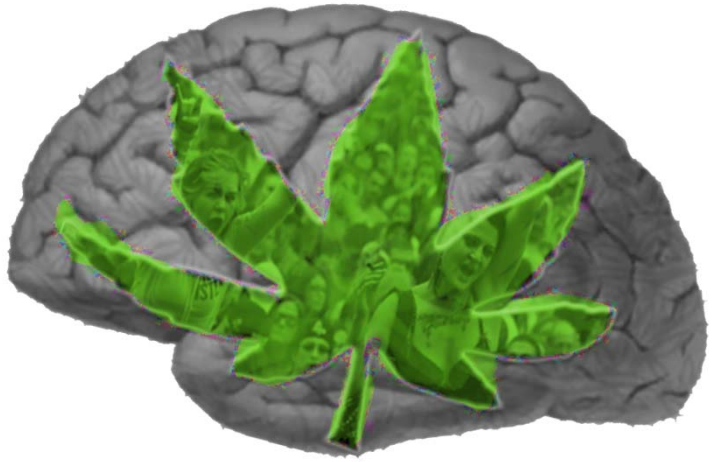
part 2

consequences?



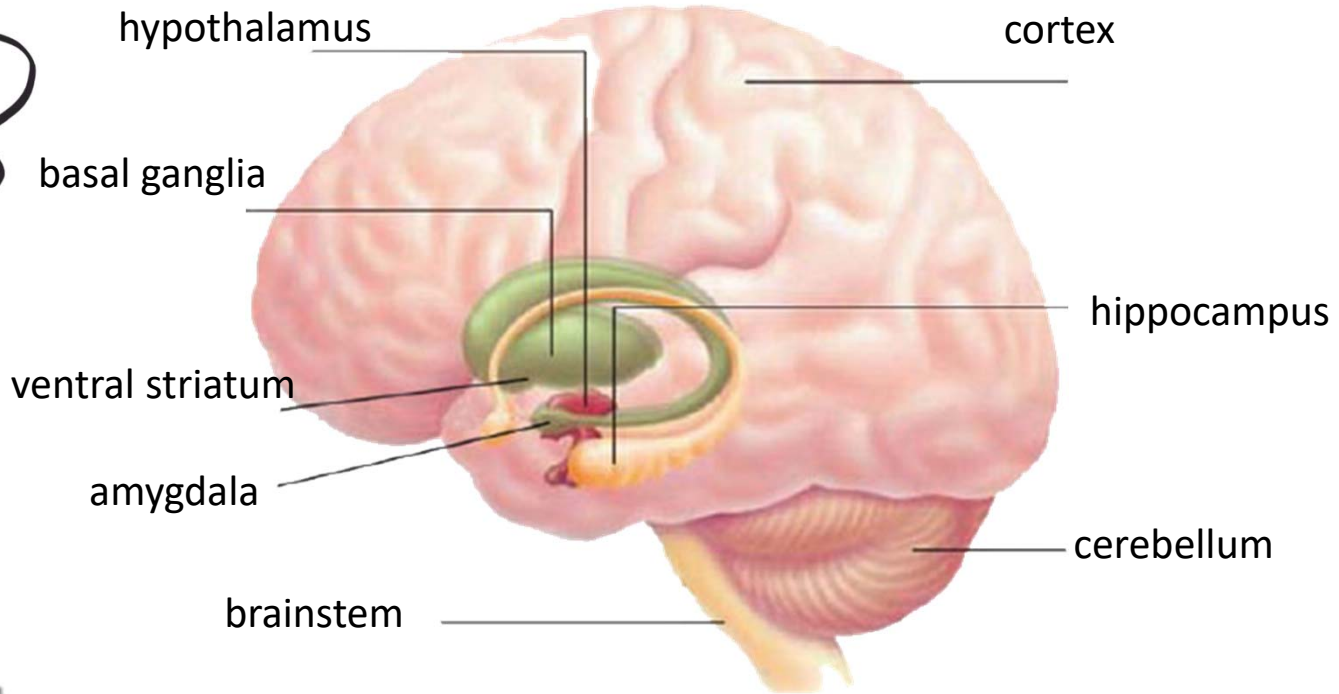
marijuana and the teen brain

MARY ET BOYLE, PH. D.

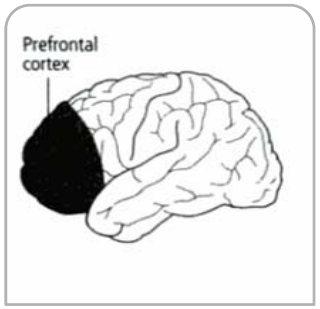
DEPARTMENT OF COGNITIVE SCIENCE

UCSD

what areas of the brain process marijuana?

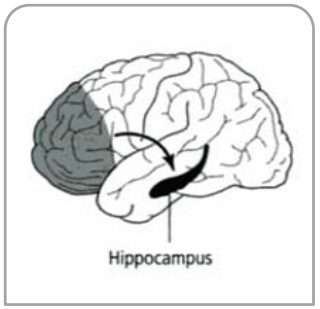


Explicit memory or declarative memory: objects, places, facts, people, and events.



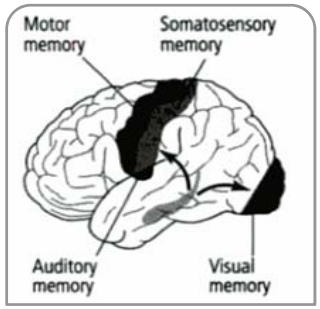
Short term explicit memory

1



Converted to long term memories

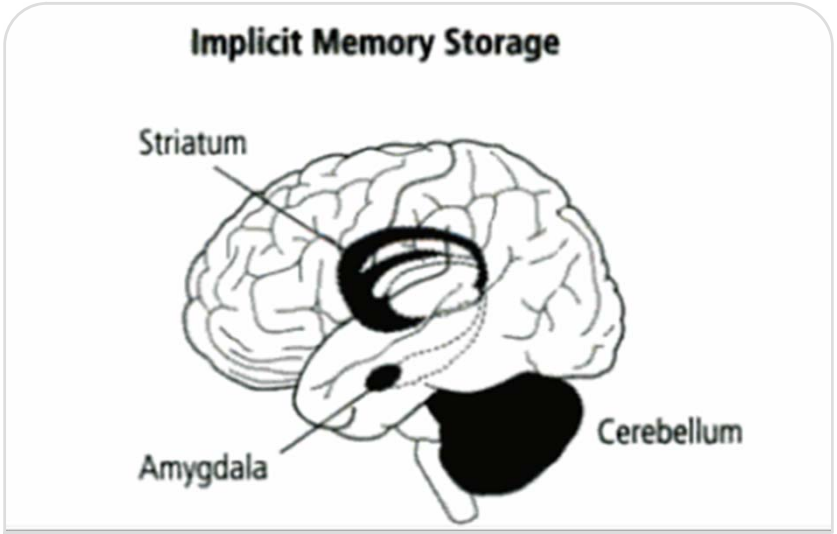
2



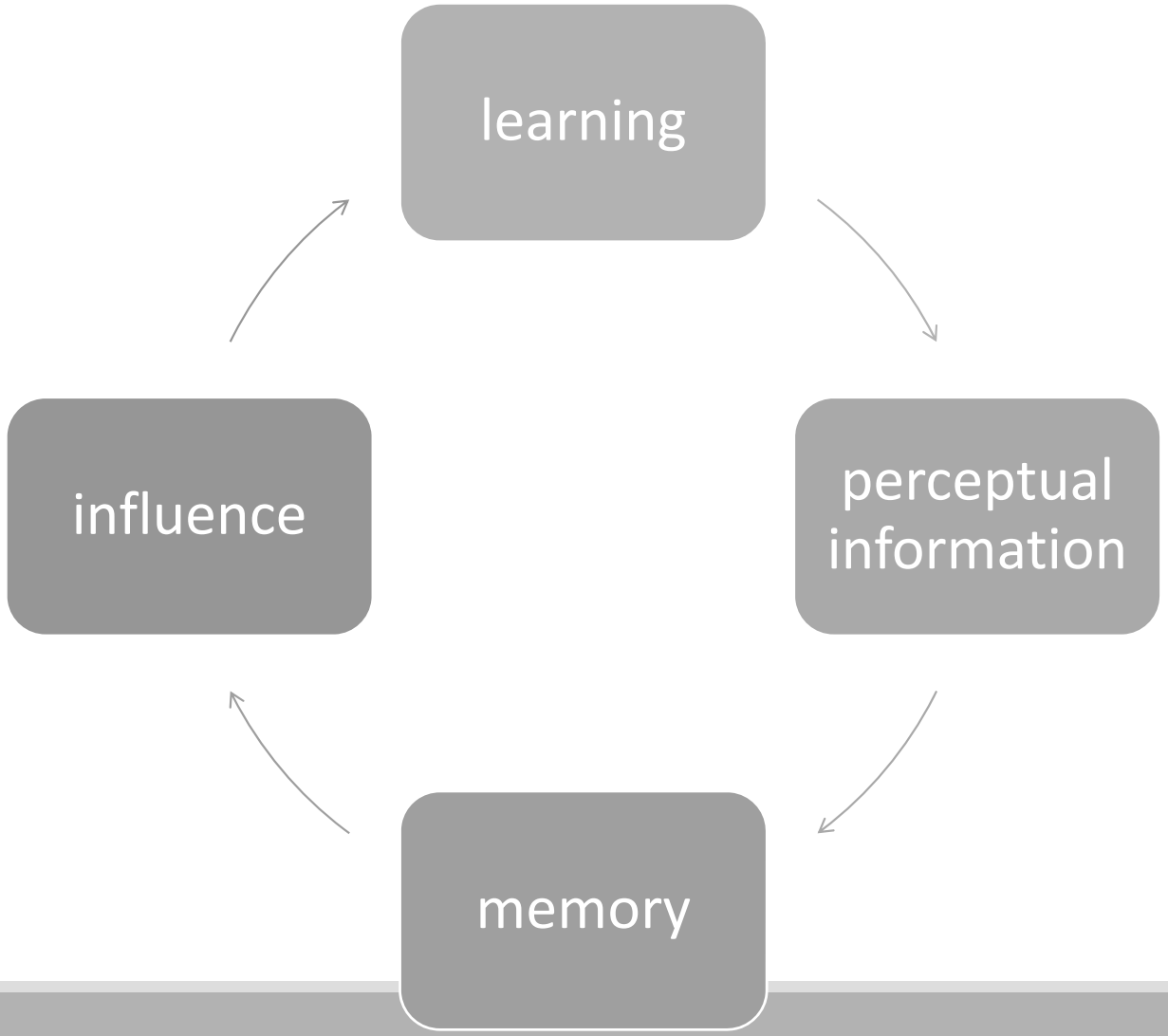
Stored in parts of the cortex that correspond to the senses involved – the same areas that originally processed the information.

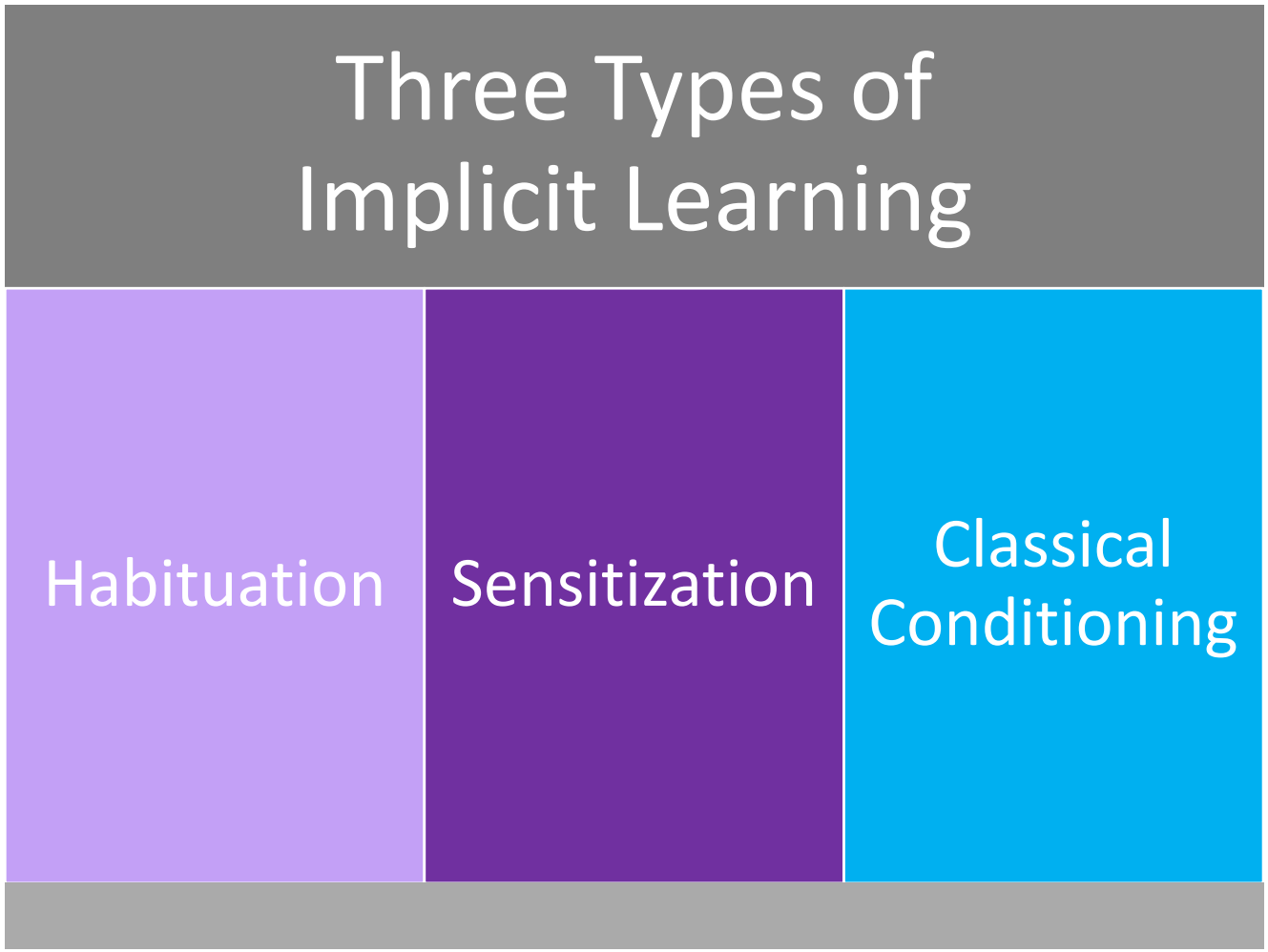
3

Implicit memory or procedural memory: skills, habits, and conditioning.



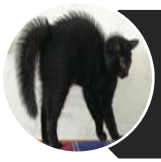
Implicit memories of skills, habits, and conditioning are stored in the cerebellum, striatum, and amygdala


learning
perceptual information
memory
influence


Three Types of Implicit Learning
Habituation
Sensitization
Classical Conditioning

habituation

Most simple form of learning



Initial response to stimuli:
very defensive -

Repeated exposure to stimuli:

Response is muted - Eventually ignored.

Purpose:
Animal needs to learn which stimuli to safely ignore

Eliminates inappropriate or
exaggerated defense responses

Important for:
Organizing perception

sensitization

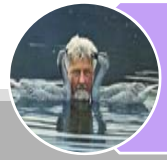
Sensitization – mirror image of habituation

After a noxious stimulus

the sensitized animal respond more strongly to all stimuli.

Purpose:
Instead of ignoring a stimulus – it is a form of learned fear. Survival.

It teaches the animal to attend and respond more vigorously to almost any stimulus



Konrad Lorenz: “An earthworm that has just avoided being eaten by a blackbird … is indeed well advised to respond with a considerably lowered threshold to similar stimuli because it is almost certain that the bird will still be nearby for the next few seconds.”

classical conditioning

Aversive Classical Conditioning

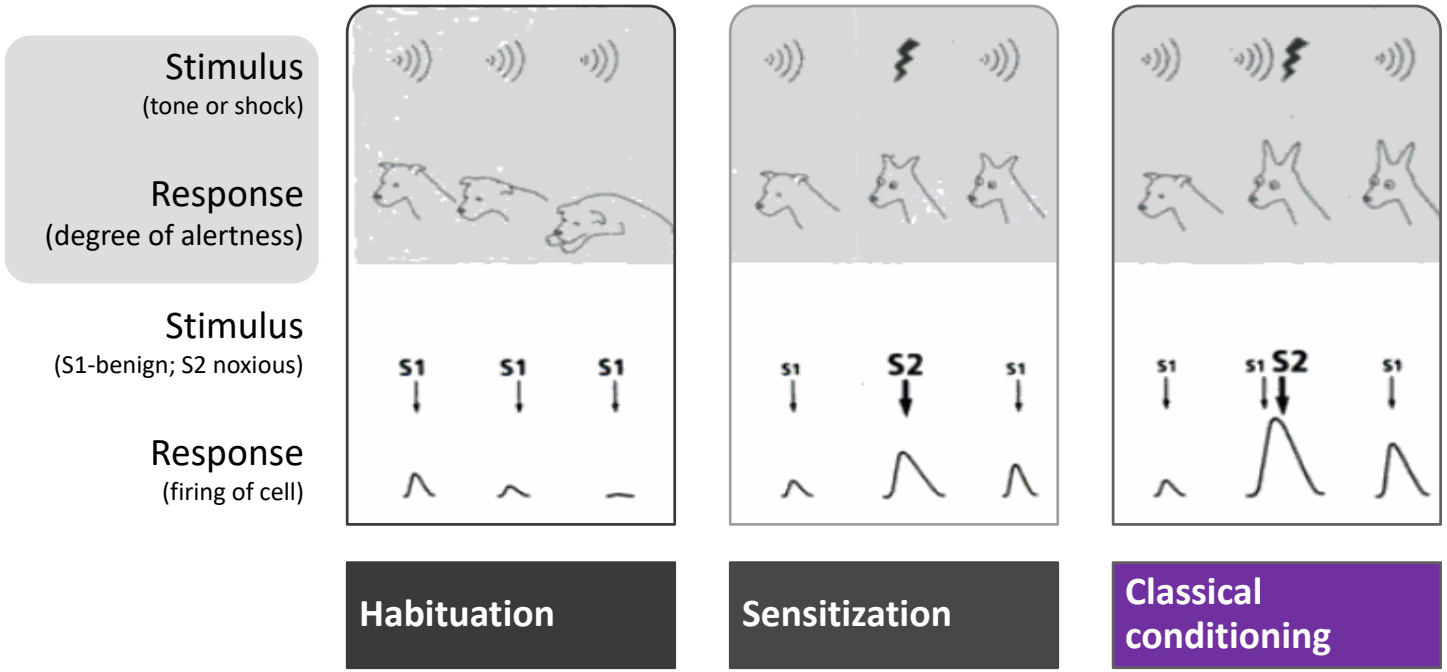
A neutral stimulus must always precede the aversive stimulus – that way the animal will come to predict it.

Pavlov: shock a dog's paw. The shock caused the animal to raise and withdraw its leg – a fear response.

Pavlov found that after several trials in which he paired the shock with a bell – first sounding the bell then the shock – the dog would withdraw his paw whenever the bell sounded.

Classical conditioning an association is formed between a pair of stimuli that occur in rapid sequence.

Teaches the animal to associate an unpleasant stimulus with a stimulus that ordinarily elicits no response.



Synaptic strength is not fixed – it can be altered in different ways by different patterns of activity.

Cellular basis of learning and memory

Cellular modification theory

- Learning changes neural responsiveness
- Enhanced functioning of existing neural circuits or the establishment of new ones.

Changes in synaptic efficiency:

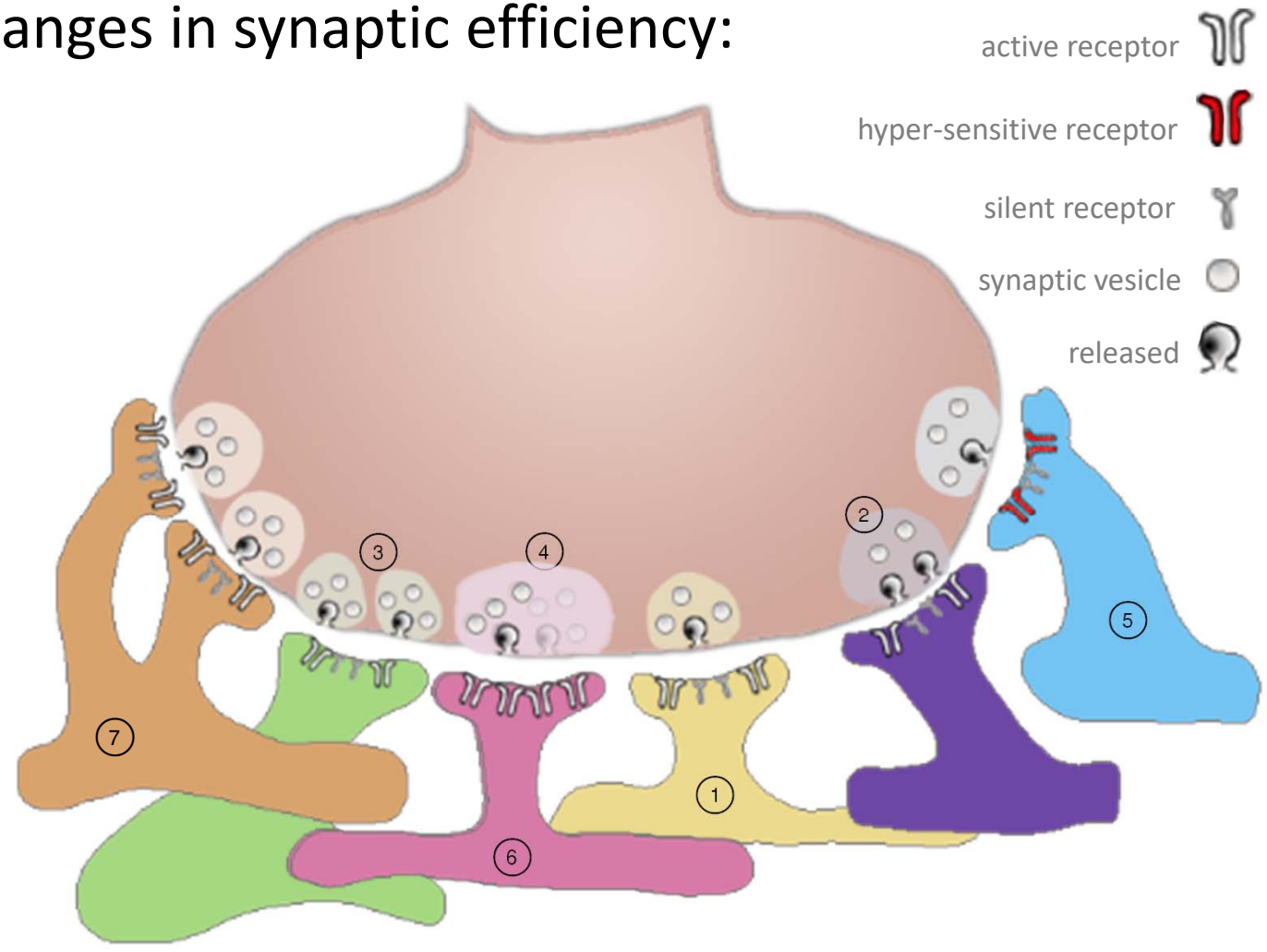
1. normal synapse

PRE-SYNAPTIC

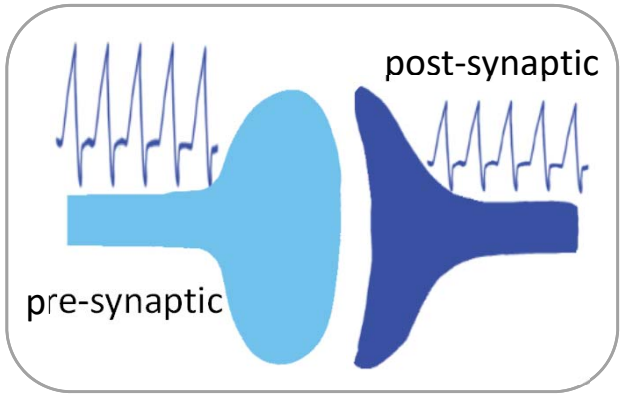
2. increase in release probability
3. increase in number of release sites
4. increase in number of vesicles

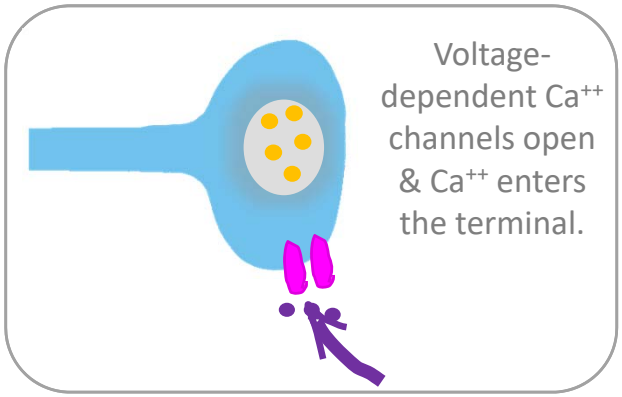
POST-SYNAPTIC

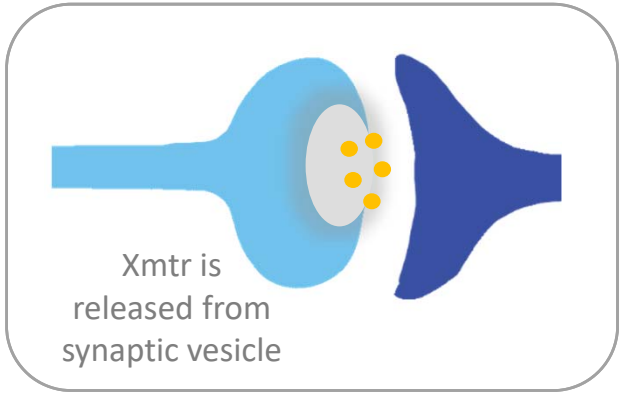
5. increase in receptor sensitivity
6. increase in the number of receptors
7. increase in number of dendritic spines

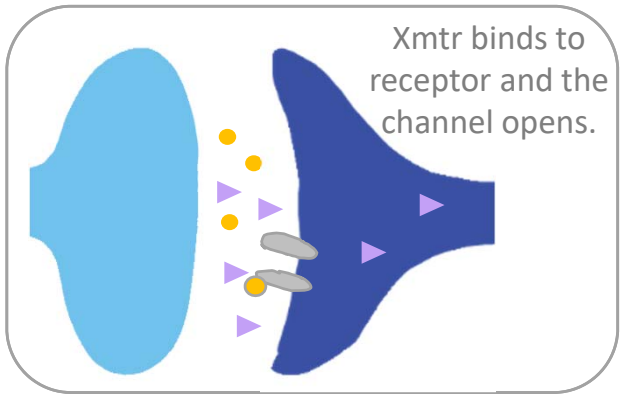


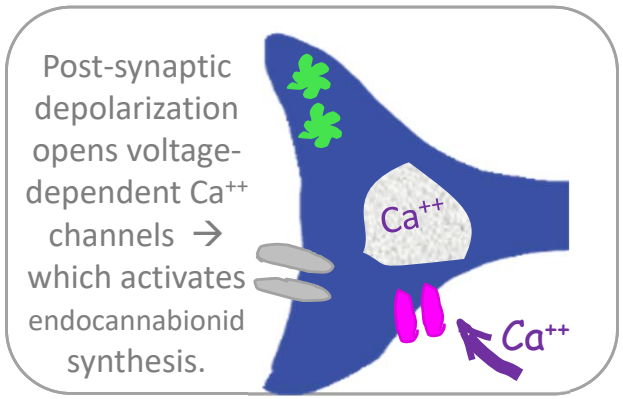
How do endocannibinoids affect synaptic transmission?

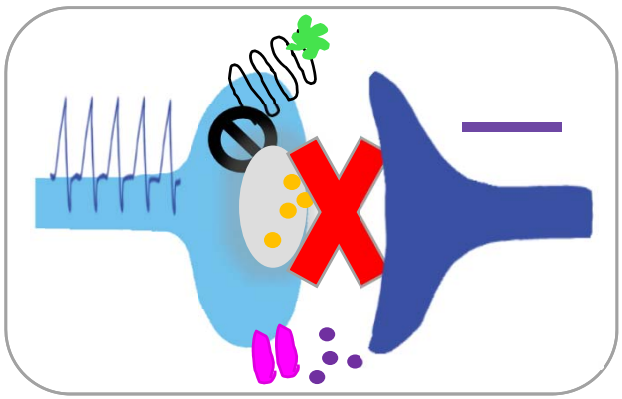




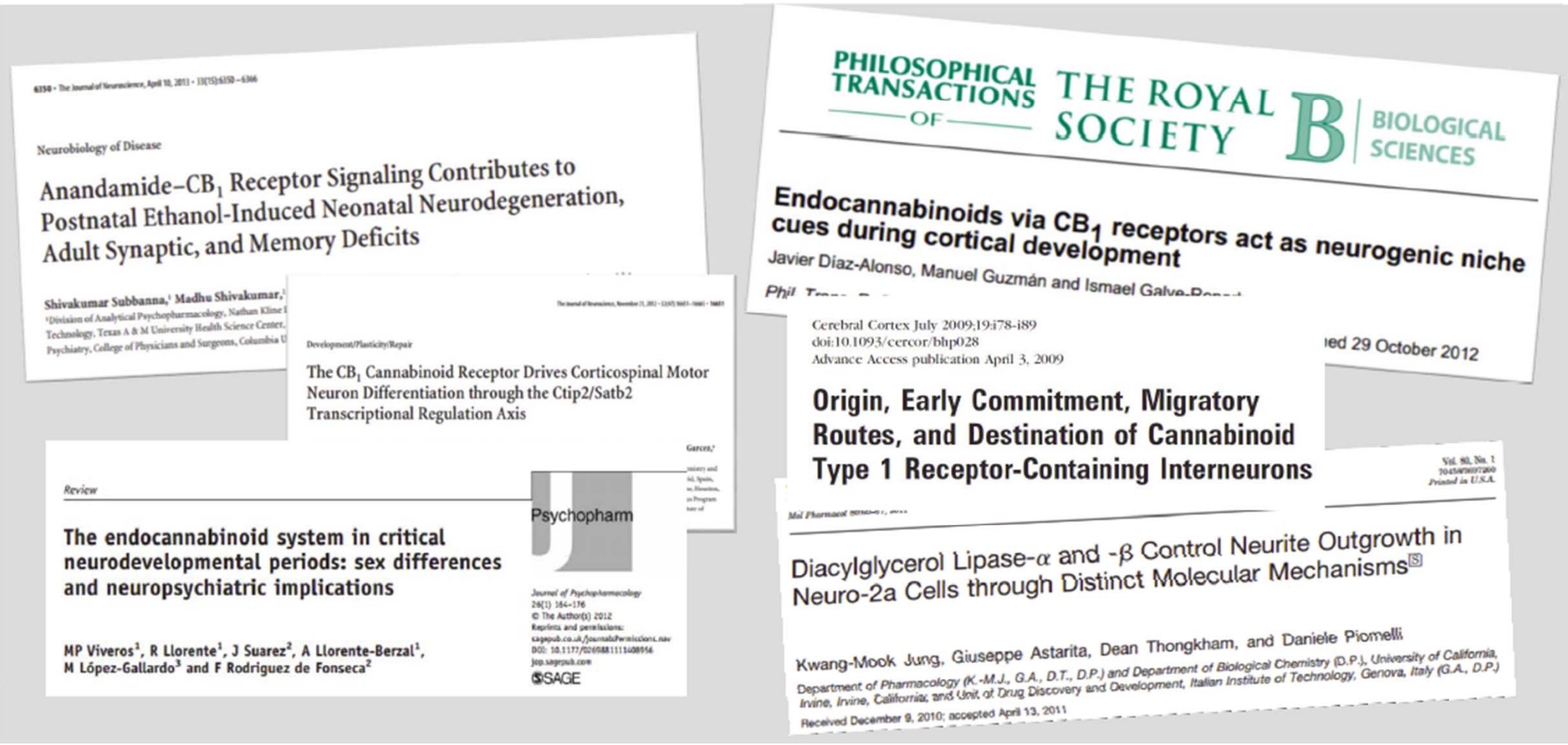




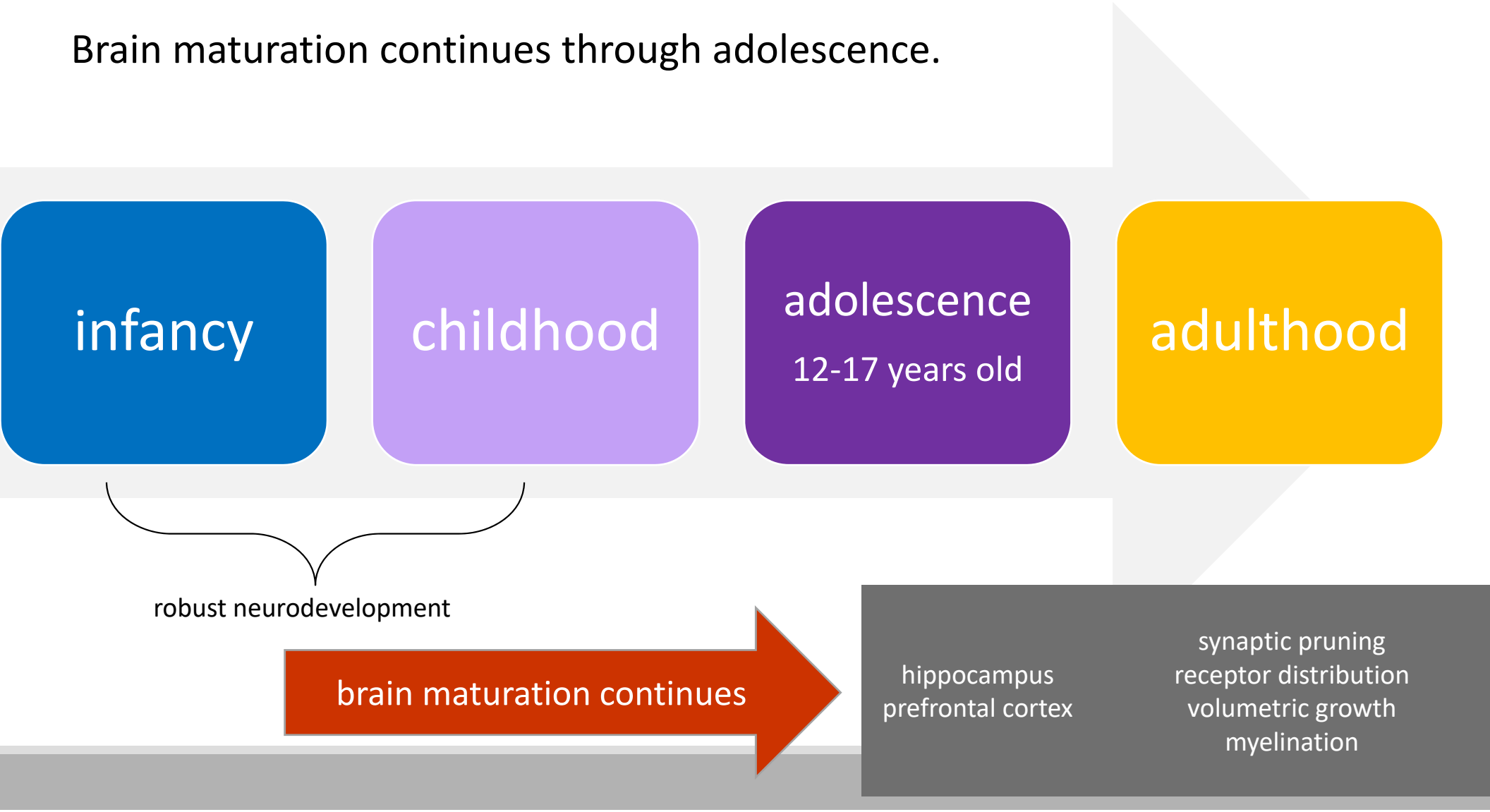




endocannabinoid signaling is critical during development



Brain maturation continues through adolescence.

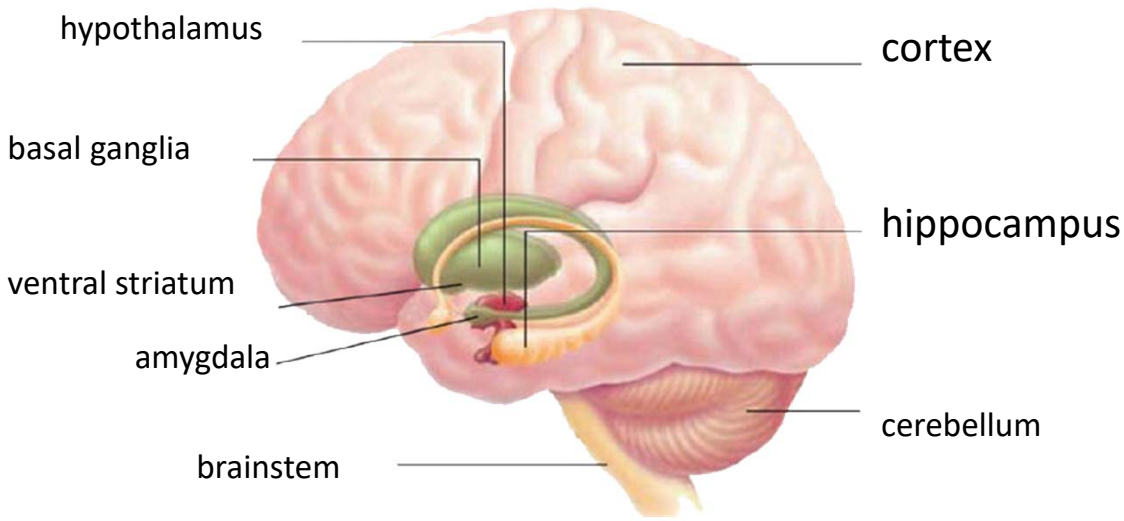


CB_1 receptors increase dramatically from infancy to young adulthood.

CB1 receptor expression **changes** over time

dramatic increase during development

frontal cortex, striatum & hippocampus



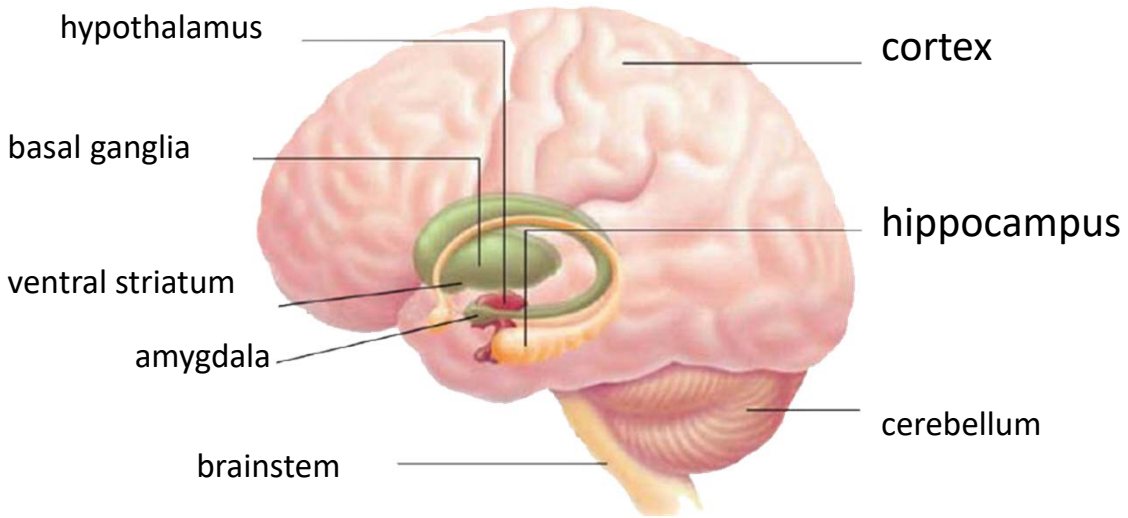
Mato *et al*., 2003

endocannabinoid ligand expression changes during adolescence.

AEA and 2-AG expression changes

AEA – onset of puberty for females in hypothalamus

2-AG expression changes in PFC & N. Accumbens



disruption of normative endocannabinoid signalling during adolescence may have long-standing consequences on adult brain function

Mato *et al*., 2003

Neuropharmacology 76 (2014) 416–424

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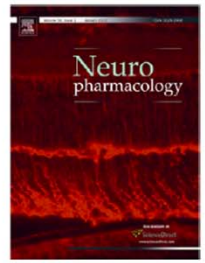

Invited review

Trajectory of adolescent cannabis use on addiction vulnerability

Yasmin L. Hurd [a,b,c,*], Michael Michaelides [a,b], Michael L. Miller [a,b], Didier Jutras-Aswad [d,e]

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[b] Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] James J. Peters Veterans Administration, Bronx, NY, USA
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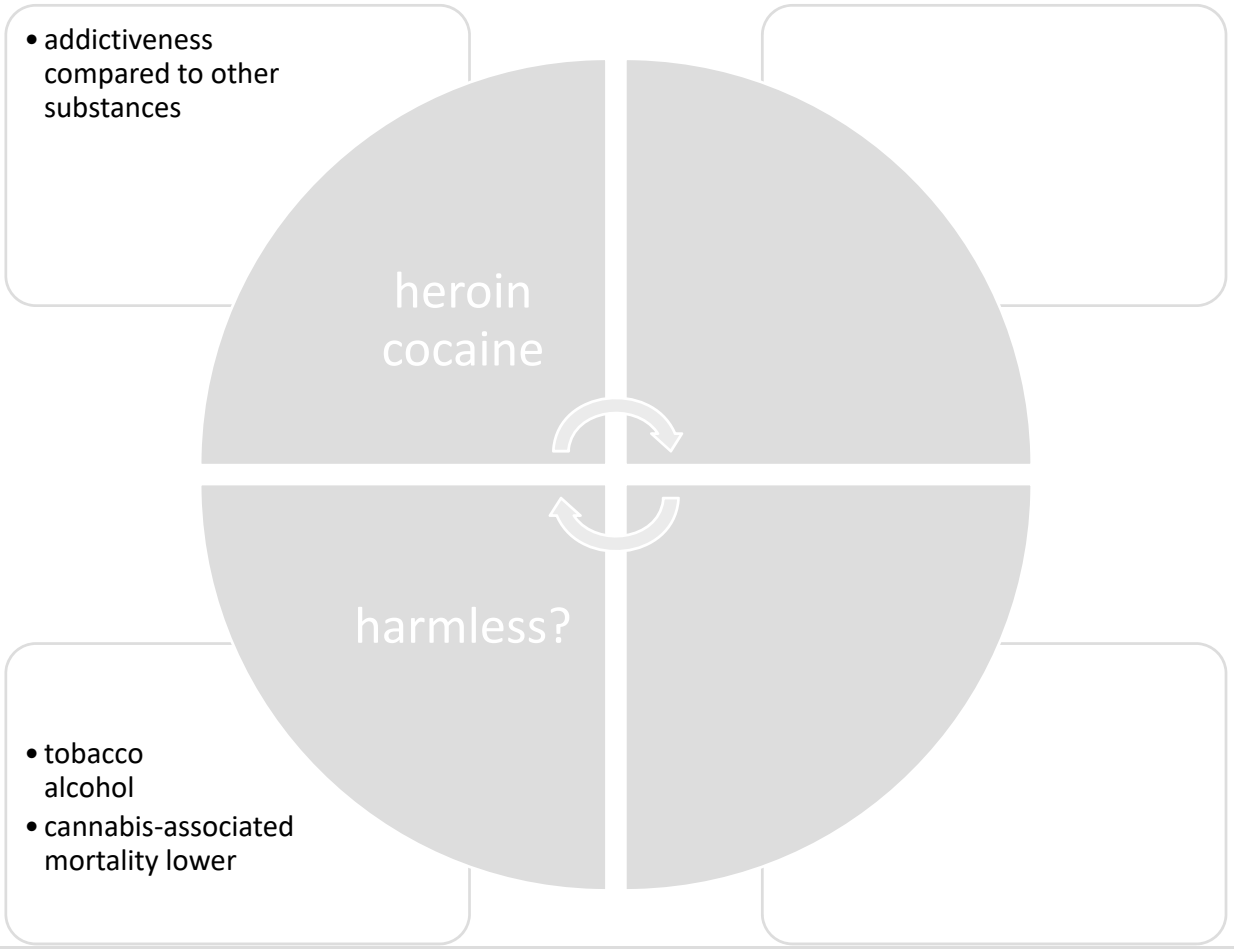
[e] CRCHUM, Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

The marijuana perception:

the reality: cannabis-dependent individuals outnumber those reporting dependence on other illicit drugs

SAMHSA, 2011



Long lasting consequences of cannabis exposure in adolescence

T. Rubino, D. Parolaro *

DBSF and Neuroscience Center, University of Insubria, via A. da Giussano 10, Busto Arsizio (VA), Italy

Received 10 January 2008; received in revised form 4 February 2008; accepted 4 February 2008

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Long lasting consequences of cannabis exposure in adolescence

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Received 10 January 2008; received in revised form 4 February 2008; accepted 4 February 2008

Abstract

Despite the increasing use of cannabis among adolescents, there are little and often contradictory studies on the long-term neurobiological consequences of cannabis consumption in juveniles. Adolescence is a critical phase for cerebral development, where the endocannabinoid system plays an important role influencing the release and action of different neurotransmitters. Therefore, a strong stimulation by the psychoactive component of marijuana, delta-9-tetrahydrocannabinol (THC), might lead to subtle but lasting neurobiological changes that can affect adult brain functions and behaviour.

The literature here summarized by use of experimental animal models, puts forward that heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse in selected individuals, and may represent a risk factor for developing schizophrenia in adulthood.

Therefore, the potential problems arising in relation to marijuana consumption in adolescence suggest that this developmental phase is a vulnerable period for persistent adverse effects of cannabinoids.

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Keywords: Cannabinoids; Adolescence; Emotional profile; Cognition; Psychosis; Gateway hypothesis

1. Introduction

Cannabis is the most commonly used illicit substance among adolescents and young adults. In 2004, 46% of 12th graders in the USA reported having tried cannabis at some point in their lifetime, 34% reported having used within the past month, and 5.6% reported having smoked cannabis daily (Johnston et al., 2004). Initiation into cannabis use typically begins in adolescence, as youths aged 12–17 constitute about two thirds of the new cannabis users (SAMHSA, 2004). Approximately 14% of adolescent-onset cannabis users develops cannabis dependence, a rate roughly twice that reported for adult-onset users (Chen et al., 1997; Chen and Anthony, 2003). Cannabis dependence is defined in the Diagnostic and Statistical Manual of Mental Disorder (4th edition, text revision, DSM-IVTR) as having at least three out of seven symptoms within one year. Moreover, very recently, record numbers of teenagers were requiring drug treatment as a result of smoking skunk, the highly potent cannabis strain containing 25 times more delta-9-tetrahydrocannabinol (THC, the psychoactive ingredient) than the resin sold a decade ago.

Despite the constantly spreading use of cannabis among adolescents, there is little information about its neurobiological long-term consequences. The adolescent brain is particularly sensitive to internal and external variables such as drug exposure, environment and gonadal hormones, since in this period several active neural changes take place (Spear, 2000). In fact, adolescence is characterized by strong neuronal plasticity, with sprouting and pruning of synapses, myelinization of nerve fibers, changes in neurotransmitter concentrations and their receptor levels in brain areas essential for behavioural and cognitive functions (Rice and Barone, 2000). The receptor for cannabinoids (CB1) belongs to the Gi/Go-protein coupled receptor family, and, in mammalian brain, is densely diffused in regions involved in the processing of emotional inputs, rewarding stimuli, habit formation, and higher cognitive functions (Herkenham et al., 1990). Endogenous cannabinoids modulate neurotransmitter release in many brain regions via CB1 receptors (Morisset and Urban, 2001; Wilson and Nicoll, 2001, 2002; Wilson et al., 2001). Accumulating evidence indicates that their peculiar mechanism of action as retrograde messengers is able to strongly influence both short-term and long-term forms of

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doi:10.1016/j.mce.2008.02.003

2002). Moreover, there is evidence for a role of the endocannabinoid system in neural development. Both cannabinoid receptors and endocannabinoid ligands can be detected in the brain during early developmental periods (Romero et al., 1997; Berrendero et al., 1999). The atypical distribution of cannabinoid CB1 receptors during the perinatal period seems to be related to a specific involvement of the endocannabinoid system in brain development. The system constituted by CB1 receptors and their putative endogenous ligands might influence the gene expression of several key genes for neural development as part of the specific function of the endocannabinoid system during this period (Fernandez-Ruiz et al., 2004). Moreover, in animal models, cannabinoid receptors have been shown to mature slowly, with maximal levels during adolescence which later drop to adult levels (Rodriguez de Fonseca et al., 1993; McLaughlin et al., 1994; Belue et al., 1995). Like dopamine receptors (Seeman, 1999), cannabinoid receptors may undergo postadolescent pruning. It is, therefore, conceivable that intake of exogenous cannabinoids, especially in vulnerable developmental periods, such as the adolescence, might induce residual effects.

Rubino, T and Parolaro, D (2008) Molecular and Cellular Endocrinology 286S S108–S113

Schizophrenia is a devastating illness.

1% of world population

emerges: late adolescence or early adulthood

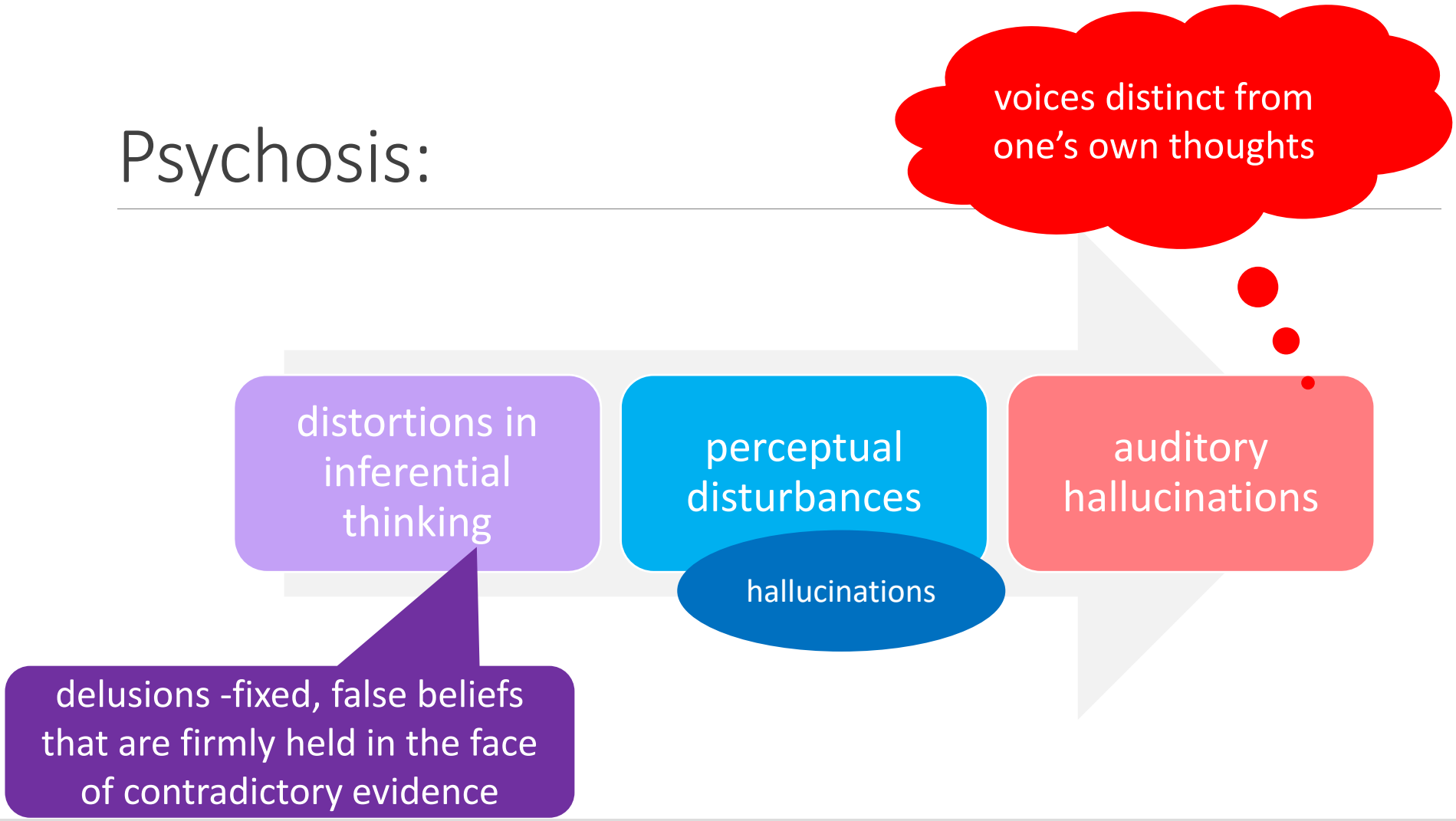
10% eventually commit suicide

most experience a lifetime of disability

high emotional family burden

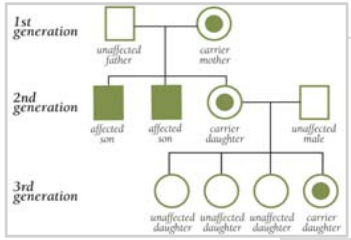
Lewis, DA, Hashimoto, T and Volk, DW (2005) Nature Reviews Neuroscience 6:312-324.

Psychosis:

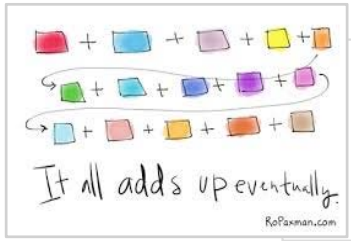


Lewis, DA, Hashimoto, T and Volk, DW (2005) Nature Reviews Neuroscience 6:312-324.

Risk of developing schizophrenia



risk is directly proportional to being genetically related to someone affected by schizophrenia



degree of risk conferred for each susceptibility gene is small

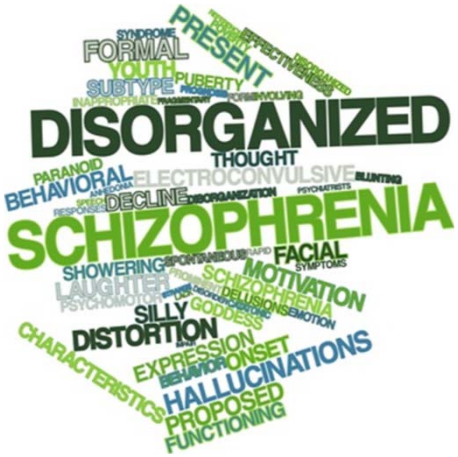
twin studies:
only 50% is accounted for by genes – the rest is environmental risk

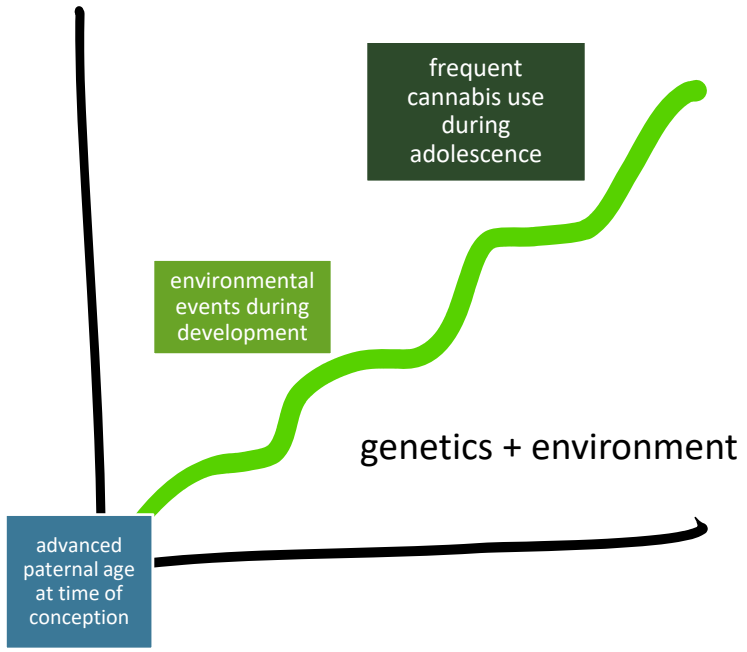
environmental events increase risk

environmental events during development

advanced paternal age at time of conception

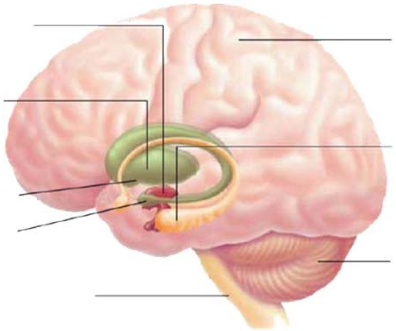
frequent cannabis use during adolescence





Schizophrenia is more than psychosis.

disturbances in brain function

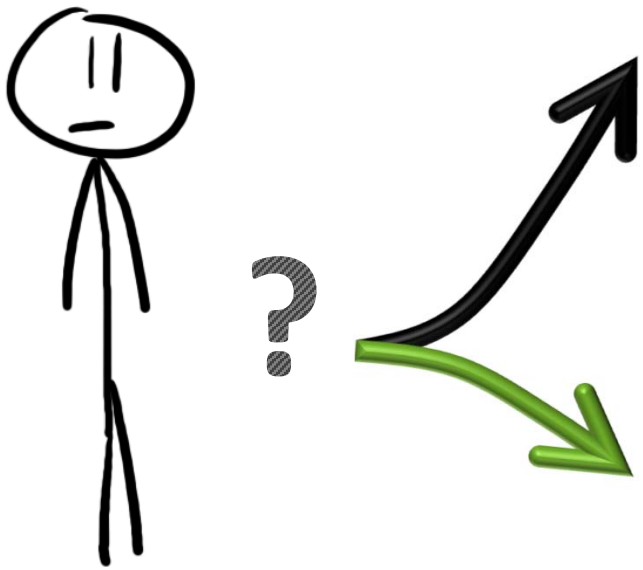


- perception
- inferential thinking
- language (fluency & production)
- expression of emotion
- capacity for pleasure
- volition
- attention

impairments

- social
- occupational

Does cannabis use increase the risk of schizophrenia?



Worldwide evidence documents that cannabis use is a modest statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms such as hallucinations and delusions to clinically significant disorders such as schizophrenia. Prospective studies estimate that cannabis use is associated with a two-fold increase in later schizophrenia outcomes, and early, adolescent-onset cannabis use is associated with a higher risk (Arseneault et al., 2004), possibly because individuals who begin to use cannabis when the brain is still developing are most vulnerable to its deleterious effects (Ehrenreich et al., 1999; Pistis et al., 2004; Pope et al., 2003; Schneider and Koch, 2003). Nonetheless, the vast majority of young people who use cannabis do not develop psychosis, suggesting the hypothesis that, if cannabis is indeed causal, some individuals may be genetically vulnerable to its effects.

Rubino, T and Parolaro, D (2008) Molecular and Cellular Endocrinology 286S S108–S113

CORTICAL INHIBITORY NEURONS AND SCHIZOPHRENIA

David A. Lewis‡, Takanori Hashimoto* and David W. Volk**

Abstract | Impairments in certain cognitive functions, such as working memory, are core features of schizophrenia. Convergent findings indicate that a deficiency in signalling through the TrkB neurotrophin receptor leads to reduced GABA (γ-aminobutyric acid) synthesis in the parvalbumin-containing subpopulation of inhibitory GABA neurons in the dorsolateral prefrontal cortex of individuals with schizophrenia. Despite both pre- and postsynaptic compensatory responses, the resulting alteration in perisomatic inhibition of pyramidal neurons contributes to a diminished capacity for the gamma-frequency synchronized neuronal activity that is required for working memory function. These findings reveal specific targets for therapeutic interventions to improve cognitive function in individuals with schizophrenia.

Lewis, DA, Hashimoto, T and Volk, DW (2005) Nature Reviews Neuroscience 6:312-324.

Research article

Open Access

Dysfunctional GABAergic inhibition in the prefrontal cortex leading to "psychotic" hyperactivation

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Abstract

Background: The GABAergic system in the brain seems to be dysfunctional in various psychiatric disorders. Many studies have suggested so far that, in schizophrenia patients, GABAergic inhibition is selectively but consistently reduced in the prefrontal cortex (PFC).

Results: This study used a computational model of the PFC to investigate the dynamics of the PFC circuit with and without chandelier cells and other GABAergic interneurons. The inhibition by GABAergic interneurons other than chandelier cells effectively regulated the PFC activity with rather low or modest levels of dopaminergic neurotransmission. This activity of the PFC is associated with normal cognitive functions and has an inverted-U shaped profile of dopaminergic modulation. In contrast, the chandelier cell-type inhibition affected only the PFC circuit dynamics in hyperdopaminergic conditions. Reduction of chandelier cell-type inhibition resulted in bistable dynamics of the PFC circuit, in which the upper stable state is associated with a hyperactive mode. When both types of inhibition were reduced, this hyperactive mode and the conventional inverted-U mode merged.

Conclusion: The results of our simulation suggest that, in schizophrenia, a reduction of GABAergic inhibition increases vulnerability to psychosis by (i) producing the hyperactive mode of the PFC with hyperdopaminergic neurotransmission by dysfunctional chandelier cells and (ii) increasing the probability of the transition to the hyperactive mode from the conventional inverted-U mode by dysfunctional GABAergic interneurons.

Tanaka, S. (2008) BMC Neuroscience 9:41

J Physiol 562.1 (2005) pp 9–26

SYMPOSIUM REPORT

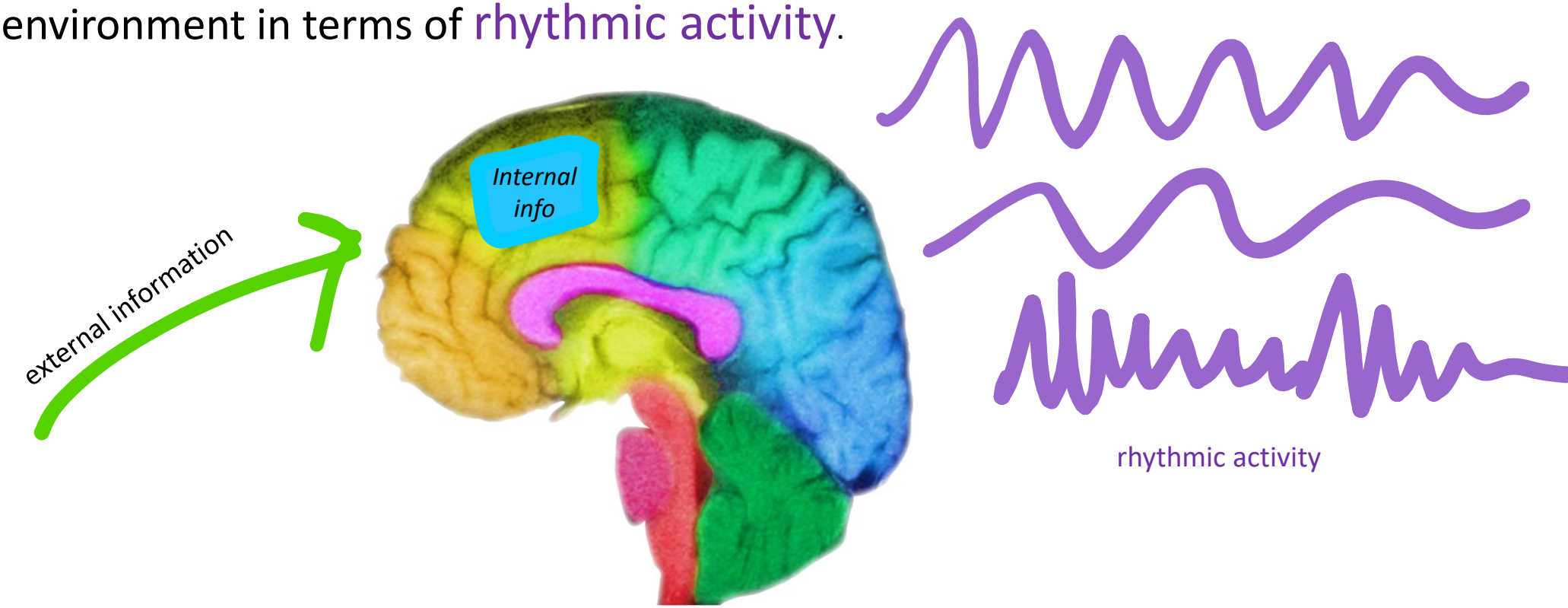
Defined types of cortical interneurone structure space and spike timing in the hippocampus

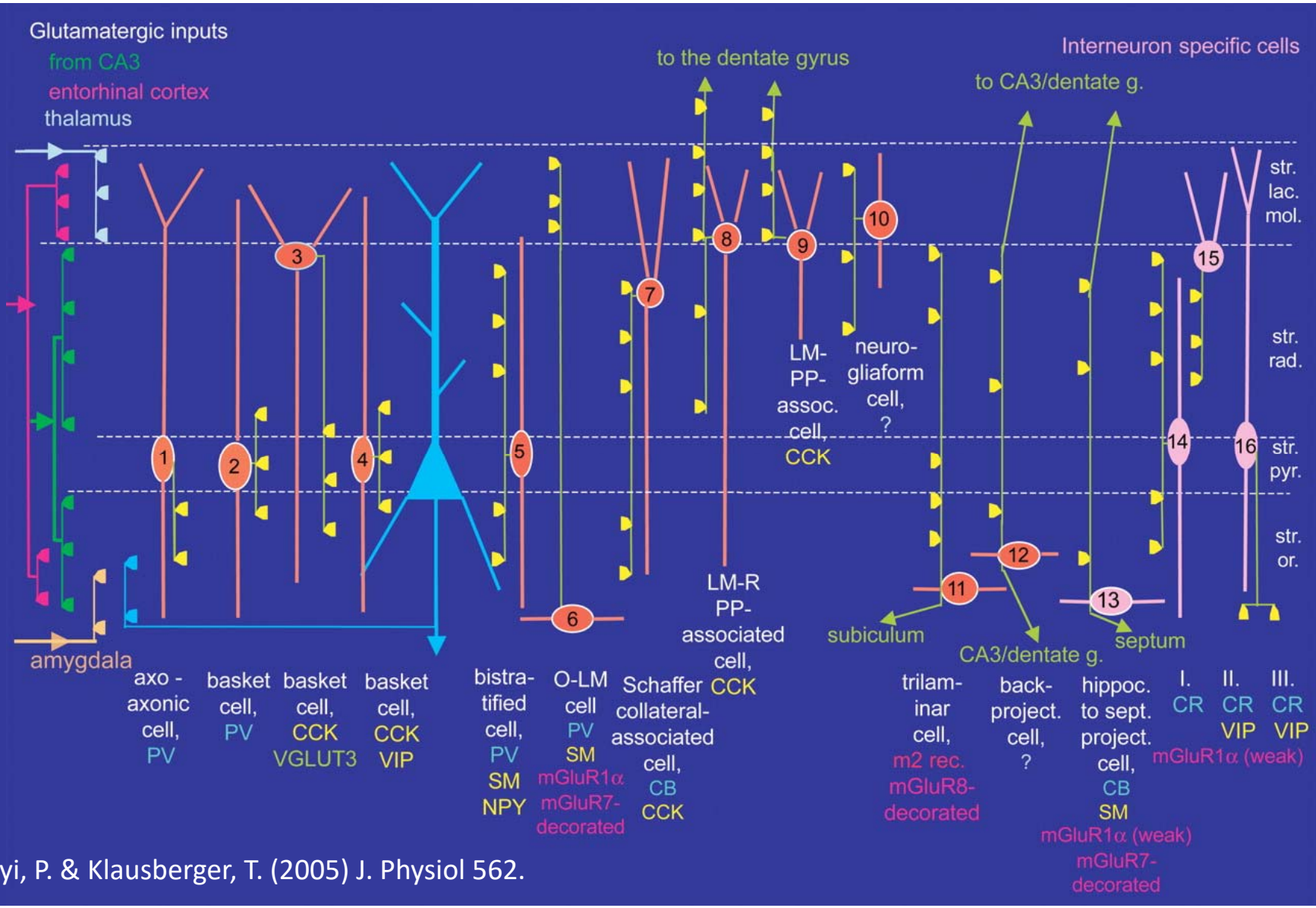
Peter Somogyi[1] and Thomas Klausberger[1,2]

[1]*MRC Anatomical Neuropharmacology Unit, Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3TH, UK*
[2]*Section of Biochemistry and Molecular Biology, Brain Research Institute, Medical University of Vienna, Austria*

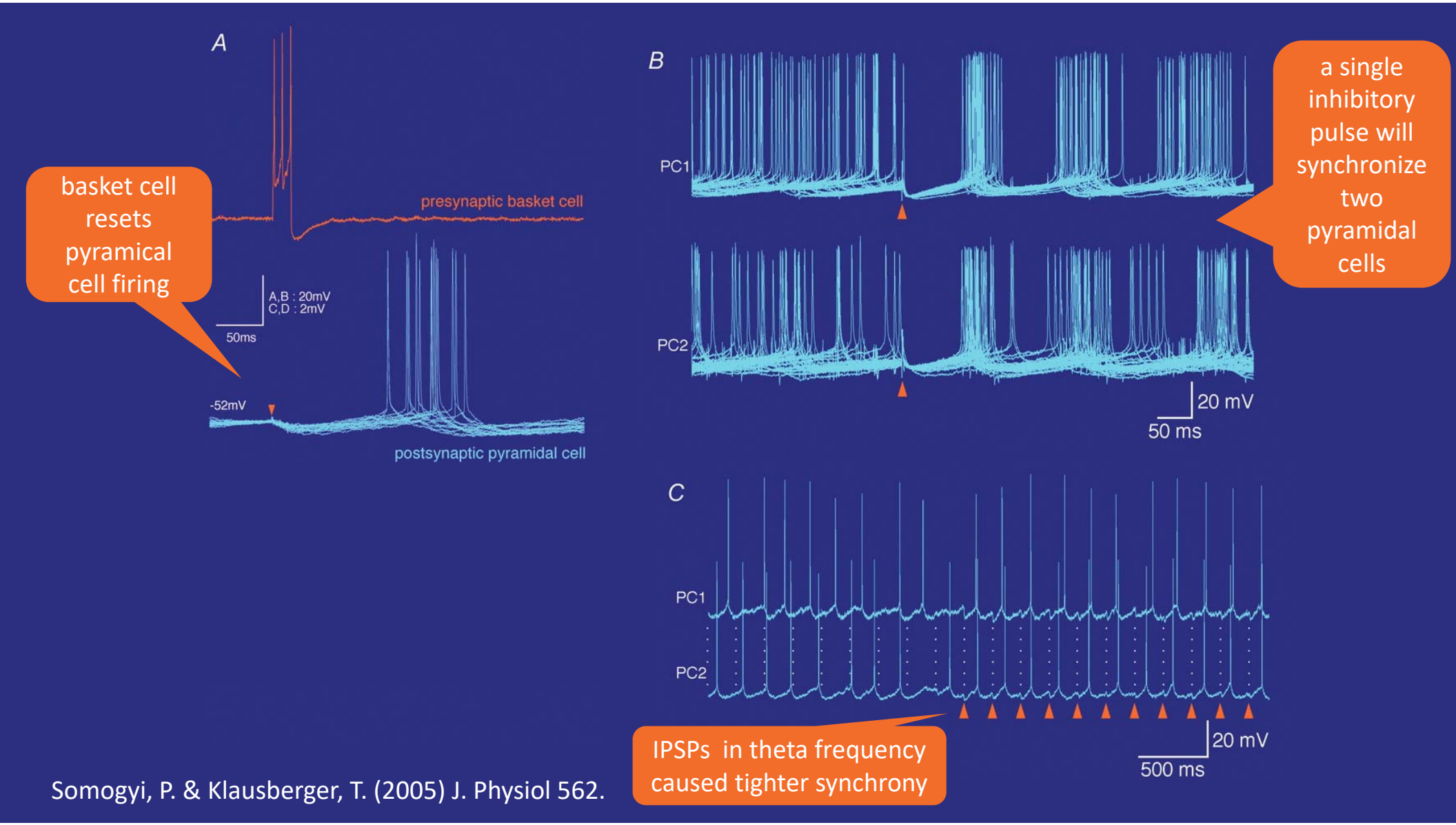
Somogyi, P. & Klausberger, T. (2005) J. Physiol 562.

The cortex encodes, stores & combines information about the ***external*** and ***internal*** environment in terms of rhythmic activity.





Somogyi, P. & Klausberger, T. (2005) J. Physiol 562.



Somogyi, P. & Klausberger, T. (2005) J. Physiol 562.

so – does cannabis use during adolescence increase the risk of Sx?

A recent study found that cannabis use was significantly associated with a decrease in age of onset of schizophrenia (Sugranyes *et al.*, 2009). This is concerning as the early onset of schizophrenia has been proven to be a negative outcome factor (Malla and Payne, 2005; Rabinowitz *et al.*, 2006). A study in Spain found that patients presenting with first episode psychosis (average age 15.5 years) had a higher rate of positive symptoms and less negative symptoms if they were cannabis users compared with non-cannabis users (Baeza *et al.*, 2009). In addition, the increases in cannabis use in the UK population over the last 30 years as reported by Hickman *et al.* (2007) were concluded by the authors to be mainly due to more prolonged use initiated at younger ages (Hickman *et al.*, 2007). Thus, despite some variables factors such as the measurement of psychotic symptoms and control for confounding factors, it appears that there is a causal link between adolescent cannabis use and the development of psychoses such as schizophrenia. With a greater amount of adolescents consuming cannabis, it has become imperative to critically evaluate whether this age group is particularly vulnerable to developing psychoses such as schizophrenia compared with adolescents that do not consume cannabis, and to elucidate mechanisms responsible for this vulnerability.

Malone, D. T., et al (2010) British Journal of Pharmacology, 160, 511–522

Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models

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Malone, D. T., et al (2010) British Journal of Pharmacology, 160, 511–522

Impact of Cannabis Use on Brain Function in Adolescents

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Research report

Altered prefrontal and insular cortical thickness in adolescent marijuana users

Melissa P. Lopez-Larson[a,b,c,*], Piotr Bogorodzki[d], Jadwiga Rogowska[e],
Erin McGlade[a,c], Jace B. King[a], Janine Terry[a], Deborah Yurgelun-Todd[a,b,c]

Genetic mediation of the link between schizophrenia and cannabis use

Wim Veling

Neurophysiological and cognitive effects of smoked marijuana in frequent users

Carl L. Hart [a,b,*], Aaron B. Ilan [c], Alan Gevins [c], Erik W. Gunderson [a], Kemi Role [c], Jana Co
Richard W. Foltin [a]

[a] *Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Co*
[b] *Department of Psychology, Columbia University, USA*
[c] *The San Francisco Brain Research Institute and SAM Technology, USA*

Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Populations in Adult Rats

Maria Ellgren[1], Sabrina M Spano[1] and Yasmin L Hurd*[,1]
[1]Department of Clinical Neuroscience, Karolinska Institutet, Psychiatry Section, Stockholm, Sweden

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis

Neuropsychopharmacology (2013) 38, 2338–2347

www.neuropsychopharmacology.org

Adolescent Cannabinoid Exposure Permanently Suppresses Cortical Oscillations in Adult Mice

Sylvina M Raver[1,2], Sarah P Haughwout[2] and Asaf Keller*[,1,2]

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Regular marijuana use during adolescence, but not adulthood, may permanently impair cognition and increase the risk for psychiatric diseases, such as schizophrenia. Cortical oscillations are integral for cognitive processes and are abnormal in patients with schizophrenia. We test the hypothesis that adolescence is a sensitive period because of the active development of cortical oscillations and neuromodulatory systems that underlie them. The endocannabinoid system upon which marijuana acts is one such system. Here we test the prediction that adolescent cannabinoid exposure alters cortical oscillations in adults. Using *in vitro* local field potential, *in vivo* electrocorticogram recordings and cognitive behavioral testing in adult mice, we demonstrate that chronic adolescent, but not adult, cannabinoid exposure suppresses pharmacologically evoked cortical oscillations and impairs working memory performance in adults. The later-maturing prefrontal cortex is more sensitive to adolescent exposure than the earlier-maturing, primary somatosensory cortex. These data establish a link between chronic adolescent cannabinoid exposure and alterations in adult cortical network activity that underlie cognitive processes.

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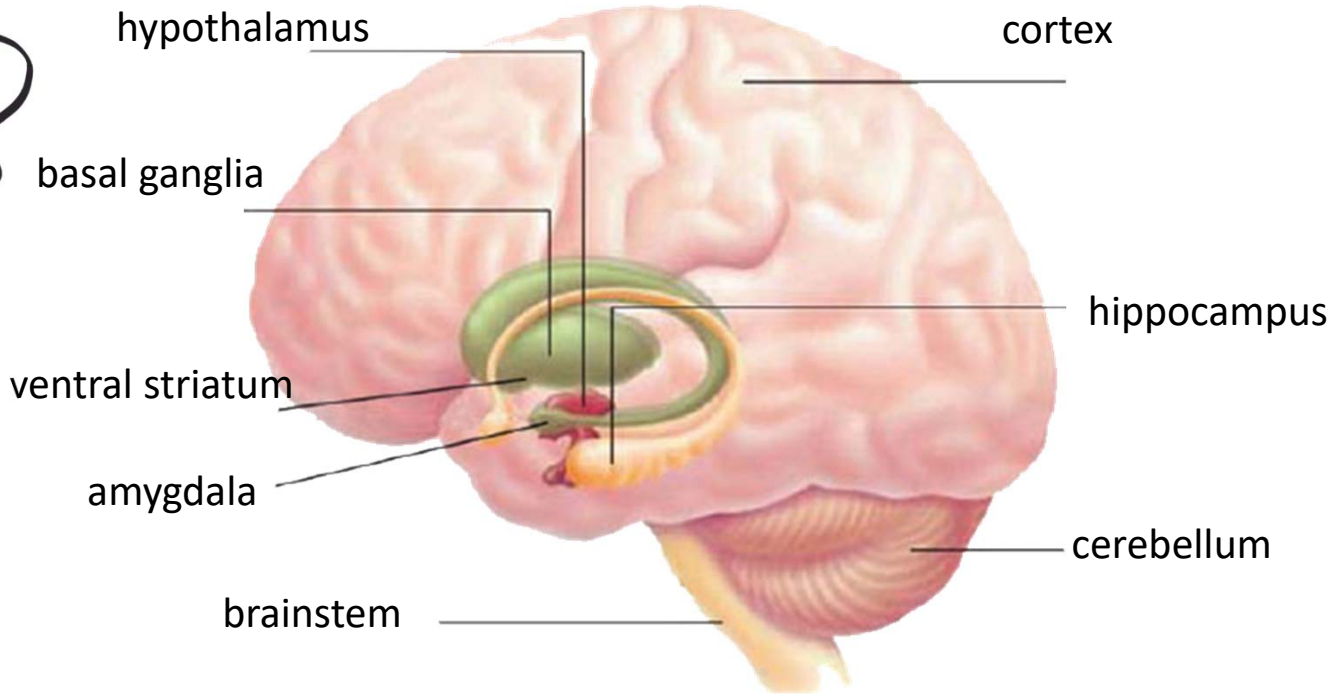
Keywords: marijuana; development; schizophrenia; Δ-^{9} tetrahydrocannabinol; novel object recognition; neural synchrony

INTRODUCTION

et al. 2004). The cortical endocannabinoid (eCB) system, in

what now?


hypothalamus
cortex
basal ganglia
hippocampus
ventral striatum
amygdala
cerebellum
brainstem