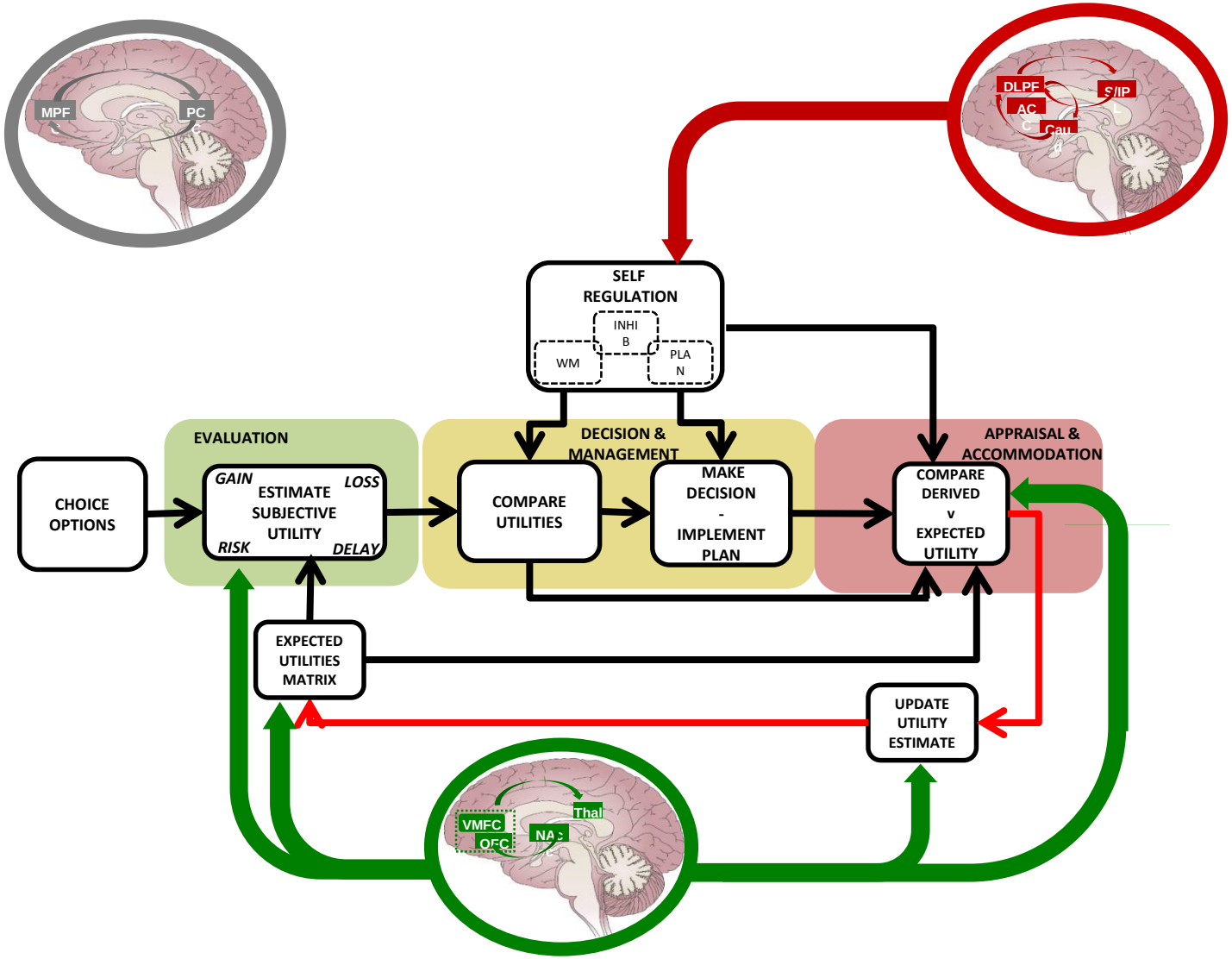
BEYOND THE USUAL SUSPECTS

COULD DM DYSFUNCTION CONTRIBUTE TO IC ADHD?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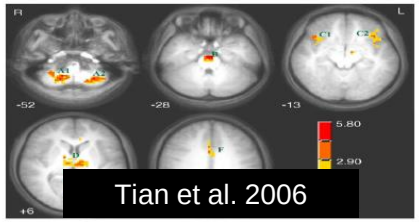
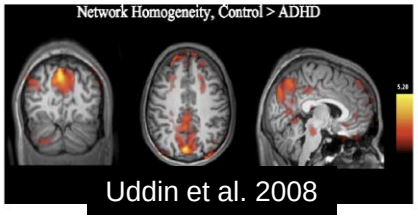
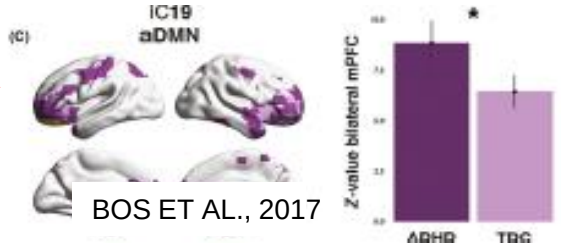
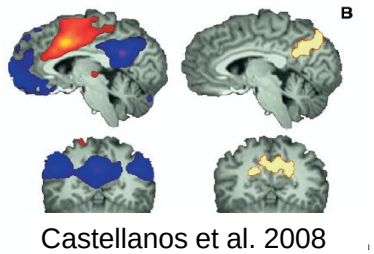
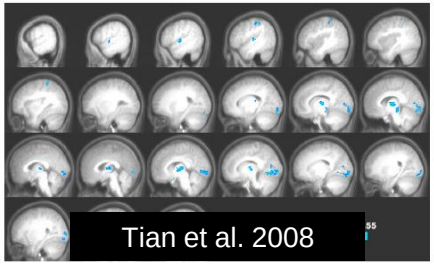
DISTURBED/IMMATURE DMN CONECTIVITY IN ADHD

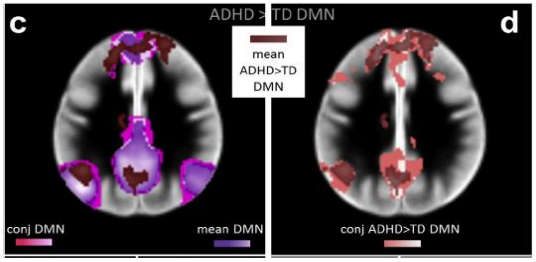


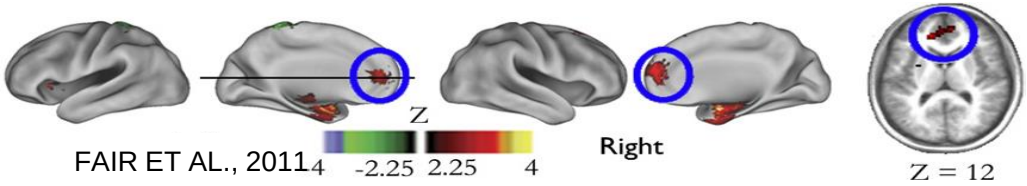










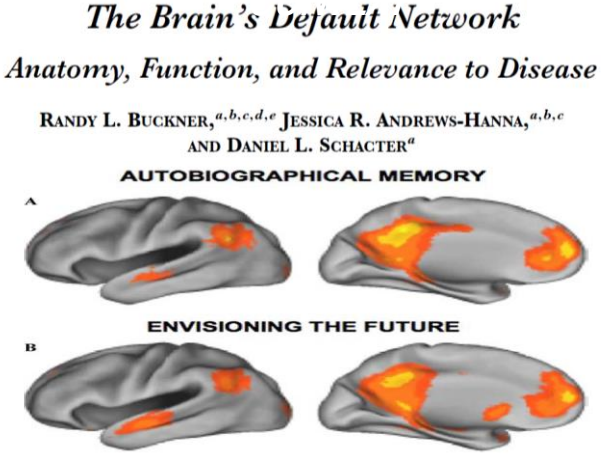


WHAT ROLE COULD DMN PLAY IN IMPULSIVE CHOICE?

A DOUBLE EDGED SWORD

WHAT ROLE COULD DMN PLAY IN IMPULSIVE CHOICE?

INTROSPECTION PROMOTES FUTURE ORIENTATED THOUGHT & PUTS DECISIONS IN CONTEXT



The Brain's Default Network

Anatomy, Function, and Relevance to Disease

RANDY L. BUCKNER,[a,b,c,d,e] JESSICA R. ANDREWS-HANNA,[a,b,c] AND DANIEL L. SCHACTER[a]

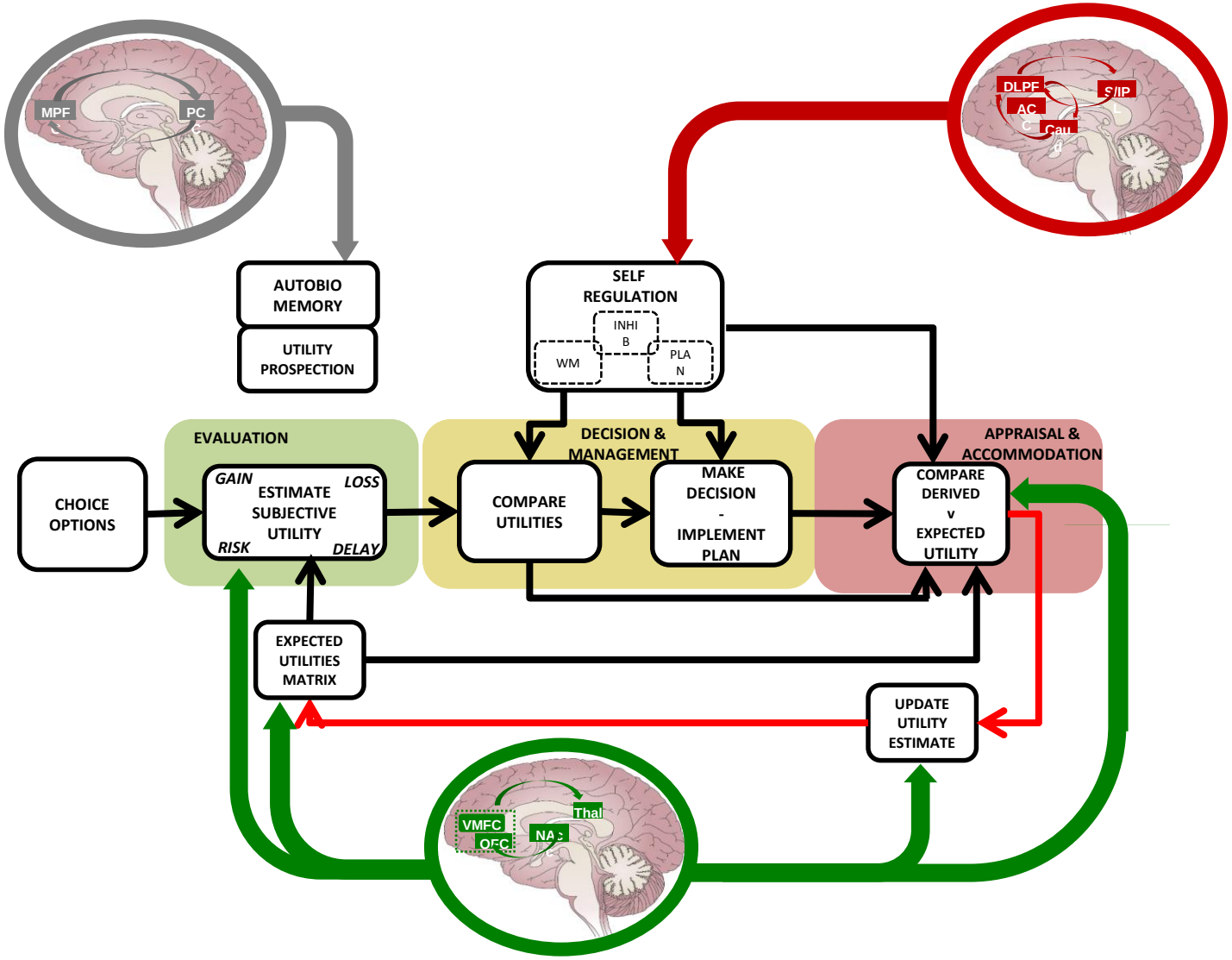
AUTOBIOGRAPHICAL MEMORY

A

ENVISIONING THE FUTURE

B

A DOUBLE EDGED SWORD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COMPARE DERIVED v EXPECTED UTILITY
EXPECTED UTILITIES MATRIX
UPDATE UTILITY ESTIMATE
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OFC
Thal
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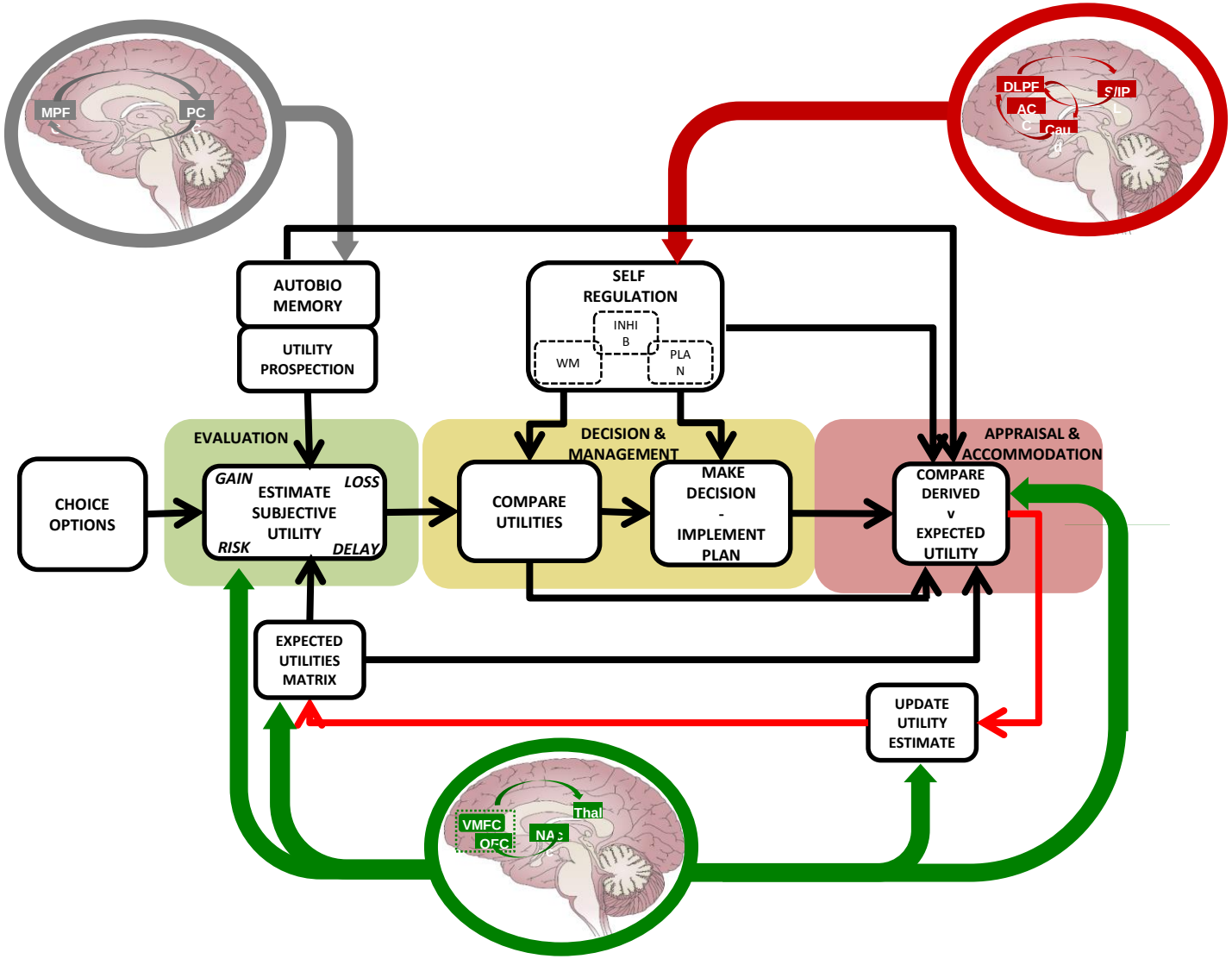
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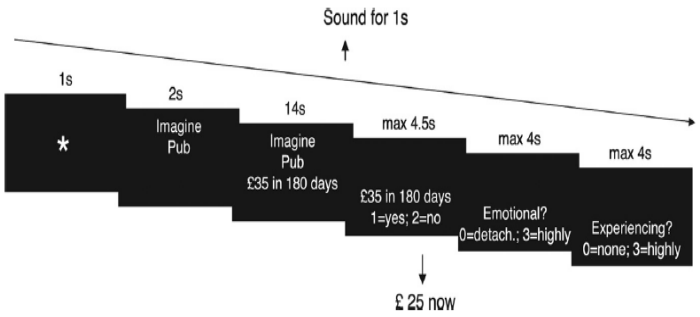
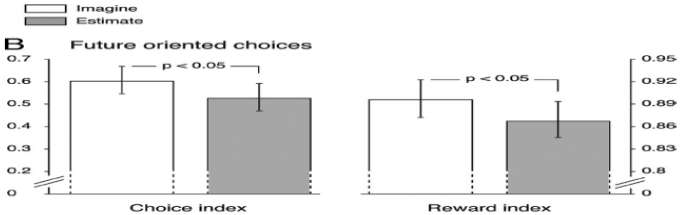
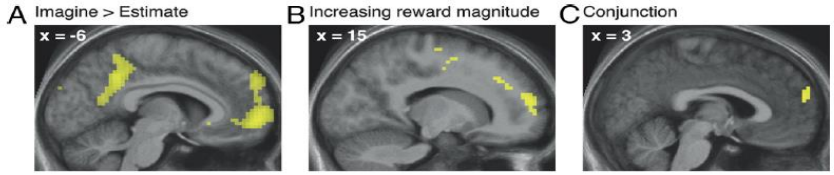
DMN-RELATED PROSPECTION REDUCES IMPULSIVE CHOICE

A Neural Mechanism Mediating the Impact of Episodic Prospection on Farsighted Decisions

Roland G. Benoit,[1,2] Sam J. Gilbert,[2] and Paul W. Burgess[2]
[1]Medical Research Council Cognition and Brain Sciences Unit, Cambridge CB2 7EF, United Kingdom, and [2]Institute of Cognitive Neuroscience, University College London, London WC1N 3AR, United Kingdom







MPFC activation predicted more future oriented choice which was moderated by reward size

The Journal of Neuroscience, May 4, 2011 • 31(18):6771– 6779 • 6771

WHAT ROLE COULD DMN PLAY IN IMPULSIVE CHOICE?

INTROSPECTION PROMOTES FUTURE ORIENTATED THOUGHT & PUTS DECISIONS IN CONTEXT

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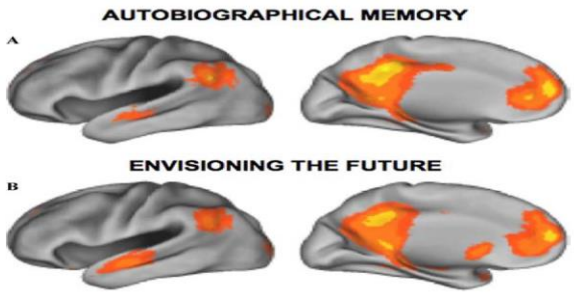

UNMODULATED ACTIVATION DURING TASKS DISRUPTS ATTENTION AND PERFORMANCE

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Review

Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis

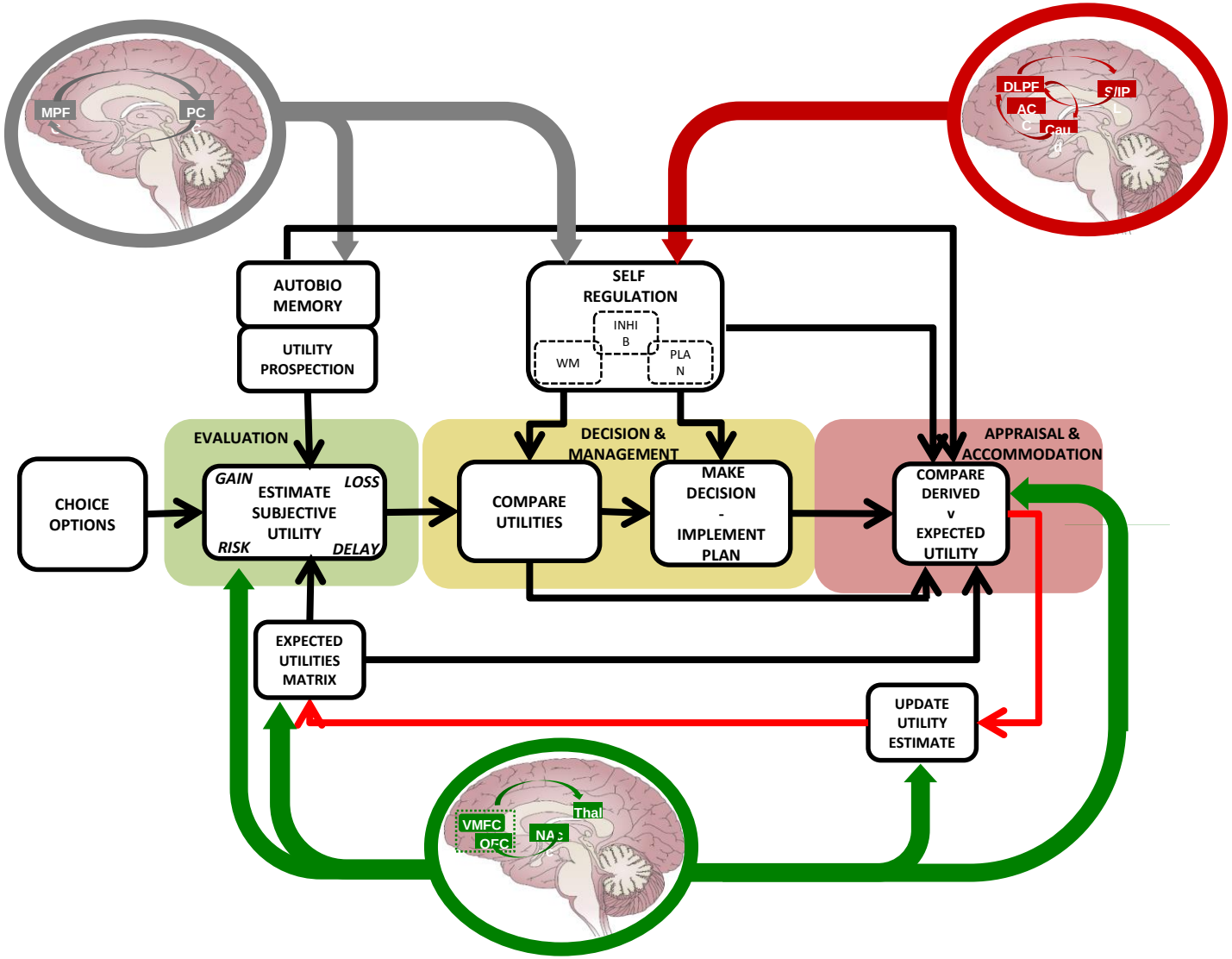
Edmund J.S. Sonuga-Barke[a,b,*], F. Xavier Castellanos[a]

[a]*Developmental Brain & Behaviour Unit, School of Psychology, University of Southampton, Southampton, SO17 1BJ, UK*
[b]*Child Study Center, New York University, USA*

Received 19 December 2006; received in revised form 23 February 2007; accepted 27 February 2007

problems arise due to periodic lapses, the result of spontaneous intrusions of unattenuated DMN neuronal oscillations during task performance.

A DOUBLE EDGED SWORD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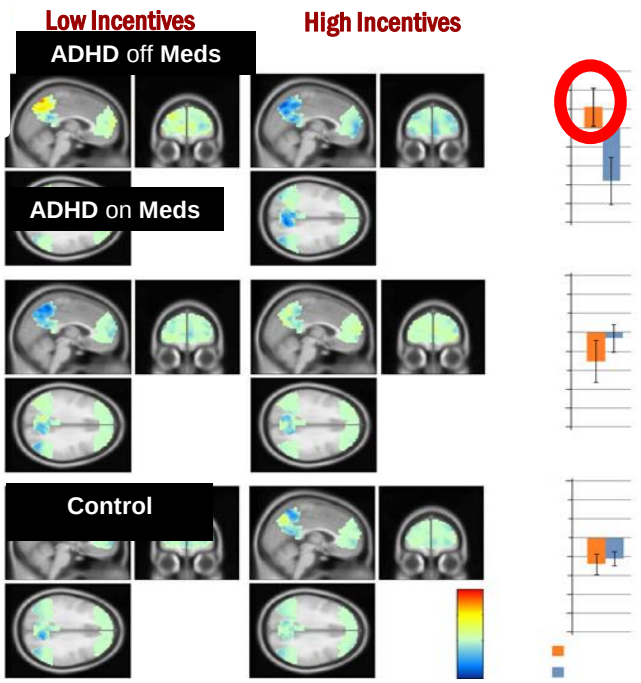
DMN IS UNMODULATED IN ADHD AND ASSOCIATED WITH ATTENTION LAPSES

Liddle et al (2011)



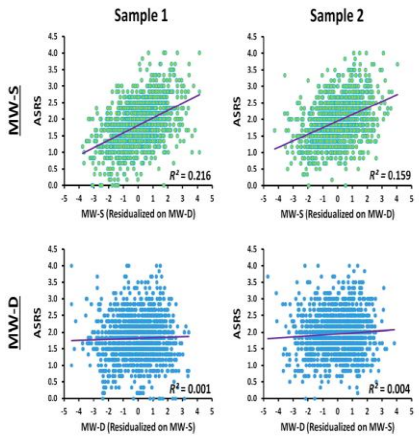
Seli et al (2016)

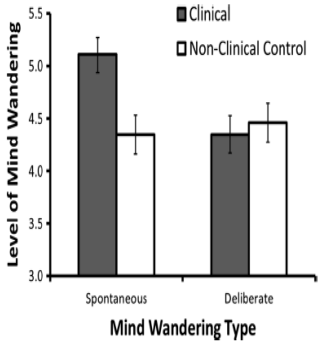
Psychon Bull Rev (2015) 22:629–636
DOI 10.3758/s13423-014-0793-0

THEORETICAL REVIEW

On the relation of mind wandering and ADHD symptomatology

Paul Seli · Jonathan Smallwood · James Allan Cheyne · Daniel Smilek





WAITING IS AN EMOTIONALLY PUNISHING EXPERIENCE FOR INDIVIDUALS WITH ADHD

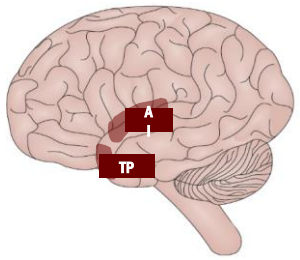
COULD THIS CONTRIBUTE TO IC IN ADHD?

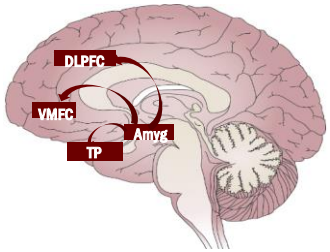
WAITING IS AN EMOTIONALLY PUNISHING EXPERIENCE FOR INDIVIDUALS WITH ADHD

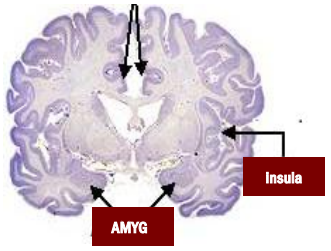
COULD THIS CONTRIBUTE TO IC IN ADHD?

Predictions

Cues of delay will elicit activation within the brain's emotional circuits more in ADHD than controls and this will mediate the aversion to delay.

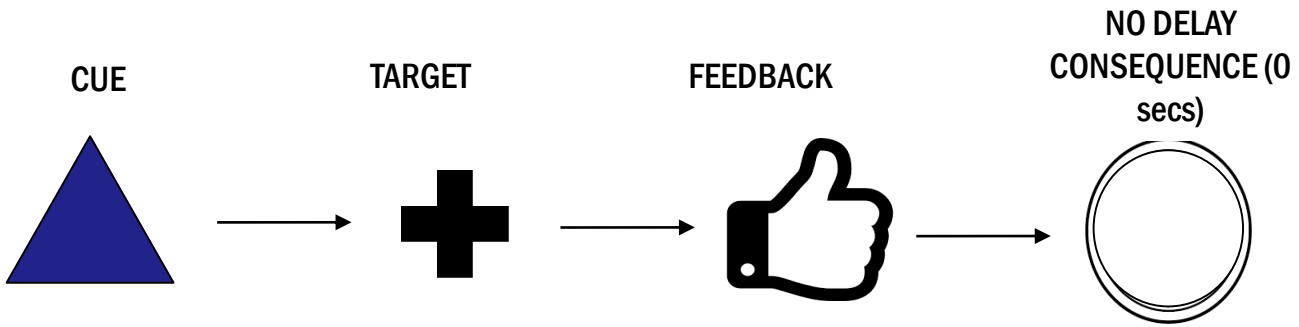






IS AMYGDALA HYPER-RESPONSIVE TO DELAY CUES?

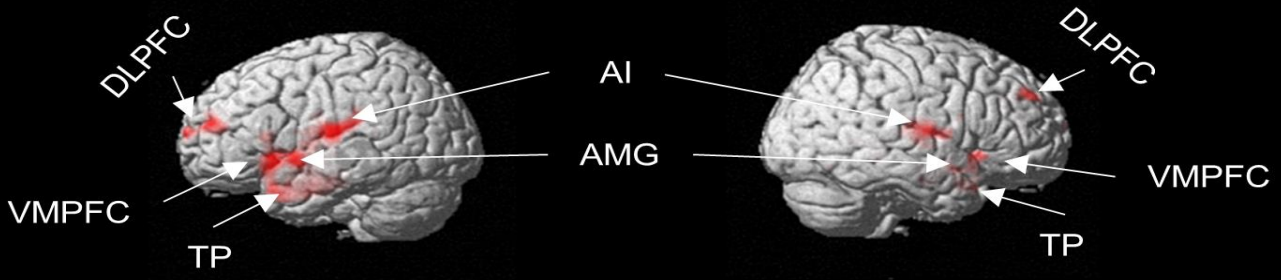
NO DELAY TRIAL



THE EDI (ESCAPE DELAY INCENTIVE TASK)

CERTAIN DELAY VERSUS NO DELAY

A.



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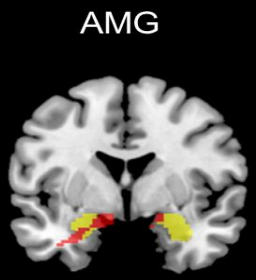

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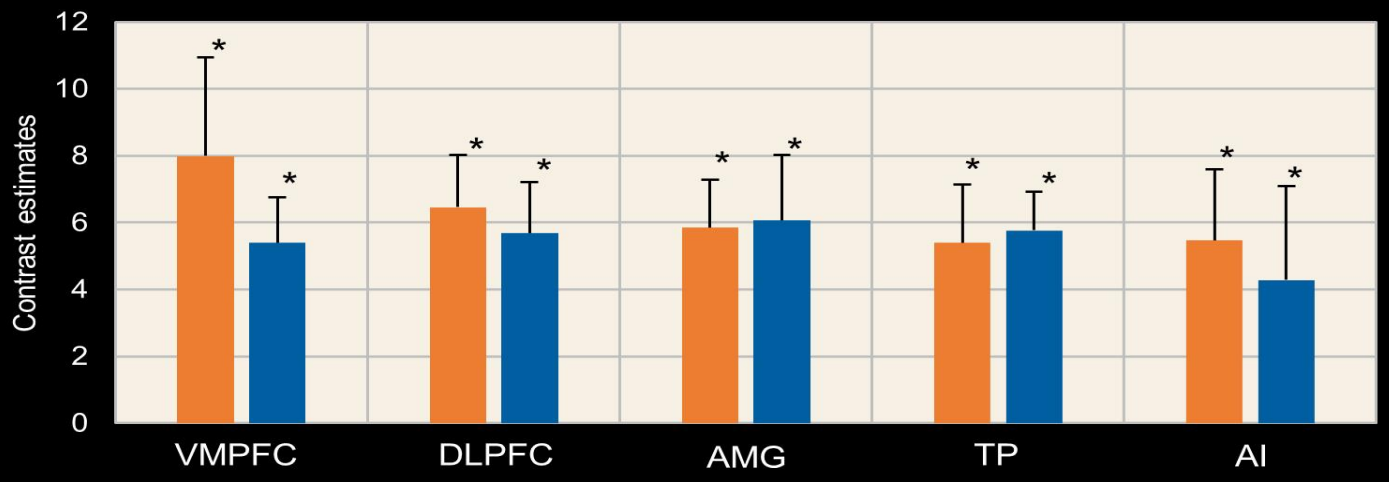

* P [FWE] < 0.05

VARIATIONS IN AMYGDALA DELAY RESPONSE MEDIATES DAv

		not at all like them				very much like them
1	will not give up, even if they have to wait a long time for something important.	1	2	3	4	5
2	is usually calm when they have to wait in queues.	1	2	3	4	5
3	will often choose a task which helps me in the long term even if they don't get anything from it right away.	1	2	3	4	5
4	are calm when waiting for things.	1	2	3	4	5
5	often give up on things that they cannot have straight away.	1	2	3	4	5
6	hate waiting for things.	1	2	3	4	5
7	try to avoid tasks that will only give them something in the long term and not straight away.	1	2	3	4	5
8	feel annoyed when they have to wait for someone else to be ready before I can do something.	1	2	3	4	5
9	Having to wait for things makes them feel stressed and tense.	1	2	3	4	5
10	The future is not important for them. They only consider the instant outcomes of their actions.	1	2	3	4	5

WHAT HAVE WE LEARNT?

- Highly heritable disorder likely implicating 1000s of common risk alleles of small effect and rare variants of large effect.

- Normative Es likely to play a marginal role once GE correlations are considered.
- Extreme post-natal adversity may override G to “cause” ADHD.

- Pathophysiologically - distributed, complex and heterogeneous.

Future progress in understanding causal complexity will require longitudinal studies of the transactions between G, E, brain structure/function, cognition, symptoms and impairment.