NEUROBIOLOGIA DELLA VIOLENZA E DIFFERENZE DI GENERE

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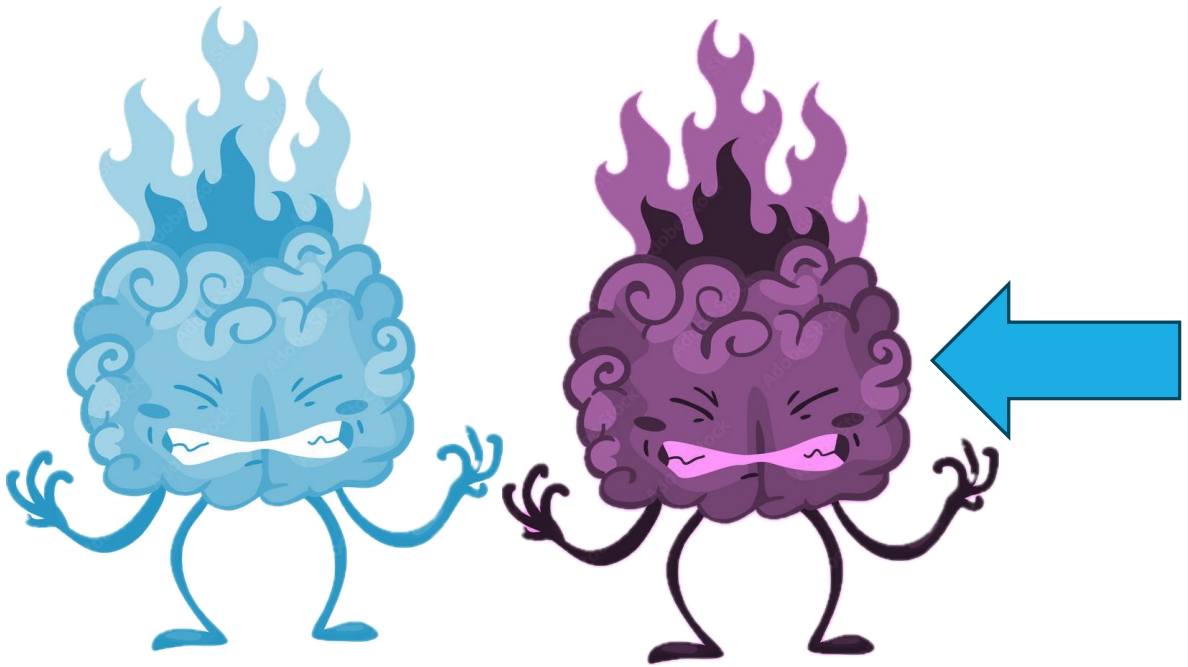
Overview



Brain Circuits

Neurotransmitters
Hormones

Genes

Environment

Violence vs Aggression

- **Aggression**
  - **Direct (physical or verbal)**
    - behaviour that is intended to cause physical or psychological harm to another person
  - **Indirect (relational or social)**
    - a type of behavior in which the perpetrator attempts to inflict pain in such a manner that he or she [often] makes it seem as though there has been no intention to hurt at all (e.g. excluding others from the group, spreading nasty rumors about others, breaking confidences, getting others to dislike a person)
- **Violence**
  - the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation

World Health Organization, 1996

Aggression types

Impulsive

- Characterized by high levels of autonomic arousal
- Precipitated by provocation
- Associated with negative emotions, such as anger or fear
- Usually represents respons to perceived stress
- Also called reactive, affective, or hostile aggression

Organized

- Planned behavior not typically associated with frustration or response to immediate threat
- Might not be accompanied by autonomic arousal
- Planned with clear goals in mind
- Also called predatory, instrumental, proactive, or premeditated aggression

Psychotic

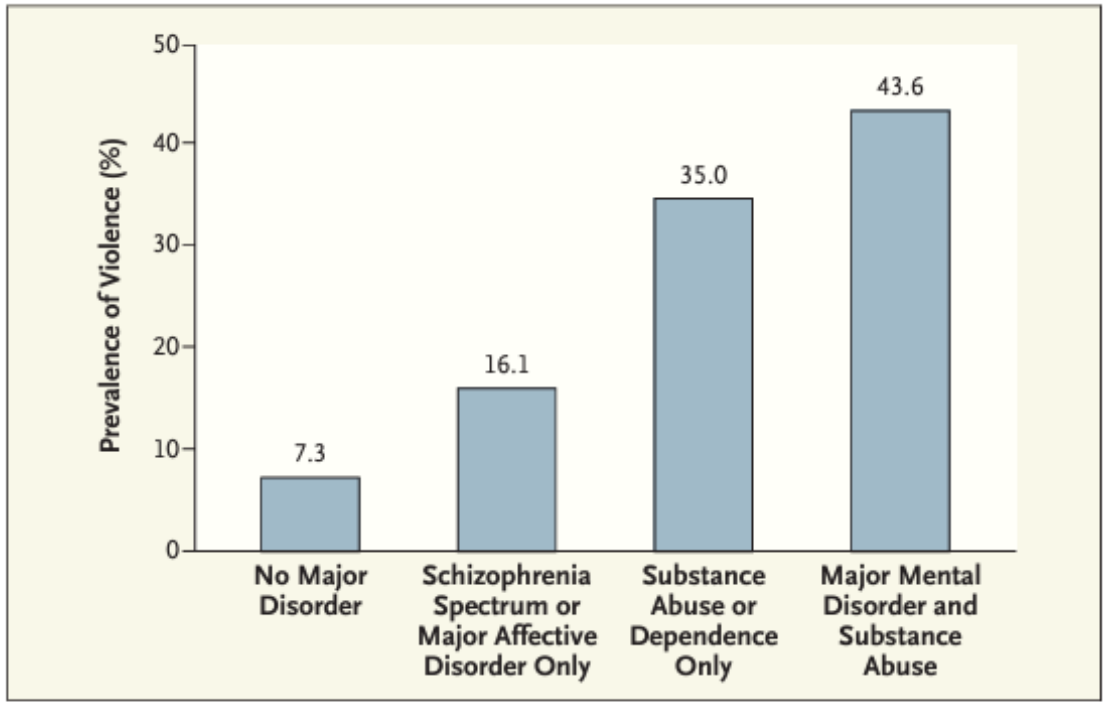
- Associated with positive symptoms of psychosis - typically command hallucinations and/or delusions
- Most severe

Violent behavior is highly heterogeneous

Stahl SM. CNS Spectr. 2014

Violence in mental disorders

- Setting:
  - Inpatients affected by severe mental illness (17–50%), and lower rates among outpatients (2–13%) in Norway
  - Inpatients affected by mental illness (32%), and lower rates among outpatients (8%) in Italy



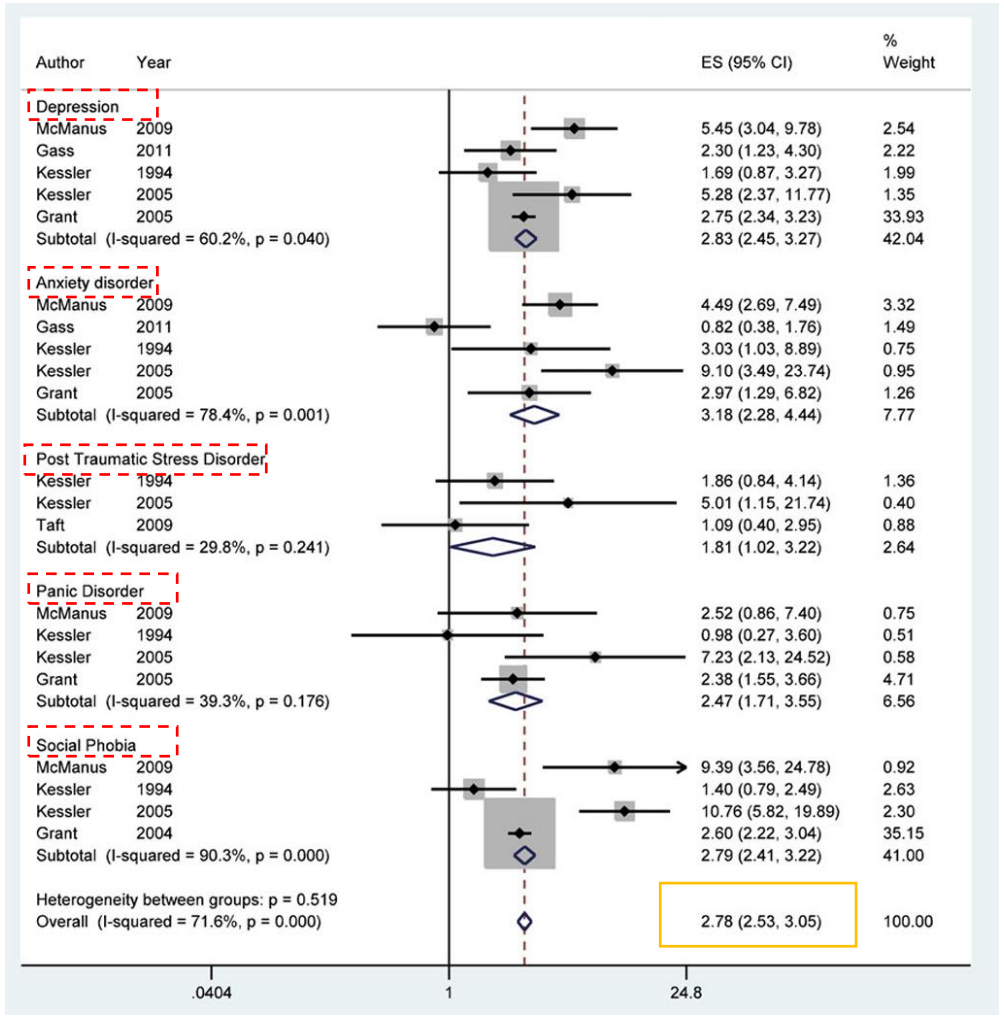
Lifetime Prevalence of Violent Behavior among Persons with or without Major Psychiatric Disorders and Substance Abuse.

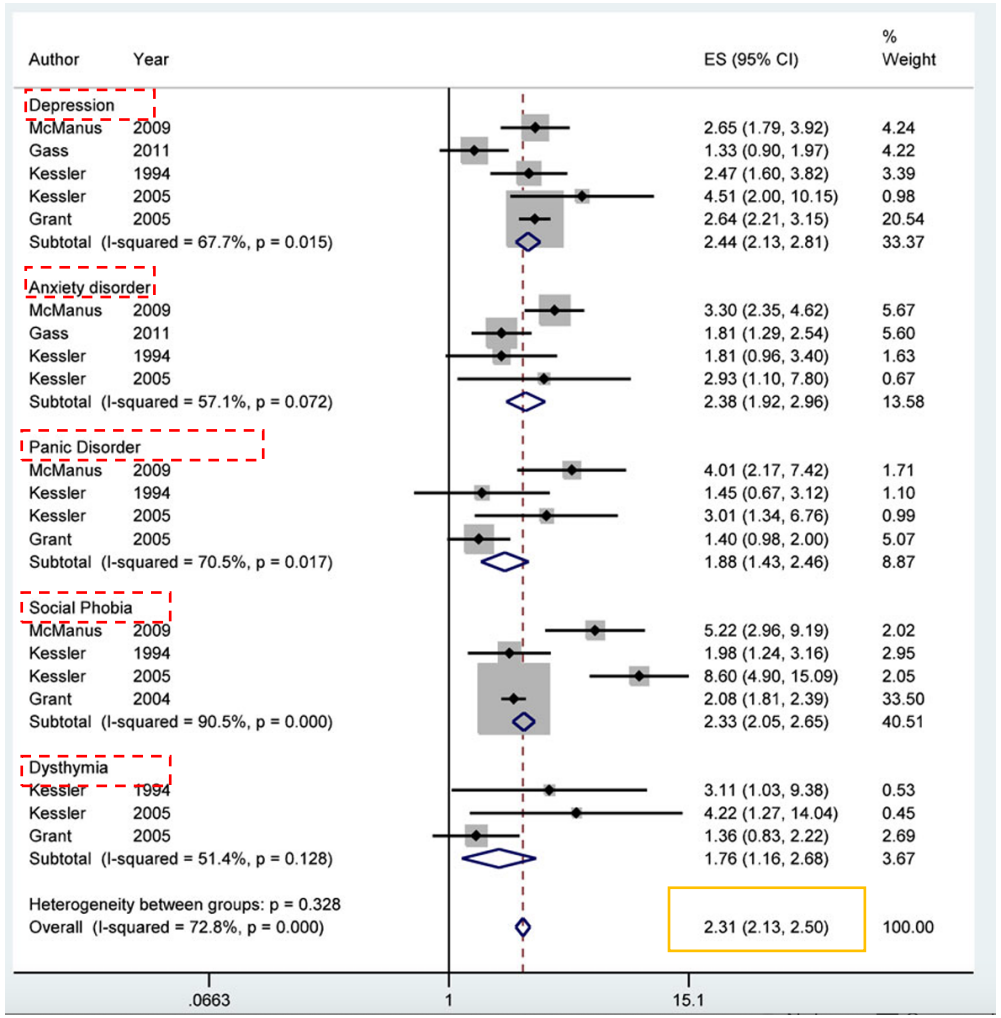
The risk of violence in mental disorders contributes little to the overall violence in the general population

Richard A Friedman. N Engl J Med. 2006 Nov 16;355(20):2064-6. doi: 10.1056/NEJMp068229

Osea SS, Lilleengb S, Pettersen I, Ruudd T, van Weeghelf J. Risk of violence among patients in psychiatric treatment: results from a national census. Nord J Psychiatry. 2017;71:551–60

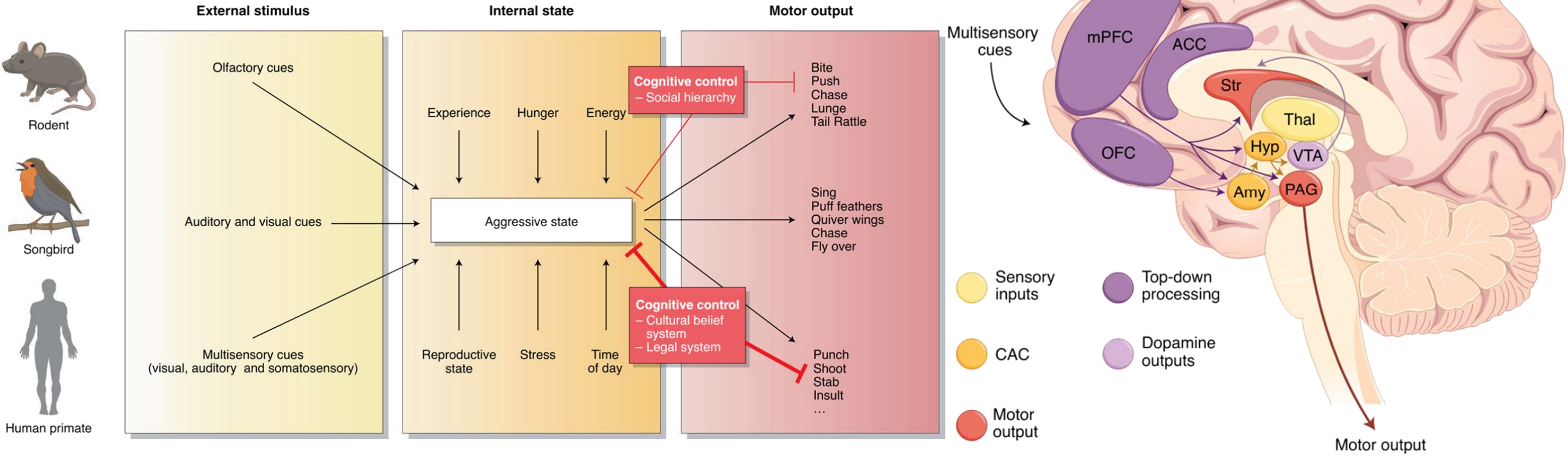
Violence in mental disorders





The risk of violence in mental disorders contributes little to the overall violence in the general population

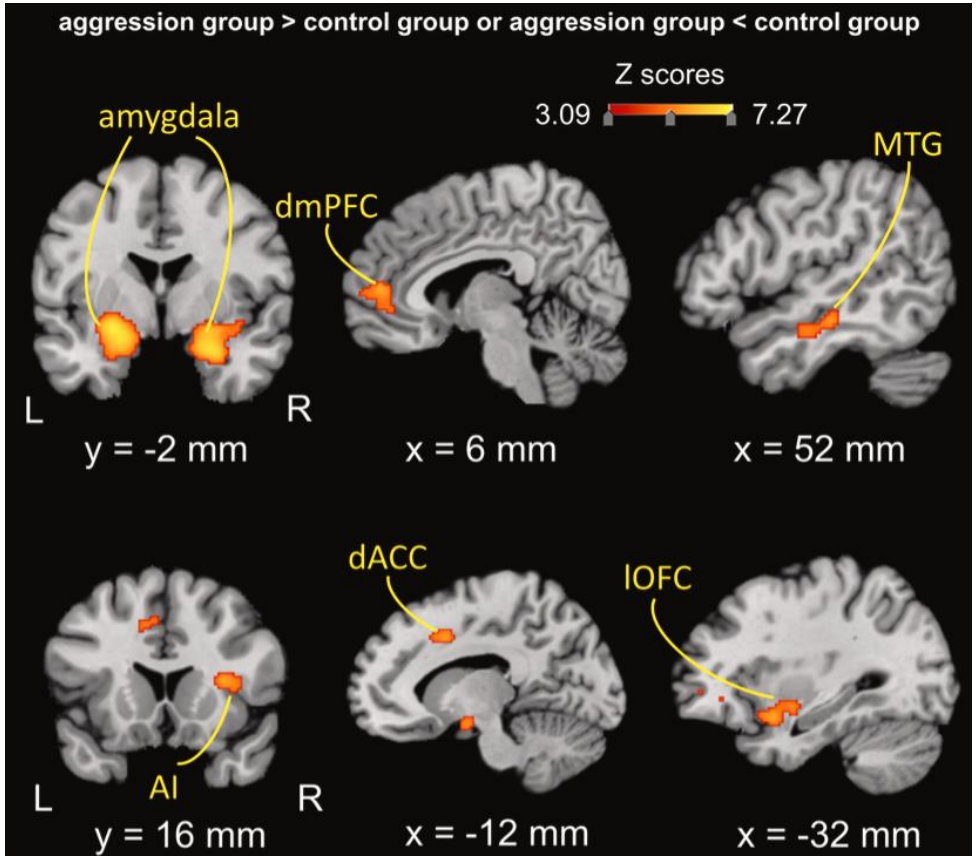
General Aggression Model (GAM)

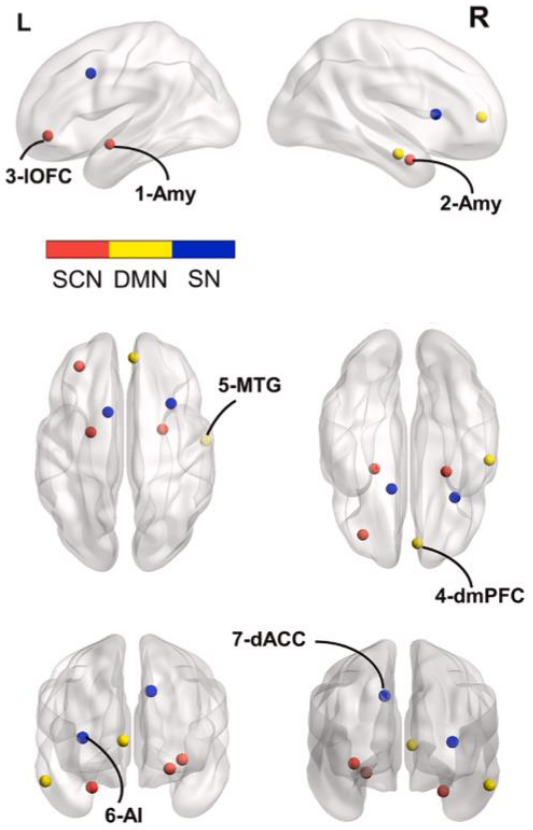


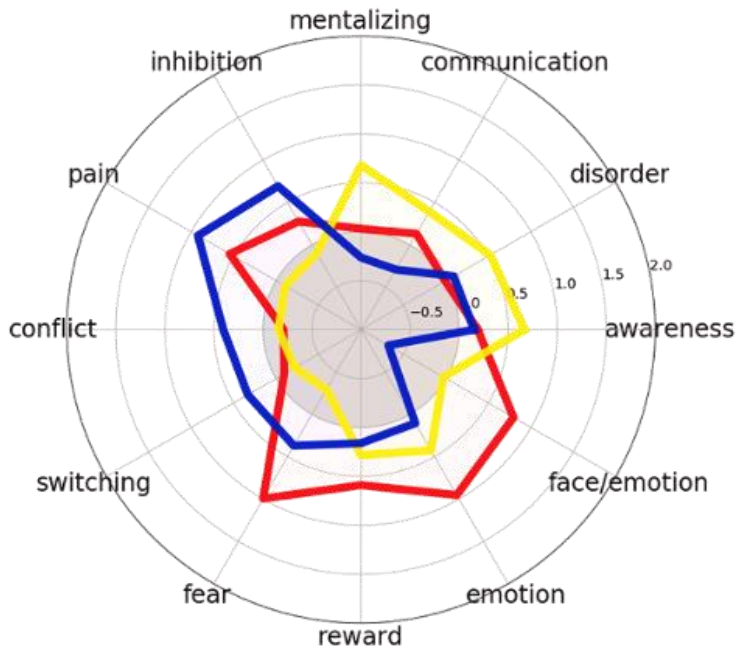
Lischinsky & Lin, Nature Rev Neurosci 2020

Aggression at a given moment can be influenced by situational, individual, and biological factors across various species

Brain regions implicated in human aggression





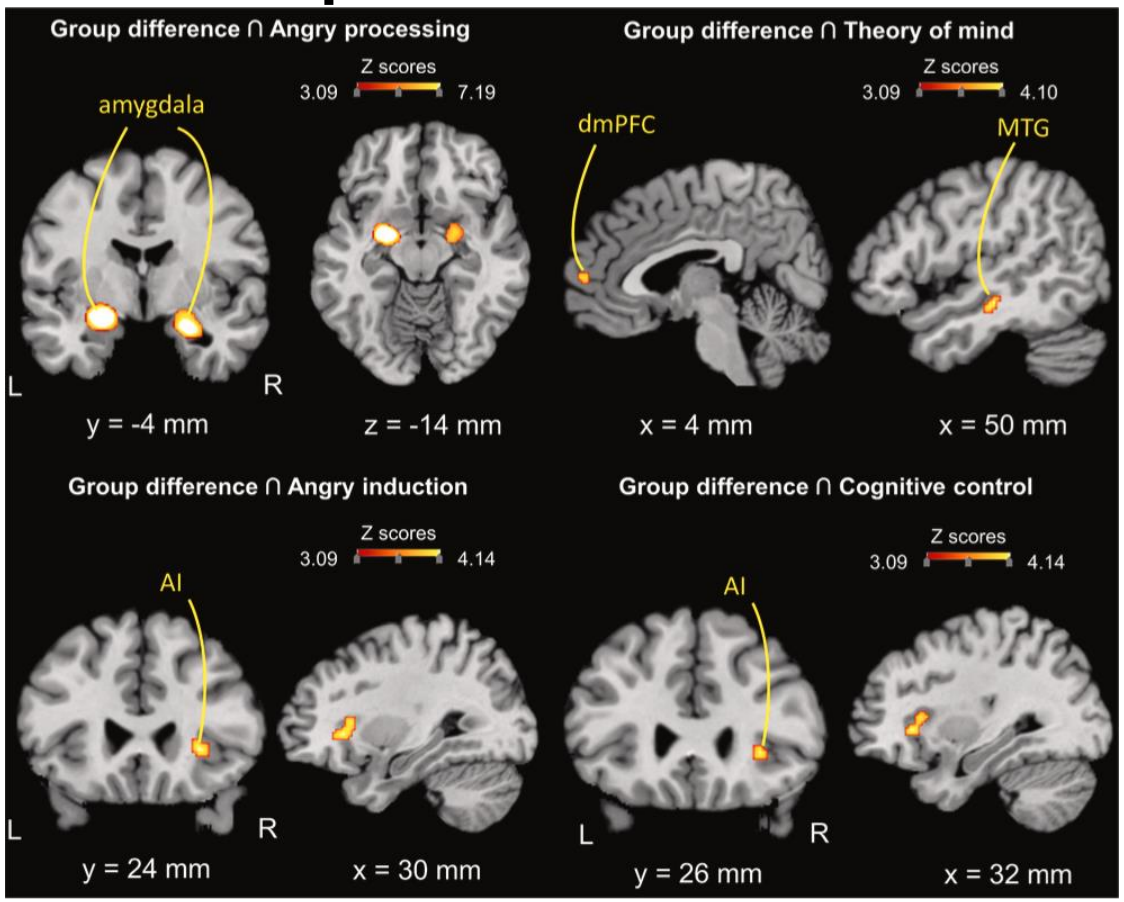


231 studies
N= 10647

Wang et al., Neuroimage 2024

Aggression is associated with brain changes in large scale brain networks

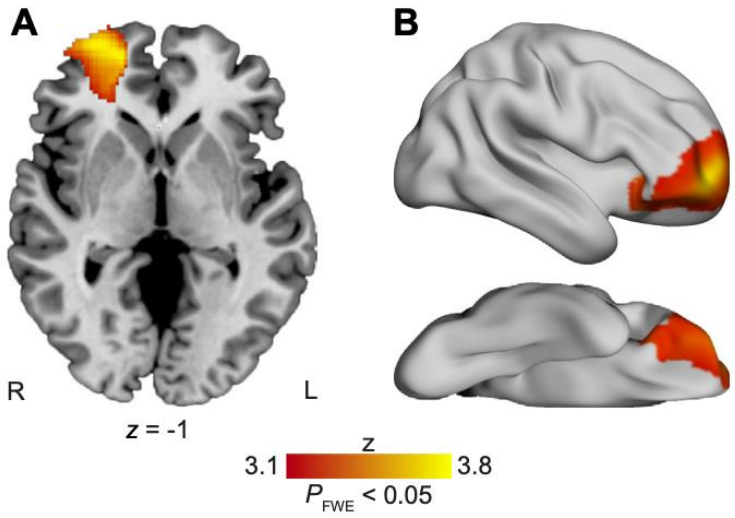
Brain regions implicated in human aggression



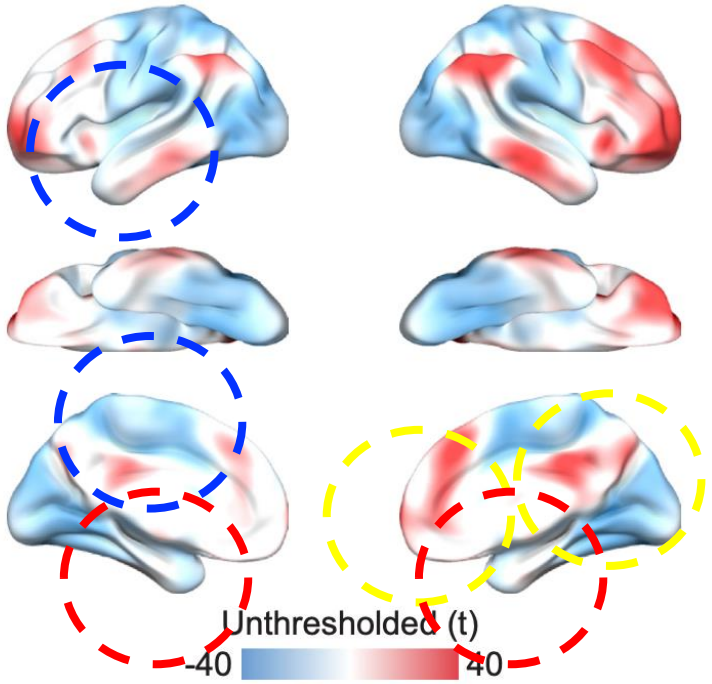
Wang et al., Neuroimage 2024

Brain areas implicated in aggression overlap with those associated with negative emotion, theory of mind and cognitive control

Brain lesion studies in aggression



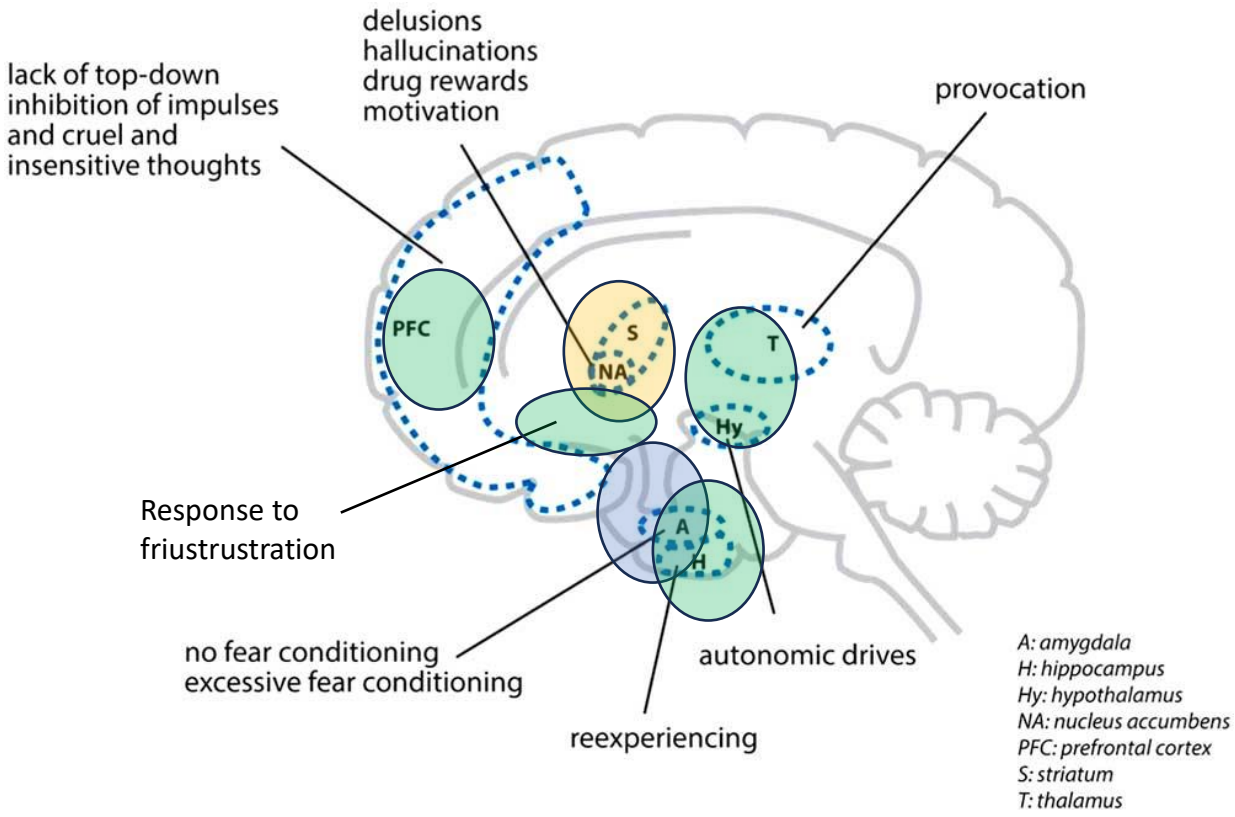
N= 182

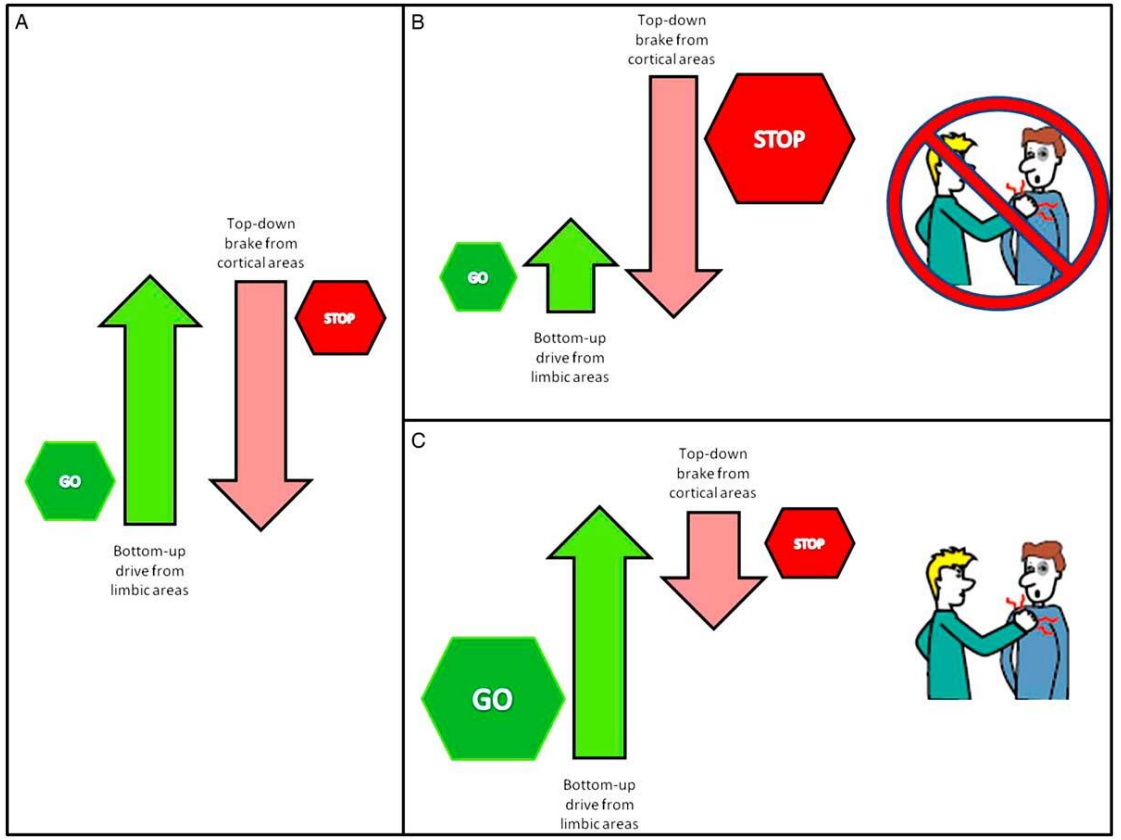


Peng et al., Biol Psy 2024

Large scale networks connected with right prefrontal cortex are lesioned in human aggression

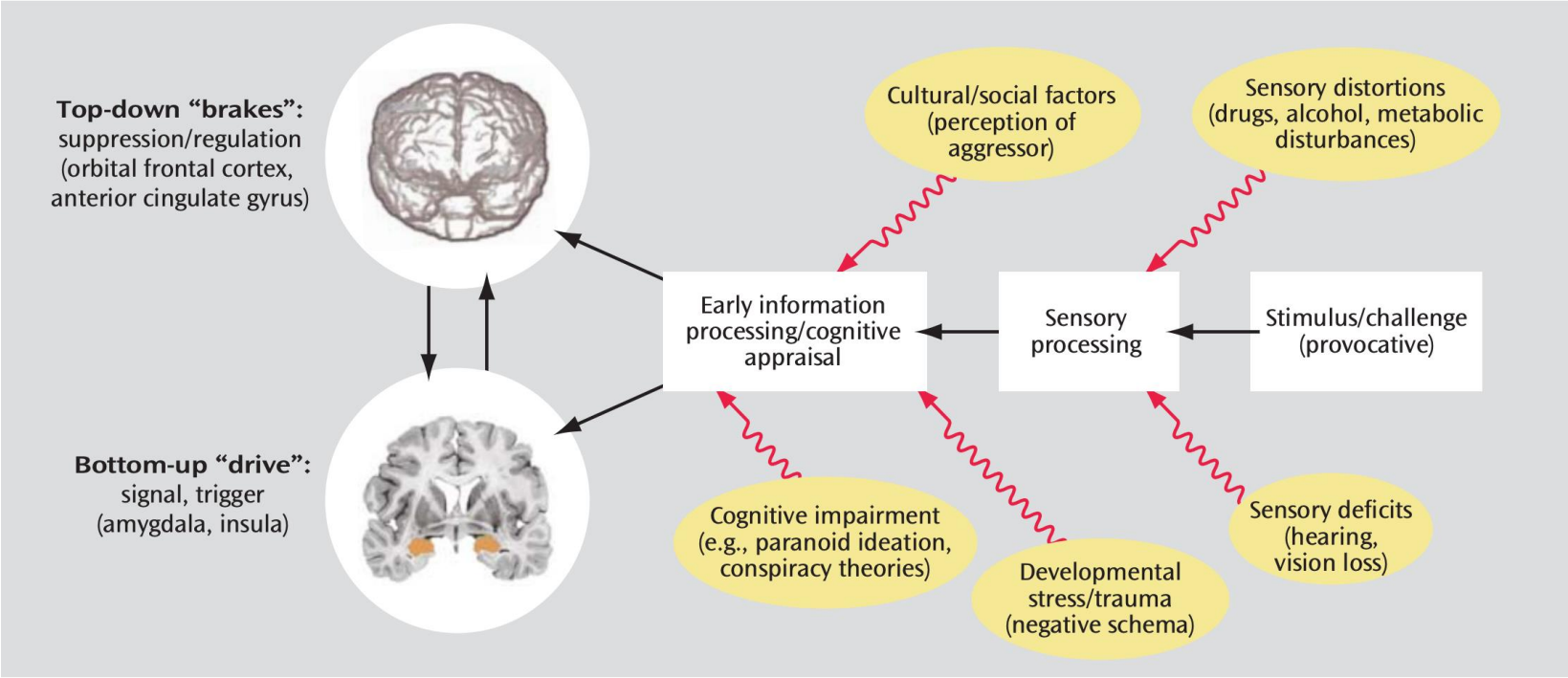
Brain mechanisms associated with violence





Distinct brain circuits can underlie violence types

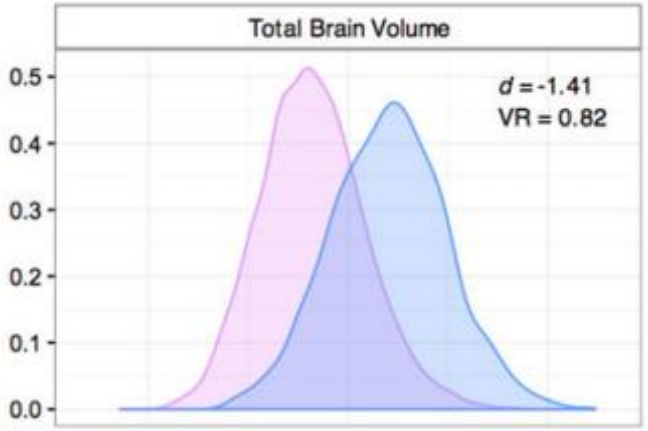
Violence: phenomenology and brain circuits



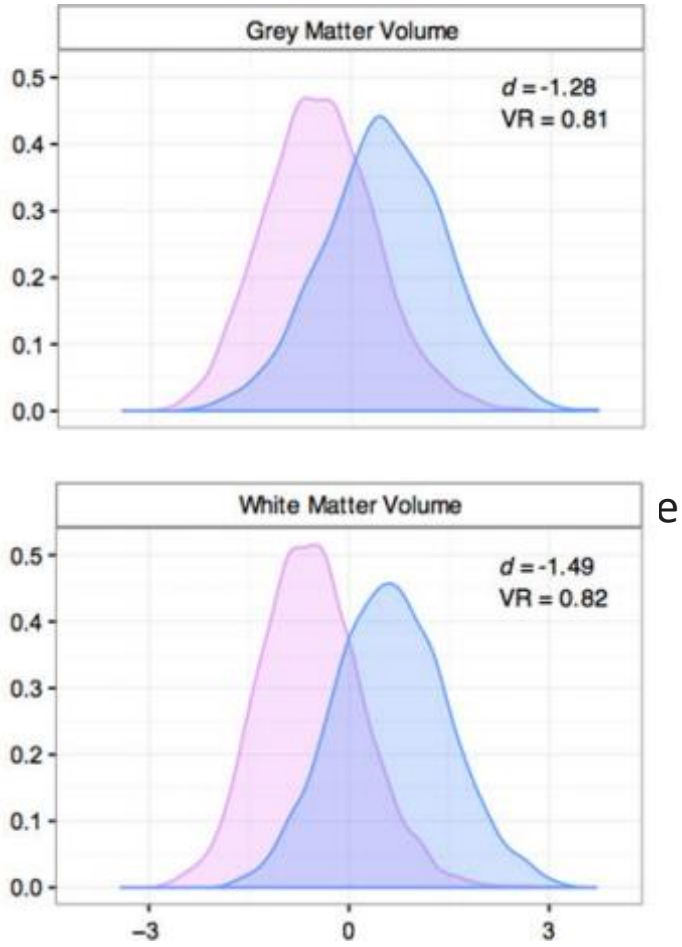
Siever et al., AmJPsy 2008

Several factors can contribute to violence, nonetheless a common circuit for violence exists

Sex-related structural differences in the brain



77 Studies
N= 14,957
Ritchie et al., Cer Cortex 2018



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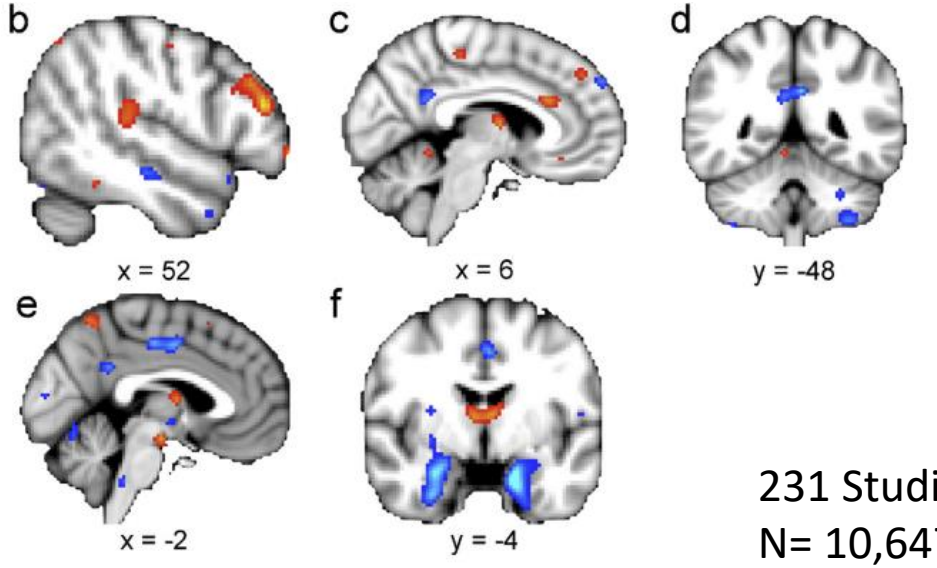


231 Studies
N= 10,647

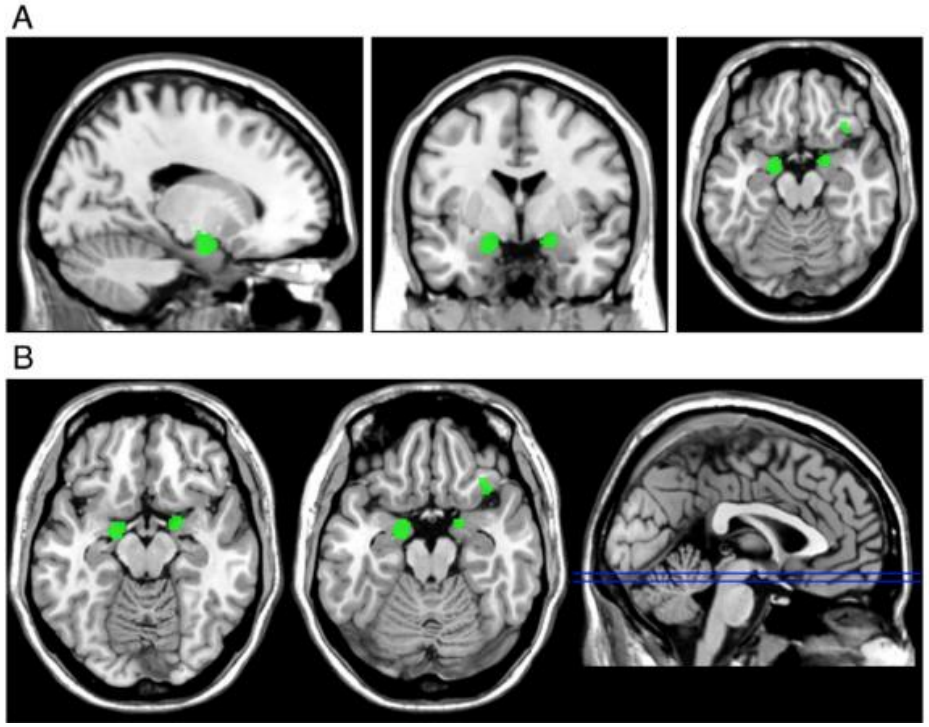
Regional differences in gray matter volume

Ruigrok et al., Neuroimage 2014

Men show larger overall brain volumes, while regional differences between sexes are minimal.

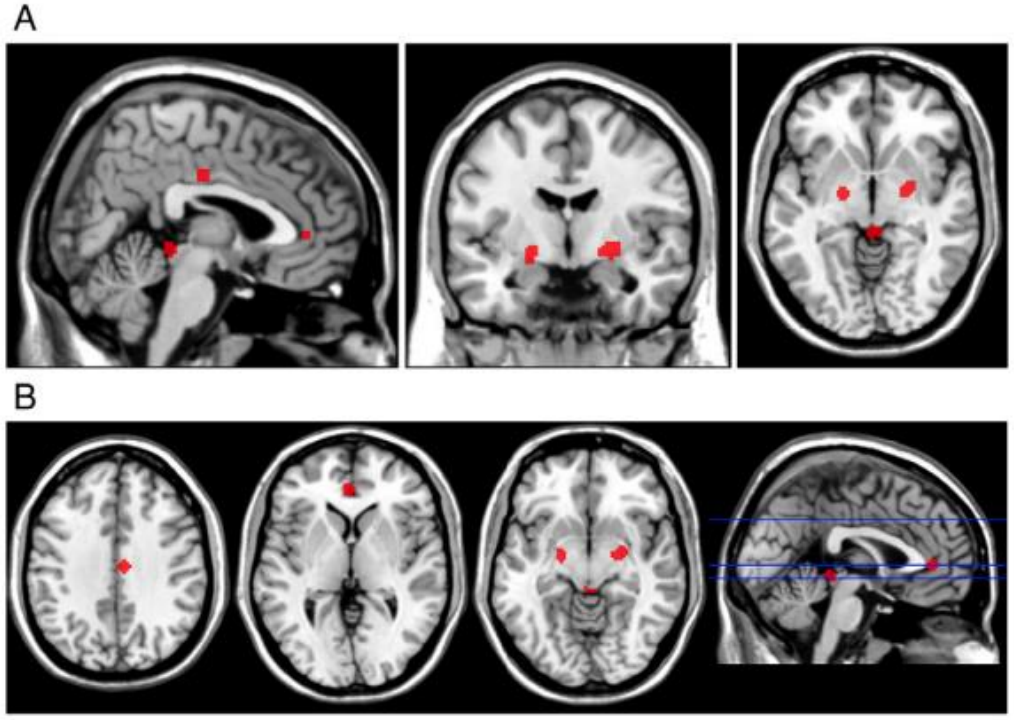
Sex-related functional differences in the brain

Emotional Processing



18 studies
N=484

Men>Women



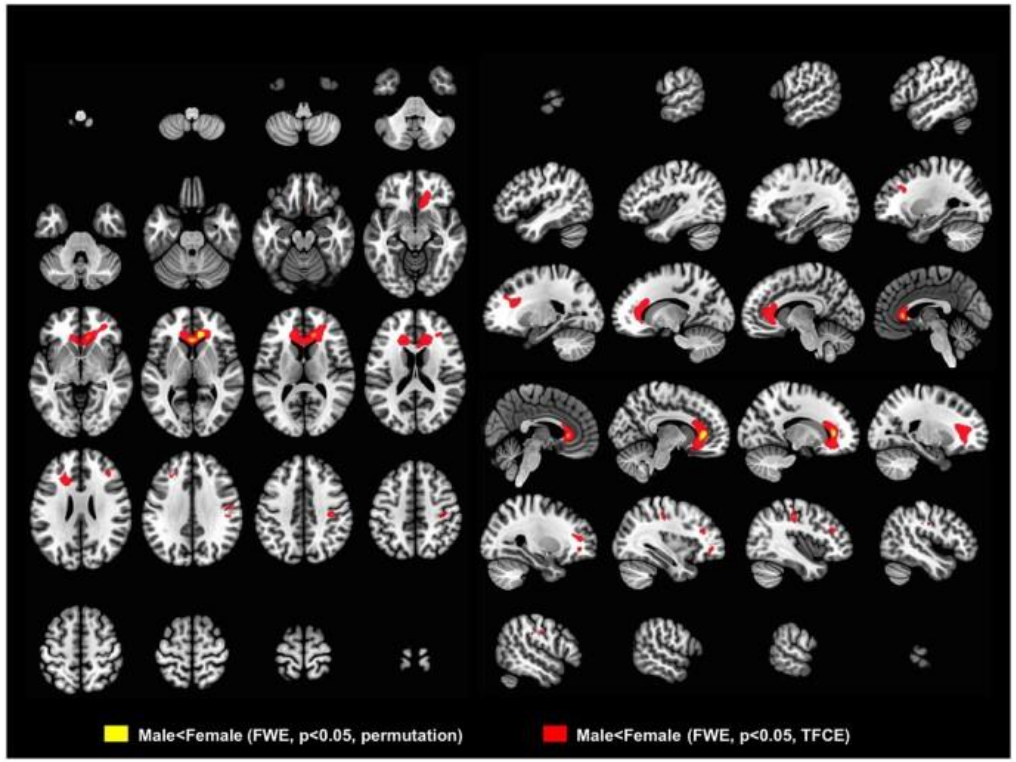
N=656

Women> Men

Sacher et al., MRI 2013

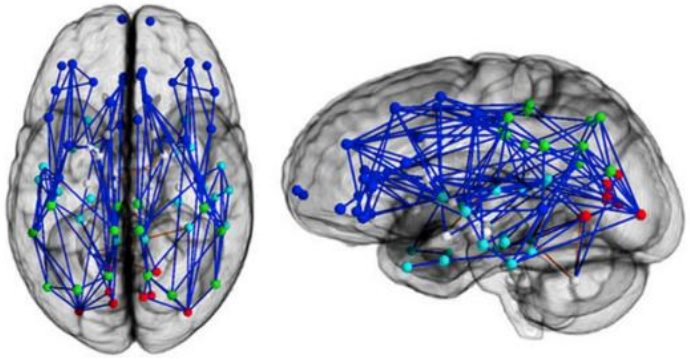
Men show greater activation in limbic regions and reduced activation in the default mode and cognitive control networks

Sex-related connectivity differences in the brain

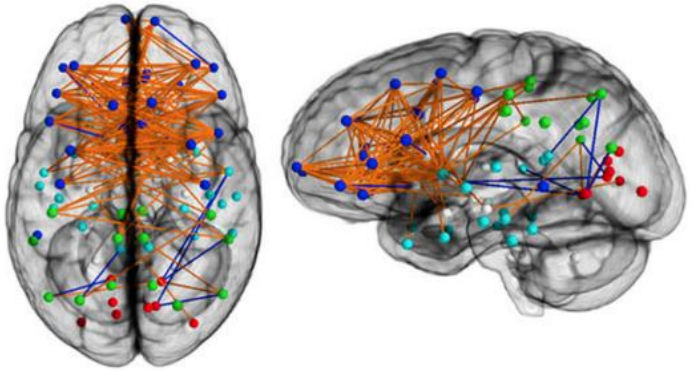


N=74 Women> Men Shiino et al., Trans Psy 2017

Men>Women



Women> Men



N=949, 8-22 ys

Ingalhalikar et al., PNAS 2014

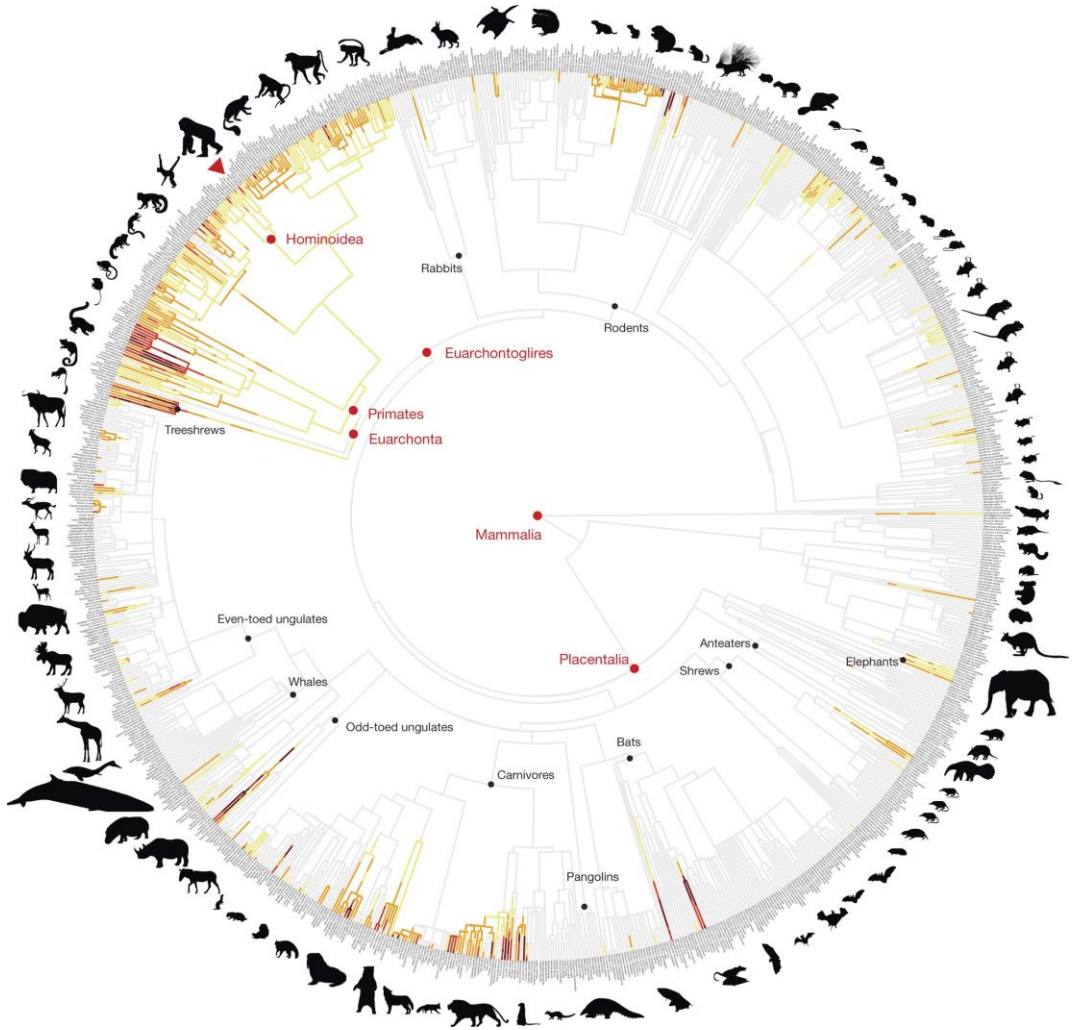
Men exhibit stronger intra-hemispheric, while women demonstrate greater inter-hemispheric structural connectivity.

LETTER

doi:10.1038/nature19758

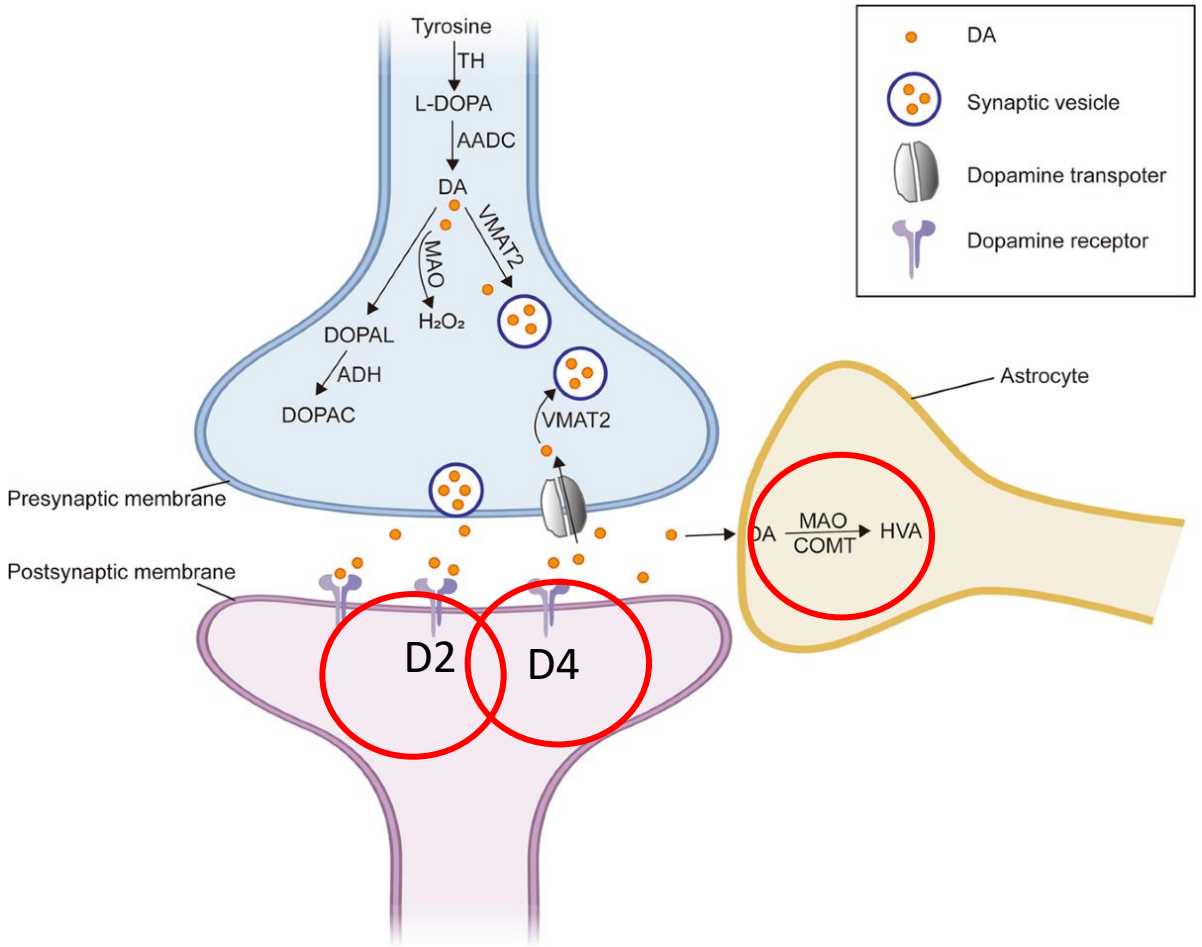
The phylogenetic roots of human lethal violence

José María Gómez[1,2], Miguel Verdú[3], Adela González-Megías[4] & Marcos Méndez[5]



Is violence in our genes?

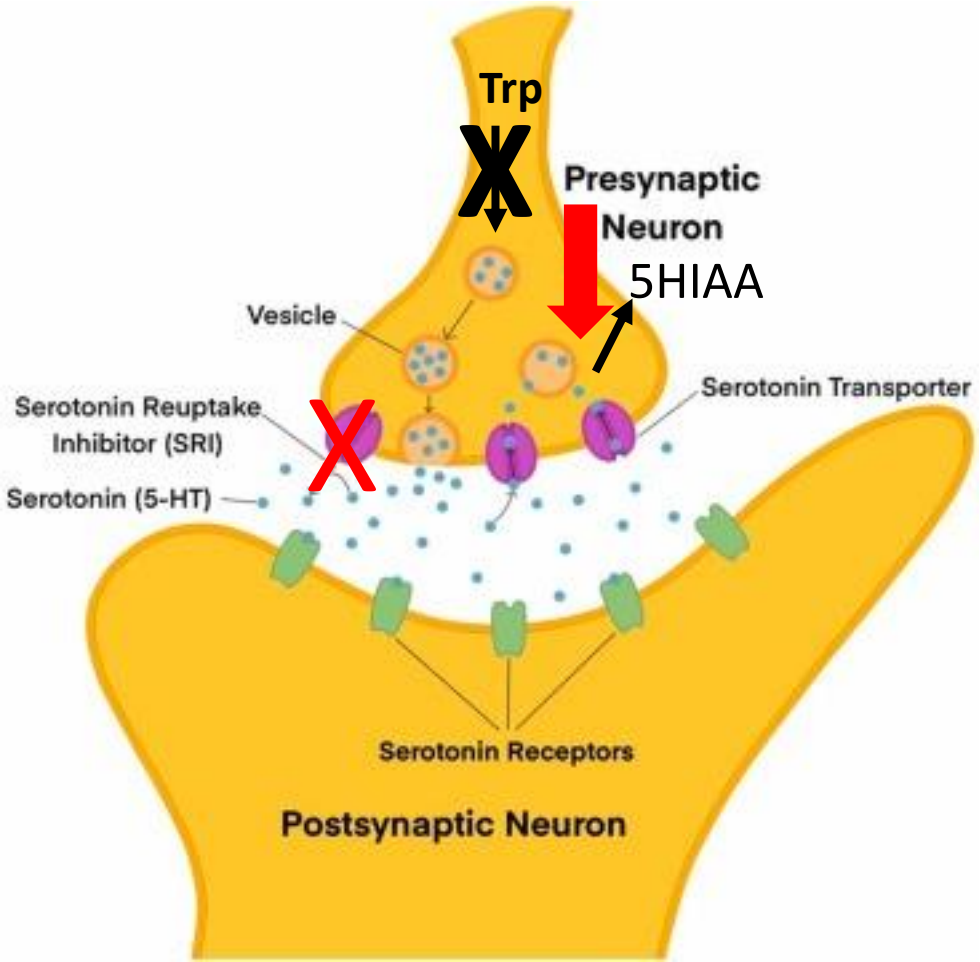
Brain Signaling: Dopamine



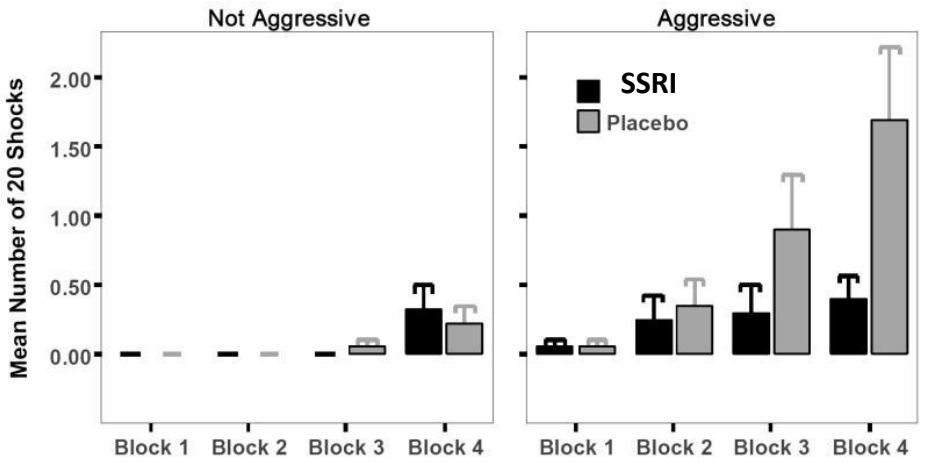
- Dopamine Metabolism:
  - COMT
    - Healthy young
    - Gender (>Males) White et al., 2014)
- Receptors
  - DRD2 – aggression in childhood (Zai et al, 2012)
  - DRD4 and ADHD in males (Qiang et al., 2004)
  - DRD4 and in males Anger (Kang et al., 2008)
  - DRD4 Long (7R) greater delinquency, short temper and thrill seeking ion males (Dmitrieva et al., 2011)

Dopamine signaling, mostly D4, can contribute to aggression

Brain Signaling: Serotonin



- Reduced 5-HIAA CSF levels (metabolite)
- Triptophan depletion/loading
- SSRI administration
- Genetics:
  - 5HT Transporter:
    - 5-HTTLPR
  - MAO-A

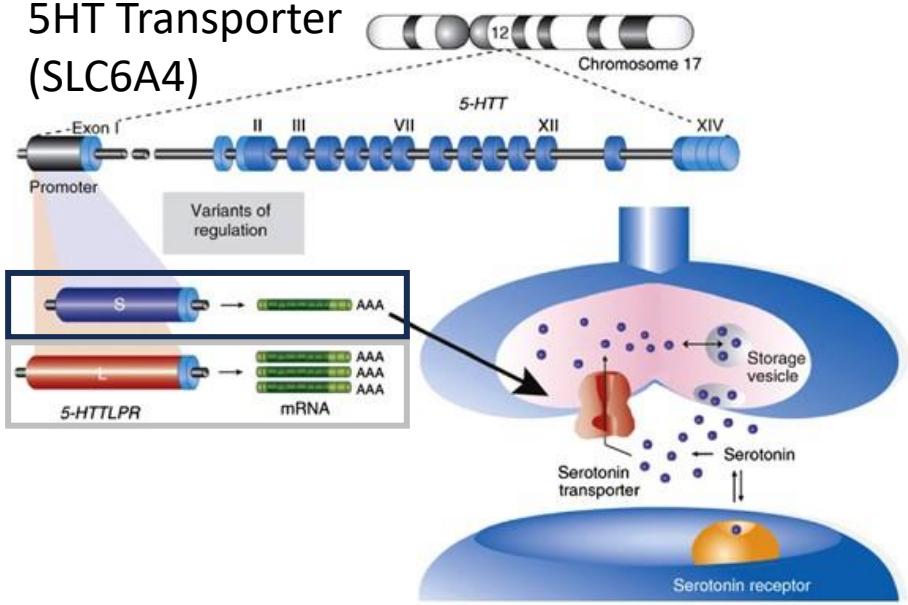


Berman et al., Psy Science2009

Reduced serotonin signaling is associated with aggression

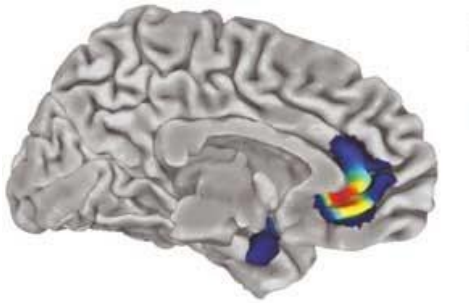
Serotonin signaling and brain networks

5HT Transporter (SLC6A4)



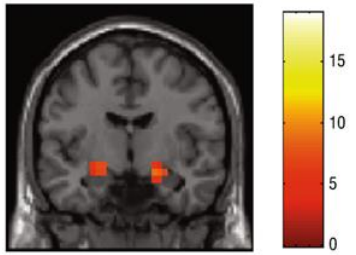
DeNeve et al, JHG11

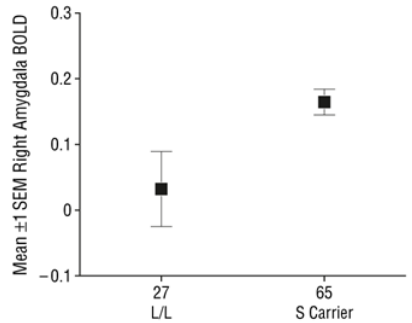
LL>S



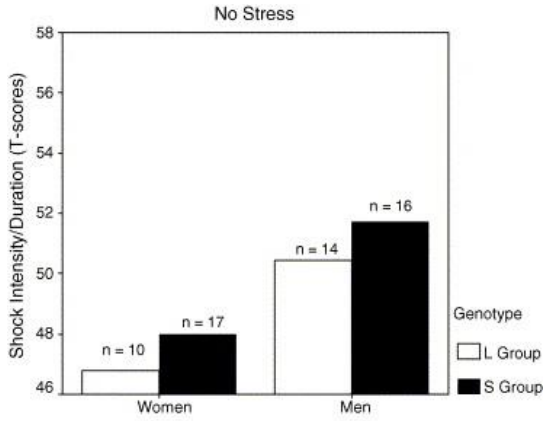
Pezawas et al, NatNeurosci05

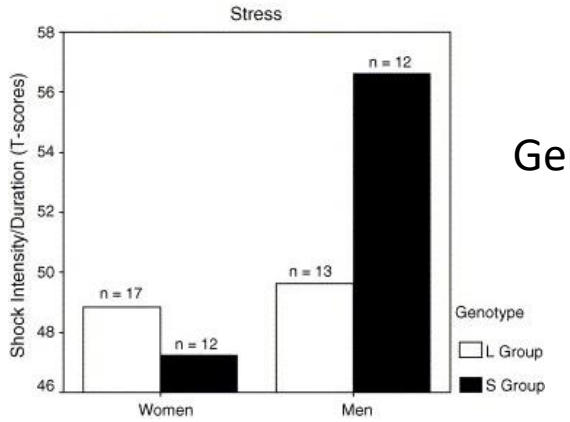
S>LL





Hariri et al, JamaPsy05





Genotype x gender

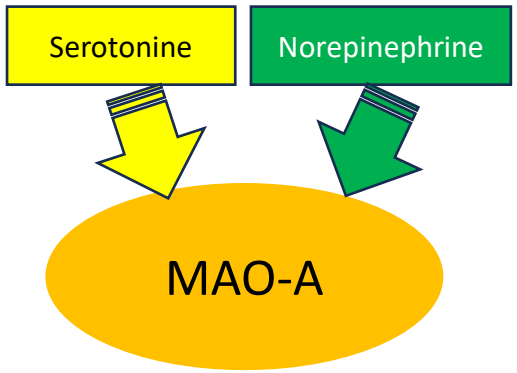
Verona et al, Biol Psy 06

Genetic variation in the serotonin transporter gene can underlie aggressive behavior

Brain Signaling: GENETICS

Brunner Syndrome

- Borderline mental retardation and aggressive behavior
- Mutations in Xpl 1.23-11.4 (MAO-A gene)



Expression

- LOW – MAO-L 

- HIGH – MAO-H 

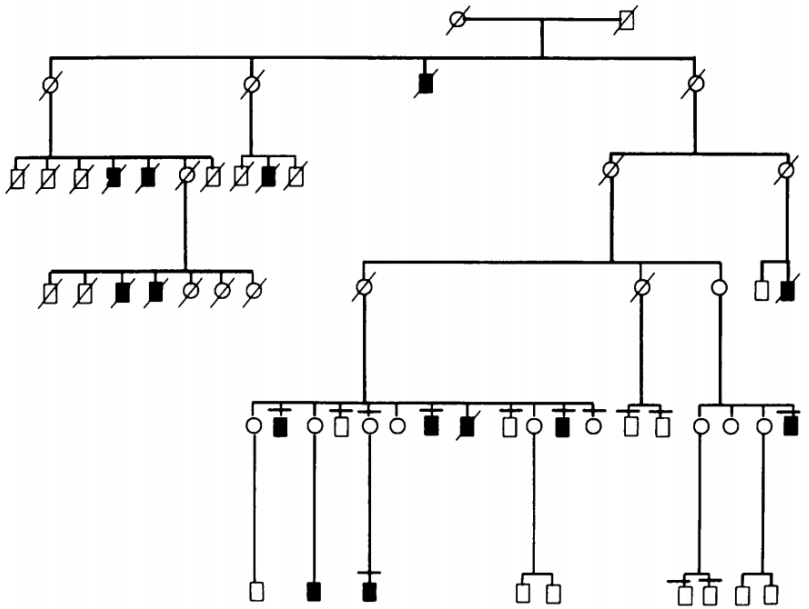


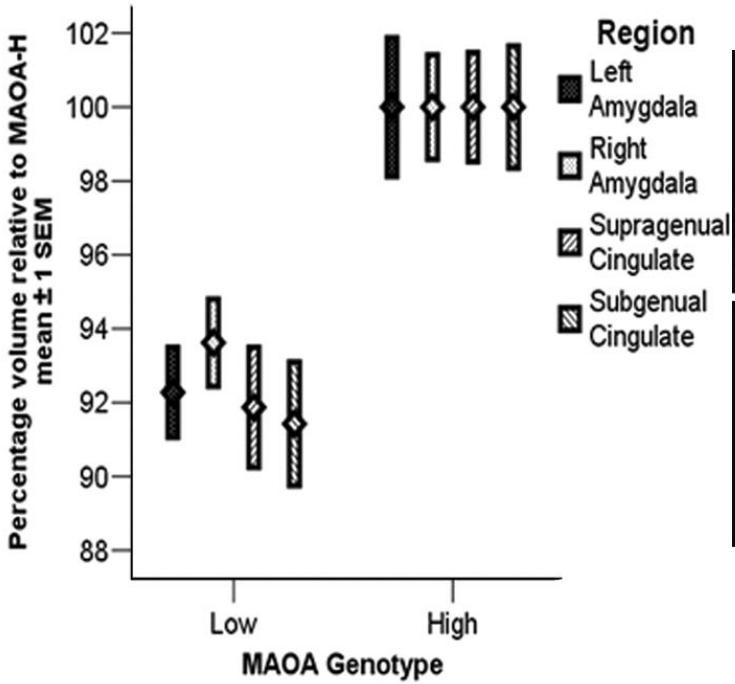
Figure 1 Pedigree of family with borderline mental retardation with prominent behavioral disturbance. Only individuals known to be at genetic risk are shown. Blackened squares denote affected males. Clinically evaluated individuals are indicated by a horizontal line above the symbol.

Brunner et al., AJMG 1993

Sabol et al., Hum Gen 1998

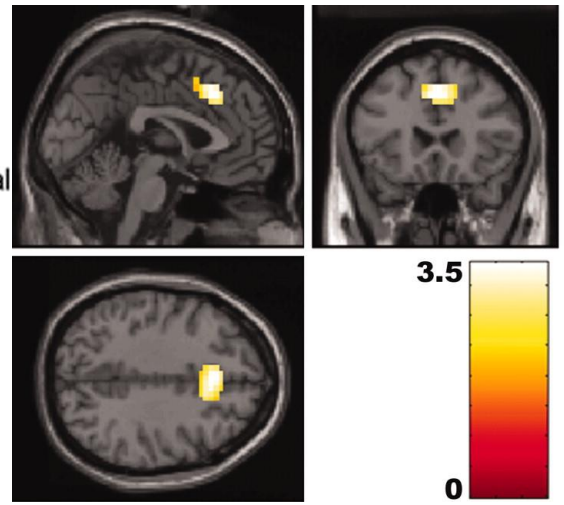
Genetic variations in MAO-A are associated with aggressive behavior

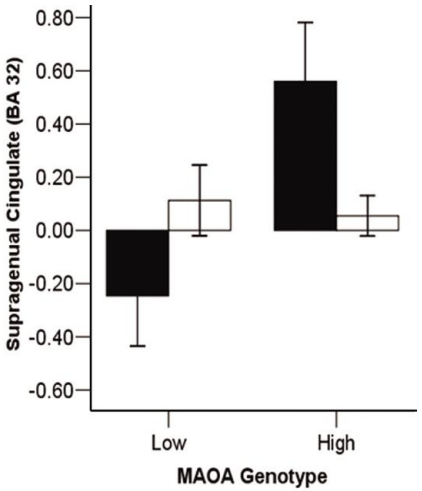
Brain Signaling: GENETICS



MAO-A-High > MAO-Low

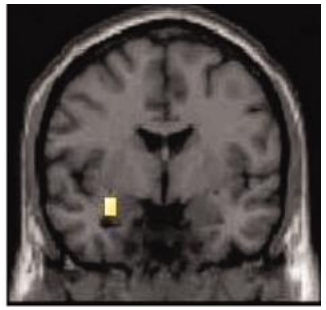
Flanker tast

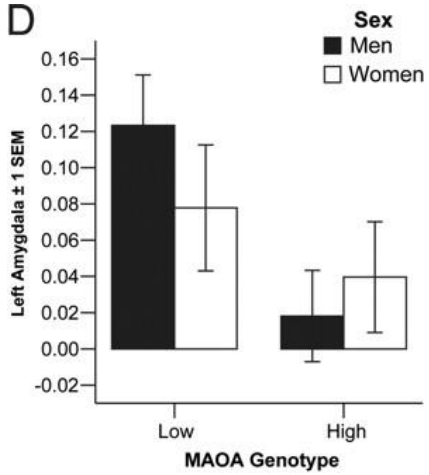




MAO-A-High > MAO-Low

Aversive emotion





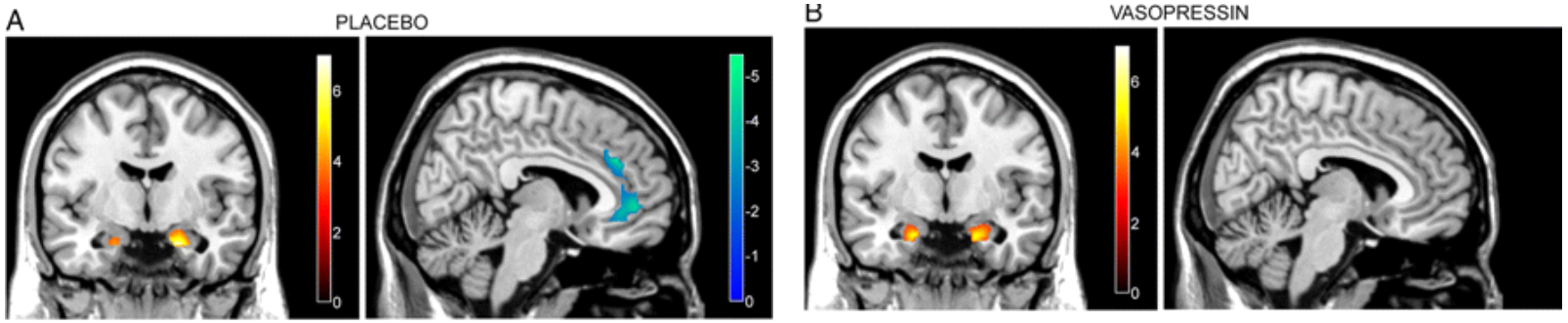
Meyer-Lindenberg et al., PNAS2006

MAO-Low >MAO-A-High

Genetic variations in MAO-A are associated with structural and functional changes in the neural network underlying aggression and altered behavior

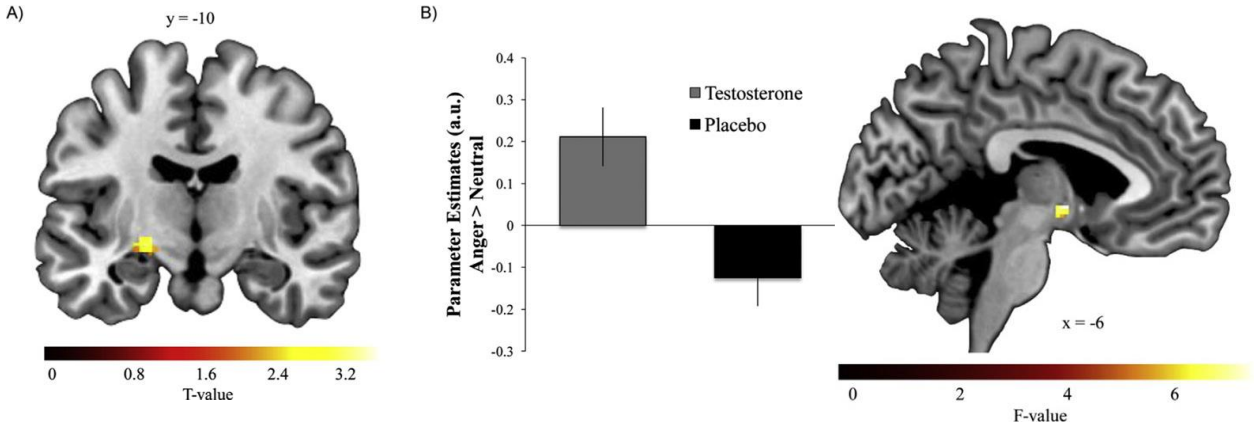
Endocrine signaling

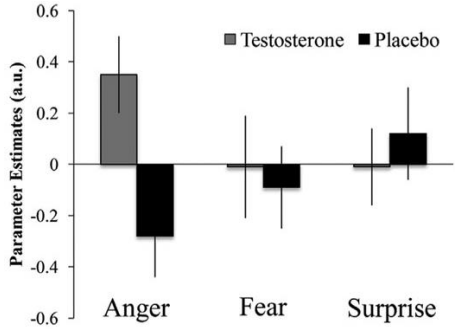
- Vasopressin

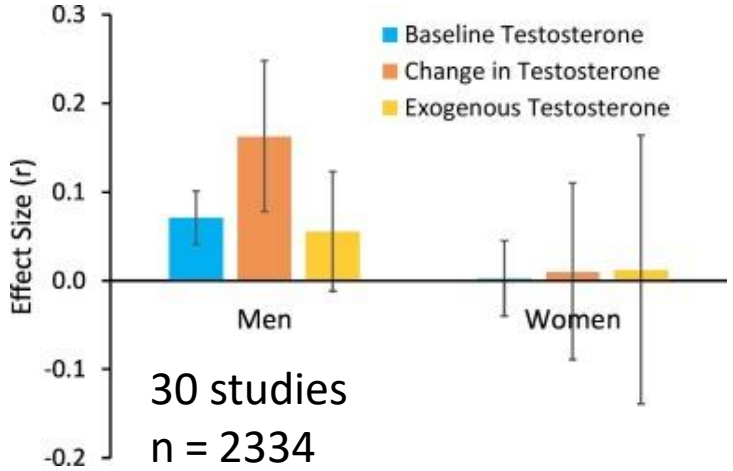


Zink et al., JoN2010

- Testosterone







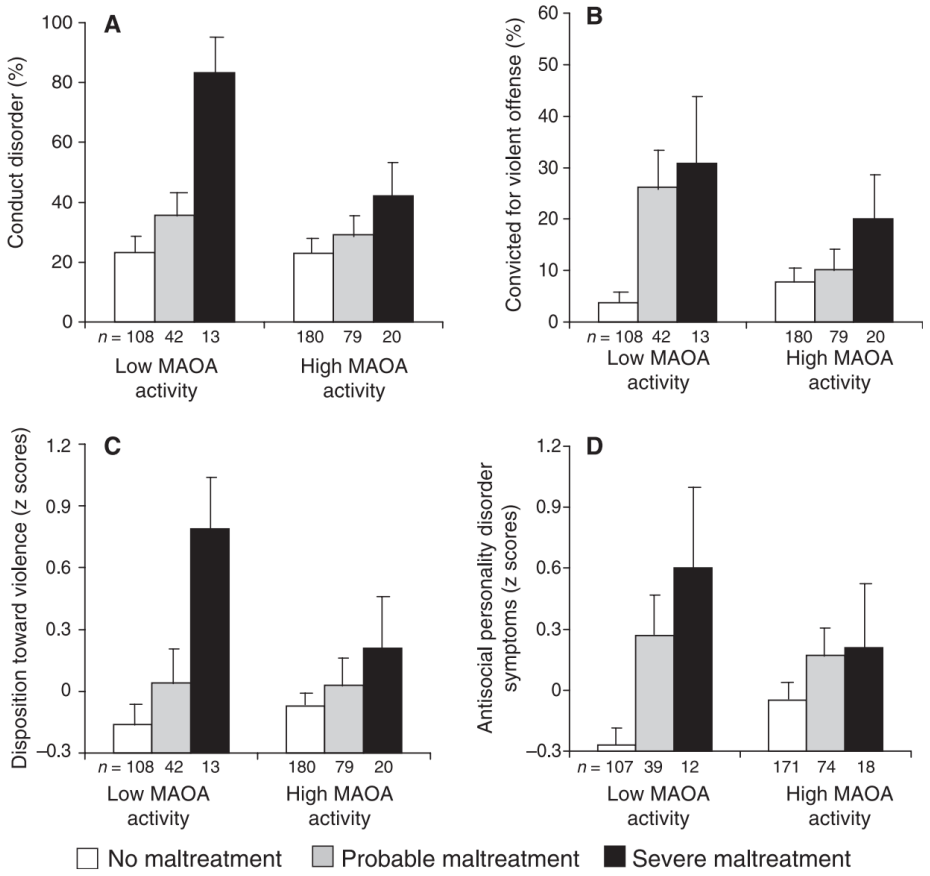
30 studies
n = 2334

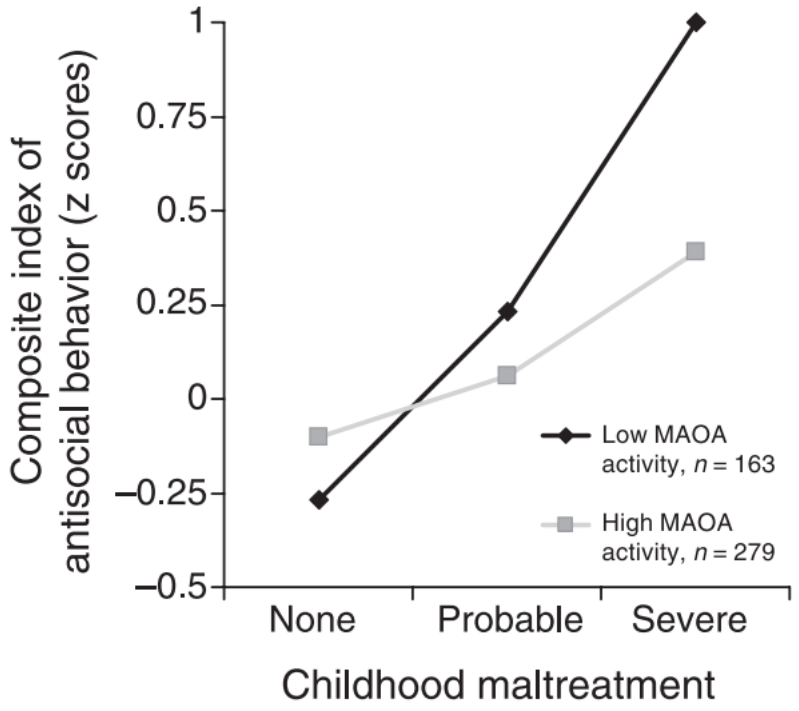
Goetz et al., Biol Psychiatry 2014

Geniole et al., Horm Beh 2020

Vasopressin and Testosterone may play a limited role on brain circuits associated with aggressive behavior

Does the environment matter?

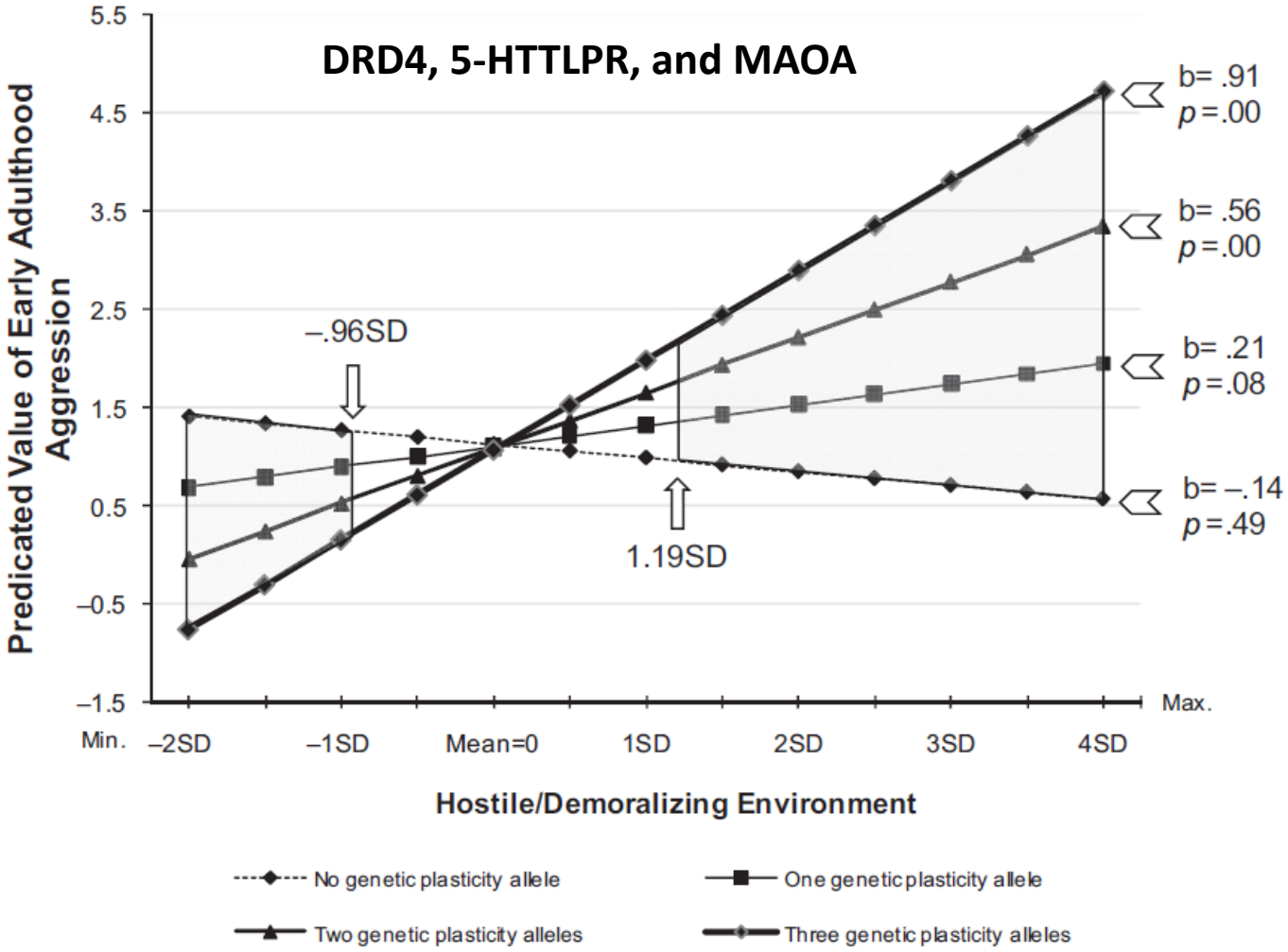


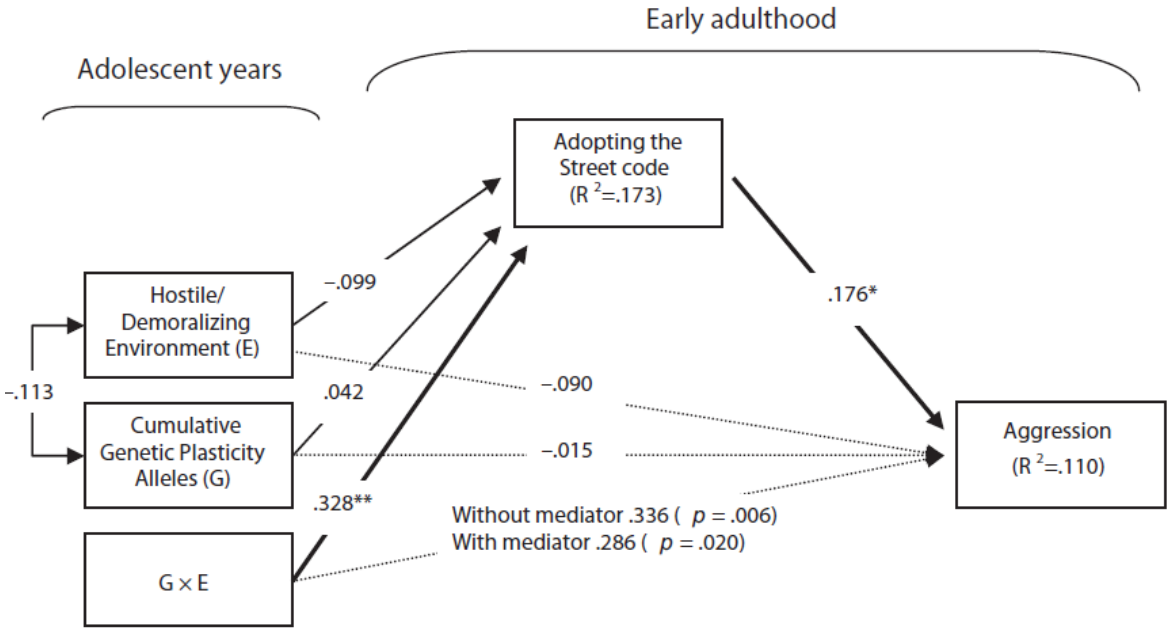


Caspi et al., Science 2003

Maltreatment can modulate the effects of genetic variation in MAO-A gene

Does the environment matter?





Simons et al., YV&JJ2012

Hostile environment can modulate the effects of the genetic variations at risk for aggressive behavior

Gene x environment x sex

Table 2 G×E interactions in relation to childhood antisocial behavior in males and females

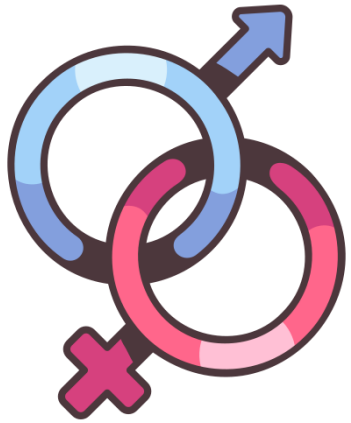
Contrast	Males			Females		
	N	IRR (95% CI)	*P*	*N*	IRR (95% CI)	*P*
Smoking during pregnancy	2547	1.43 (1.22–1.68)	**<0.0001***	2394	1.78 (1.51–2.09)	**<0.0001***
Maltreatment	1431	1.97 (1.65–2.35)	**<0.0001***	1298	1.99 (1.66–2.40)	**<0.0001***
MAOA-L (males)/HL (females)	2235	1.01 (0.87–1.17)	0.91	2090	1.03 (0.81–1.31)	0.80
MAOA-HH (females)					1.08 (0.85–1.37)	0.54
rs4714329 GG	2547	0.95 (0.79–1.15)	0.63			
rs9471290 AA	2547	1.16 (0.96–1.41)	0.13			
rs2764450 TC				2383	1.07 (0.86–1.33)	0.56
rs11215217 TC				2370	0.97 (0.80–1.18)	0.76
MAOA-L (males)/HL (females)×smoking during pregnancy	2235	1.00 (0.70–1.43)	0.99	2089	1.15 (0.63–2.10)	0.64
MAOA-HH (females)×smoking during pregnancy					1.23 (0.68–2.25)	0.49
MAOA-L (males)/HL (females)×maltreatment	1266	1.35 (0.90–2.03)	0.15	1135	3.27 (1.74–6.14)	**0.0002***
MAOA-HH (females)×maltreatment					2.09 (1.11–3.93)	**0.0227**
rs4714329 GG×smoking during pregnancy	2547	1.95 (1.29–2.94)	**0.0015***			
rs4714329 GG×maltreatment	1431	0.76 (0.47–1.25)	0.28			
rs9471290 AA×smoking during pregnancy	2547	2.18 (1.47–3.24)	**0.0001***			
rs9471290 AA×maltreatment	1431	1.28 (0.71–2.31)	0.42			
rs2764450 TC×smoking during pregnancy				2382	1.22 (0.75–1.97)	0.43
rs2764450 TC×maltreatment				1291	1.61 (0.89–2.91)	0.11
rs11215217 TC×smoking during pregnancy				2369	0.69 (0.40–1.19)	0.18
rs11215217 TC×maltreatment				1285	0.47 (0.29–0.75)	**0.0018***

All analyses were adjusted for socioeconomic status, single-parent status, and the first ten genetic principal components, including covariate interaction terms for the G×E models

Ruisch et al ., EAPCN 2019

Genetic variations and environmental factors may show different effects on antisocial behavior in men and women

Conclusions



X

Environment
- maltreatment
- substance abuse
- other factors

Genes
- serotoninergic system
- enzymes
- transporters
- receptors
- dopaminergic system

Epigenetic

Neuronal dysfunction/loss

Neurotransmission imbalance

Frontolimbic dysfunction

Brain structures
- cingulate gyrus
- insular cortex
- orbital frontal cortex
- hippocampus
- subcallosal gyrus
- amygdala
- thalamus
- hypothalamus
- basal ganglia

Types of harm
- lesions
- volumetric alterations
- inefficient processing
- altered activity

Changes in neurotransmitters synthesis, metabolism, uptake, transport and connectivity in below systems

- raphe nuclei neurons send serotonin projections to ventromedial and cingulate cortexes
- serotonin connectivity between ventromedial prefrontal cortex, cingulate cortex and amygdala
- substantia nigra neurons send dopamine projections to cingulate cortex and central nucleus of amygdala
- γ-aminobutyric acid inhibitory neurons are located in intercalated cell clusters of amygdala
- basolateral amygdala sends glutamatergic inputs to nucleus accumbens
- amygdala efferents to nucleus basalis affect acetylcholine activity

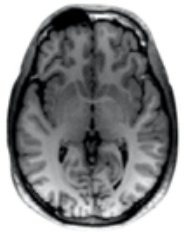
Cupaioli et al., PNBP21

Conclusions

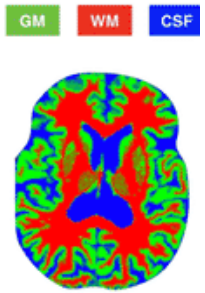
- Violence is a behavior influenced by a complex interplay of multiple factors.
- Psychiatric disorders contribute only marginally to the overall occurrence of violence.
- Neuroscience has identified specific brain circuits involved in aggressive behavior and highlighted the influence of genetics on these circuits.
- A combination of genetic, epigenetic, sex-related, hormonal, and environmental factors significantly contributes to the manifestation of violence.
- Environmental factors, such as early experiences, trauma, and socioeconomic conditions, are critical in shaping violent behavior
- Current research is limited by insufficient statistical power to examine sex-specific effects, reliance on non-ecological reductionist models, and experimental designs that hinder the generalizability of findings.

Neuroimaging techniques

Structural MRI

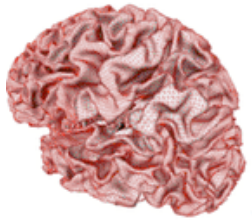


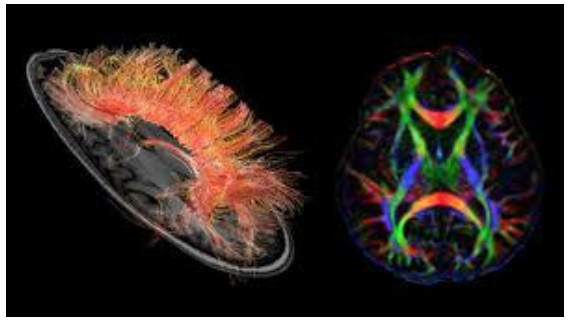
T1 weighted Image in Native Space



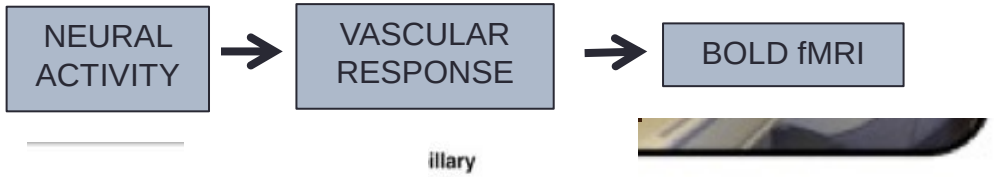
Segmented Image in Standard Space

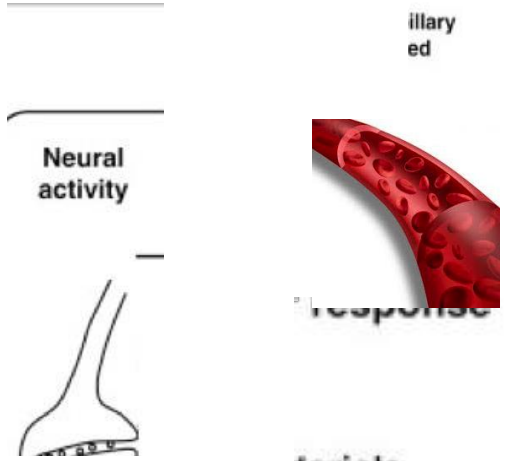
Pial and inner surfaces generation





functional MRI



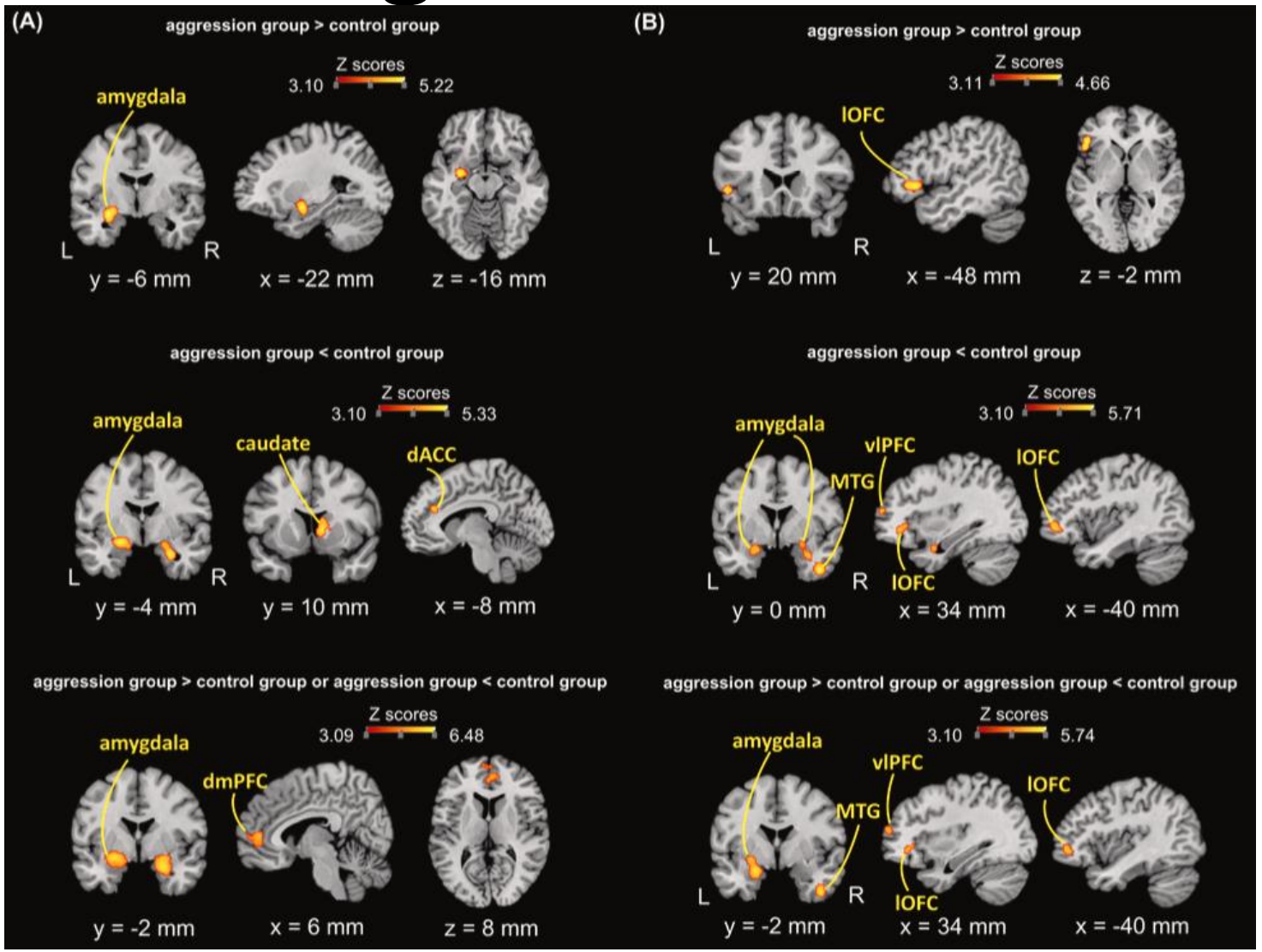


Based on the **BOLD** (**B**lood **O**xygenation **L**evel **D**ependent) signal

- A measure of inhomogeneities in the magnetic field due to changes in the level of O2 in the blood
- Indirect measure of neural activity
- Strongly correlated with post-synaptic activity

Logothetis et al., 2001

Brain changes in violence



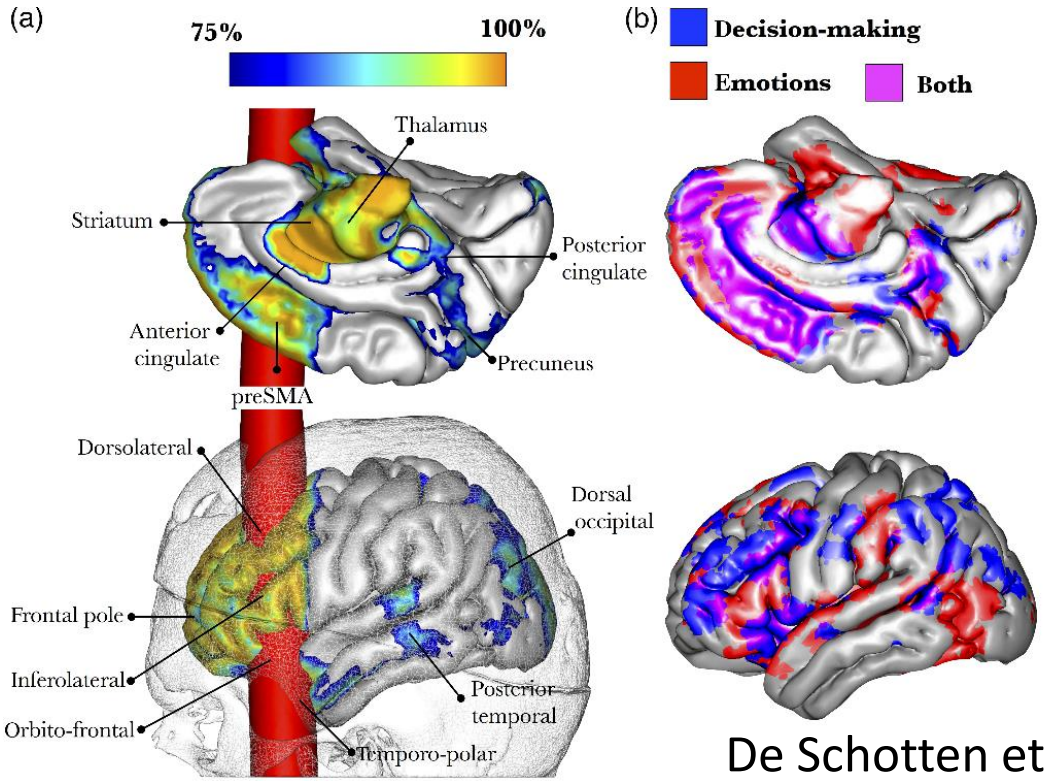
Amygdala
Striatum
Medial Prefrontal cortex
Ventrolateral Prefrontal cortex
Orbitofrontal cortex
Anterior Cingulate
Temporal

Wang et al., Neuroimage 2024

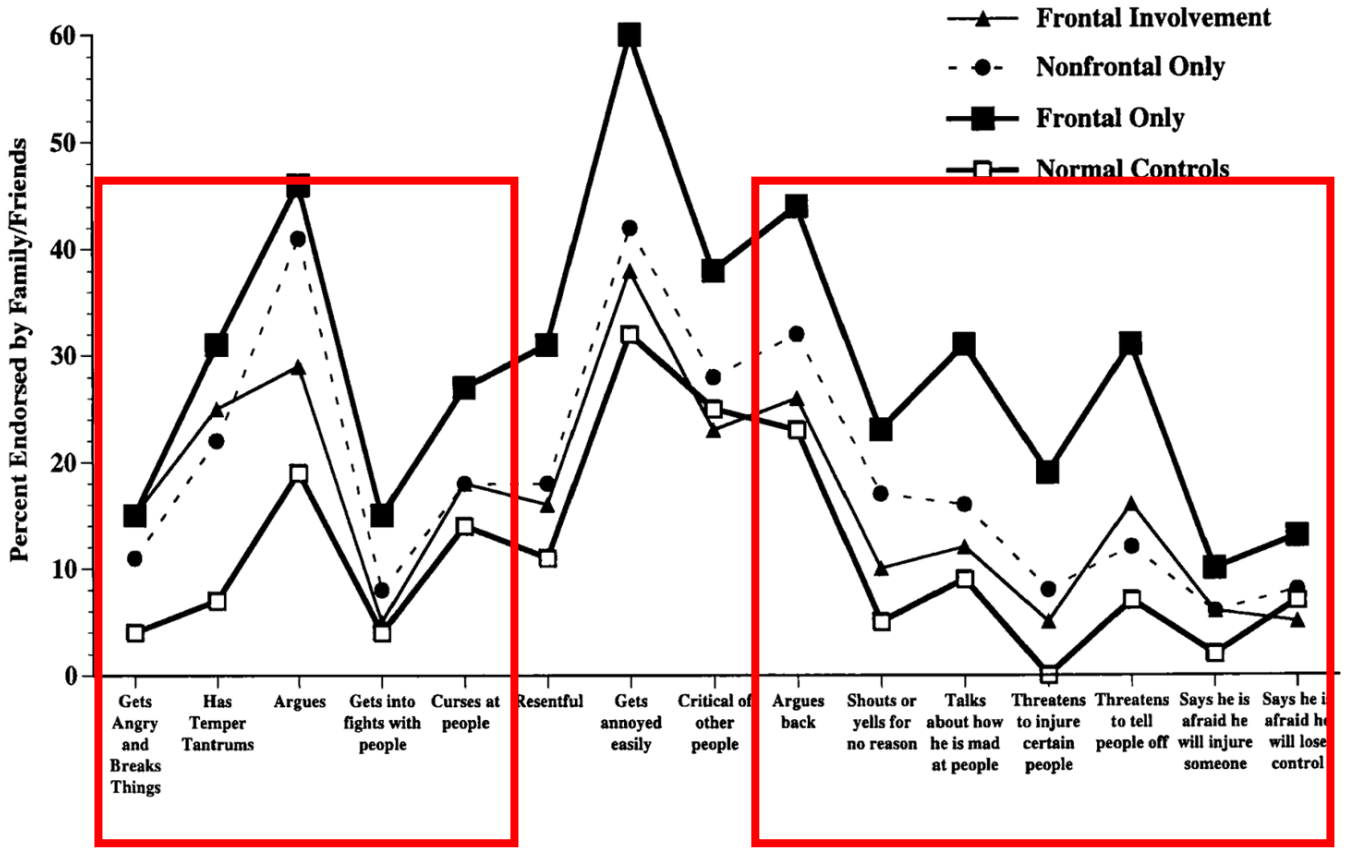
Cognitive control network: Prefrontal cortex

Phineas Gage

Imaging Meta-analysis



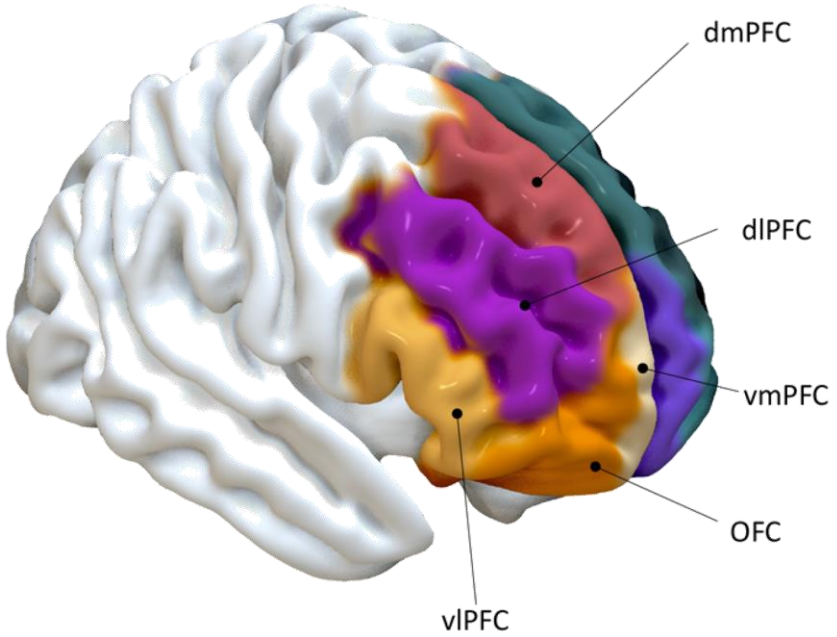
De Schotten et al., Cer Cor2015



Grafmann et al., Neurology1996

Altered function in frontal cortex contribute to aggression/impulsivity

Cognitive control network: Prefrontal cortex - subregions

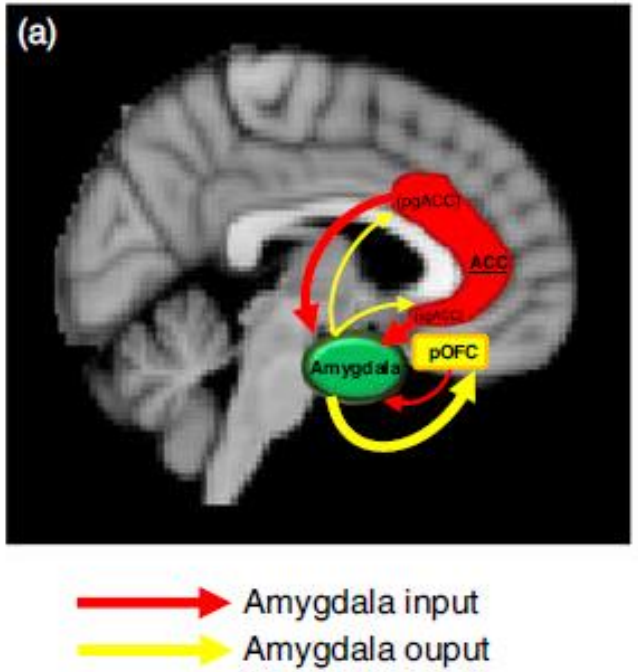


- Ventromedial prefrontal cortex
  - triggering the affective/emotional signals of long-term outcomes
  - facial emotion recognition
  - risk evaluation, moral judgments, probabilistic reinforcement learning based on negative feedback
  - inhibitory control over aggressive impulse
- Dorsolateral and dorsomedial prefrontal cortex
  - controlling responses to environmental stimuli
  - risk/benefit evaluation
  - problem solving and cognitive control and self-control
  - reward processing

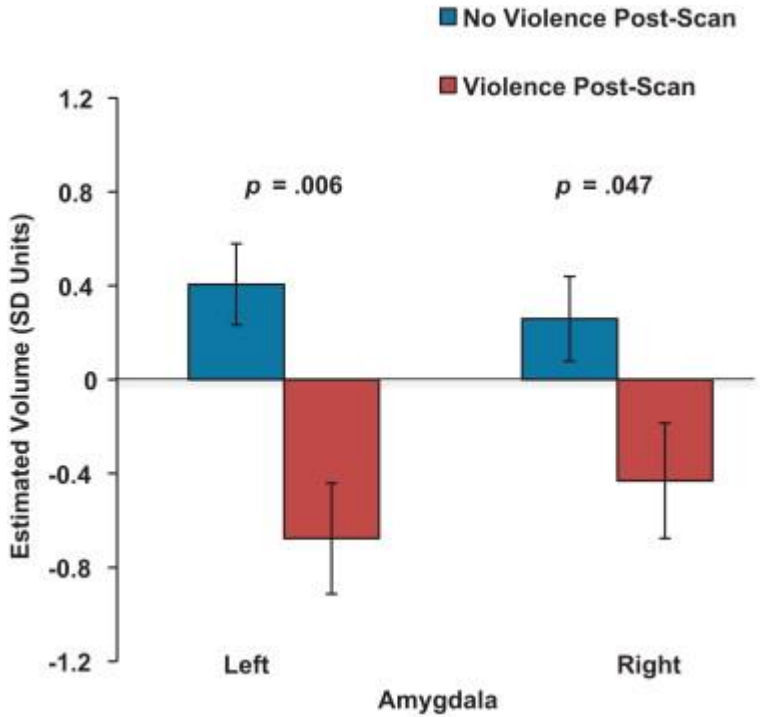
Cupaioli et al., PNPPBP 2021

Prefrontal cortex subregions can play distinct roles in violence

Limbic system:
Cingulate, Amygdala and Hippocampus



Rosell and Siever, CNS Spectrum 2015



Pardini et al., BioPsy2014

Amygdalar and hippocampal atrophy are associated with violent behavior

Brain responses in violent individuals

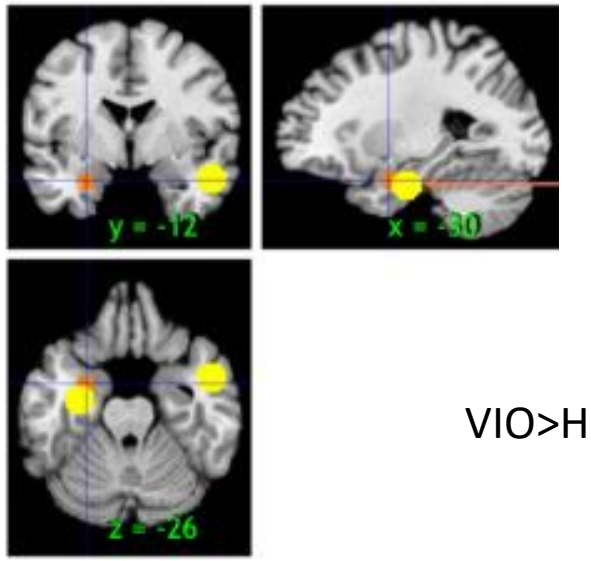
Subjects

- Major disorder or personality disorders with violent behavior
- charged with, convicted, or incarcerated for aggressive behavior
- High aggression score

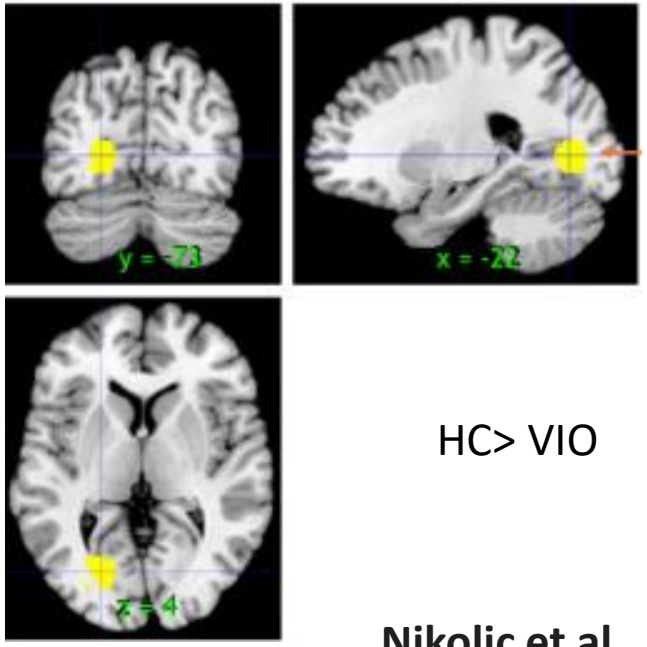
Tasks

- script-driven-imagery tasks
- a personal-space intrusion task
- an anger-eliciting task
- viewing emotional images and videos

N=9 studies
230 PTS
235 HCs



VIO>HC



HC> VIO

Nikolic et al., Maja Nikolic PNPBP 2022

Brain Signaling: serotonin receptors

- 5HT Receptors:
  - 5HT1A
    - Negative relationship w/aggression depending on Personality Disorder diagnosis
  - 5HT2A
    - *Postmortem*: binding was positively correlated with lifetime history of aggression (Oquendo et al, 2006)
    - *PET*
      - OFC levels w/Aggression in Intermittent Explosive DIsorder
      - trait aggression in patients with Borderline Personality (Soloff etal., 2014)
      - impulsivity in a highly assaultive population with Antisocial Personality Disorder (Ryland et al., 2012)
    - ?5HT1B and 5HT3
      - Mouse and hamster models

5HT1A and 5HT2A modulation is associated with aggression

MAO-A and Trials

The Get Out of Jail Free gene

The sentence of one killer in Italy has been reduced as he possesses a 'violent gene'. Can DNA be used as a defence?

Table 1
Legal proceedings with evidence of MAOA-L genotype from 1995 to March 1, 2016.

Case (year) court	MAOA-L	Reason for test	Court proceedings	Outcome
Mobley (1995) U.S.	N/A	Murder	S	No sentencing reduction; death penalty
Bayout (2009) Italy	+	Murder	A	Appeal upheld; 9 years reduced to 8 years
Waldroup (2011) U.S.	+	Murder Attempted murder	G	Charge reduction; first-degree murder reduced to voluntary manslaughter
Albertani (2011) Italy	+	Murder Attempted murder (2)	A	Appeal upheld; life reduced to 20 years
Bourassa (2012) U.S.	+	Murder	S	Sentenced to life; spared death penalty
Adams (2014) U.S.	+	Murder (3) Attempted murder	S	No sentencing reduction; death penalty
Duran (2014) U.S.	N/A	Attempted murder	A	Appeal dismissed; 15 years
Driskill (2015) U.S.	+	Murder (2)	S	No sentencing reduction; death penalty
Colbert (2015) U.S.	+	Murder	S/A	No sentencing reduction; life sentence
Yepez (2015) U.S.	+	Murder	G	Evidence inadmissible; second-degree murder
Bathgate (2016) U.S.	N/A	Murder	A	Habeus corpus dismissed; evidence procedurally defaulted

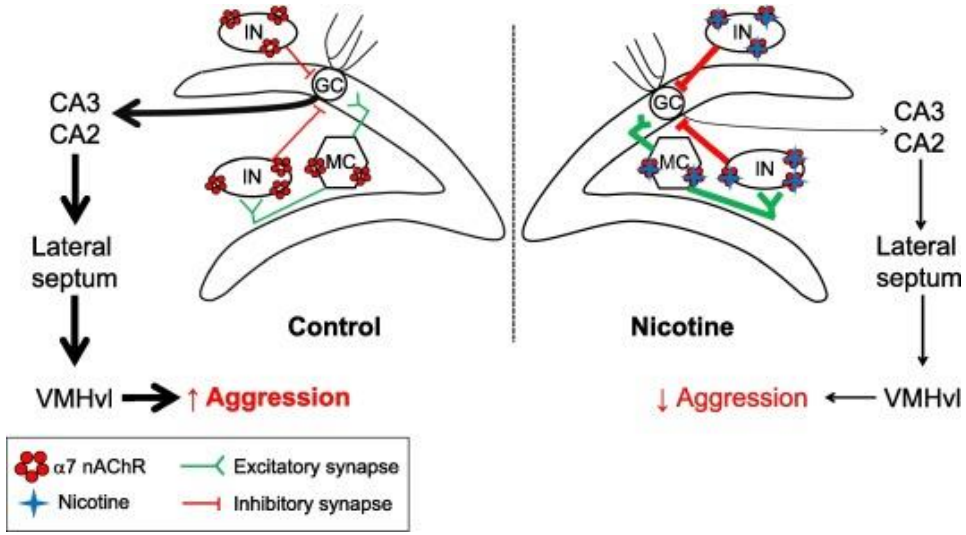
Note. + = MAOA-L genotype carrier; A = appellate phase; G = guilt phase; N/A = no test undertaken; S = sentencing phase.

McSwiggan et al. 2017

Genetic variations in MAO-A have been used in murder case trials for sentence reduction

Brain Signaling: Glutamate/GABA and ACH

- Acetylcholine
  - Nicotine -> reduces aggression
    - Polymorphims nAChRs *CHRNA7*
  - Heterogenous results



- GABA/Glutamate
  - GABA-A R modulators may enhance aggression
  - Glu enhancement increases aggression
  - imbalance in the GABA/Glu

Lewis et al., Neuropharmacology20

Other neurotransmitter system may contribute to aggressive behavior