HOW TO USE THIS E-COURSE

1. **(References)** in **BOLD** are clickable and will pop up the PDF file for the paper referenced in the text.
   We encourage you to pop up and read the referenced papers.
   This e-book is not a typical text book. Rather, it is a growing organism which will update as new research emerges. New references will be added frequently and the text will be revised. The core content are the papers we have selected to highlight our main themes.

2. **SIDE BARS_**
   Click on the **SIDE BARS_** and you will be taken to additional information and enhanced content dealing with the issue discussed. This content may be pdf files of research papers, power point presentations, links to video lectures by the author, and more. You will also find an email address with an invitation to join dropbox folders which contain pdf files of the research papers cited in the **Side Bars_.**
   Again, we encourage you to work your way through the **SIDE BARS_**. This effort will be rewarded by a deepened understanding and an increasing awareness on the controversies in the field.

3. **Overview of the content of the e-course**
   Note:
   The e-course is a big file. It may take a few minutes to load depending on your connection speed.
   The initial sections are meant to clear away some conceptual brush and confusion that bedevils psychiatry. This lack of clarity has consequences for our understanding and ultimately our practice of psychiatry.
   Psychiatry is one of the practical applications of neuroscience (other applications are neuro-economics, neuro-ethics, neuro-philosophy among others). Psychiatry is the science of mapping experiences (perceptual, emotional, intentional-both conscious and unconscious), behaviors (intentional or reflexive/automatic) and beliefs (both conscious and unconscious) onto brain circuits. Until recently such mapping was of somewhat limited value as the relationships of brain states (lesions, regional metabolic activity, anatomical changes) were correlational, being subject to the criticism that "correlation is not causation." Optogenetic studies now allow the in vivo mapping of brain circuits (at the level of individual neurons) in the freely moving conscious animal onto mental states such as fear, depression (or its behavioral manifestations in animals) and show how learning and motivational states are implemented in the brain. These studies establish the causal links that have been subject to doubt before.
   Psychiatry is pervaded by mind/body dualism, a view best captured by the "biopsychosocial" approach to psychiatric illness. This view has adverse consequences such as the stigmatization of "mental" illness and the discrimination by insurance companies and society at large.
   The initial sections of the e-book place place psychiatry into the field of physical science. ***Everything that we experience is implemented in the brain without any residual***.
   Consciousness is a natural phenomenon amenable to scientific study (and explanation).
   Evolution is the engine that has brought us here.

A satisfying description of “mental” states (better “brain states”) requires a vertical integration from the level of the gene (and its epigenetic modifications through experiences) to proteins, neurons and circuits.
In later chapters we will describe psychiatric conditions with such a framework in mind.

Important online resources:

National Neuroscience Curriculum Initiative
http://www.nncionline.org

3D Brain
http://www.nncionline.org/?course=basic-neuroscience-3-d-brain

Please visit our web site
www.behavioralhealth2000.com.

This web site has a number of features, the most important perhaps is an e-course which is entitled The New Psychiatry.
Now, this e-course is not a regular text book, rather it is a constantly updated learning tool, kept refreshed and current with the newest findings in neurobiology and psychiatry.
The e-course should be studied carefully and slowly, because we have added a great number of links which will direct you to the primary research articles which form the foundation of the science we are discussing.
In addition we have other resources such as a growing series of video lectures. We have lectures of mindfulness and its effects on the brain, we will have lectures on mind-body dualism. This is the idea that mind and body belong to two different worlds, the body to the world of physics and chemistry and the mind to a world not composed of atoms and molecules (the spiritual world).

This mind-body dualism is deep in the bone marrow of psychiatry and ,in our view, is harmful to this area of medicine.
We will discuss ways to analyze and overcome this separation of mind and body.
This separation of mind and body may be one reason why many psychiatrist don't like to deal with medical problems, even those medical problems that they cause or at least contribute to by prescribing certain psychiatric medications which can have severe side effects and may in fact contribute to premature death from conditions such as obesity, diabetes, hypertension and increased "bad lipids" in the blood stream. This collection of problems have been called the "metabolic syndrome."
There will be a lecture on the metabolic syndrome soon.
The metabolic syndrome is well known in internal medicine. Psychiatrists, however, pay little attention and seem quite oblivious to their contribution to this syndrome. Psychiatric patient are particularly susceptible to developing

this condition which is part of those forces which shorten their life span by 10 to 20 years.
Other lectures will expand on the theme of metabolic syndrome and examine its effects on brain function. There are exciting recent findings, which show that Insulin-resistance does only occur in the body but also in the brain, directly impacting the hippocampus, an area critical for memory encoding and retrieval.
Other lectures will deal with the foundations of psychopharmacology.

The current training of young psychiatrists is build on shaky foundations. For example, little attention is paid to the questions of how the brain produces the phenomenon of consciousness. All psychiatric disorders are really disturbances of consciousness, or experiences of mood, false (delusional) beliefs about the world and oneself, abnormal perceptions as hallucinations and many others come to the mind. So we will spend some time to look at research findings that undermine the idea that consciousness belongs in a category different from those categories that contain items like “body”, “chemistry”, “atoms”.

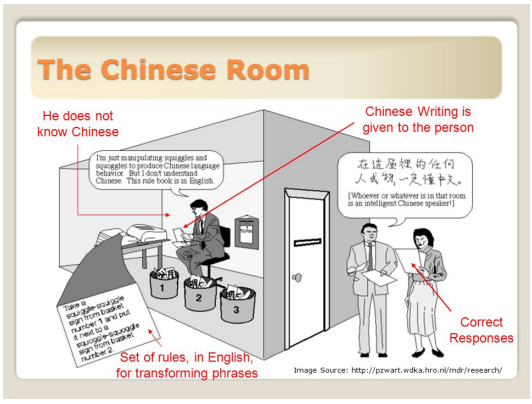
Many people don’t like the idea that consciousness is a natural phenomenon produced in brains and understandable by science. Because this idea would argue against some long held ideas in psychiatry.
One of those ideas is the bio-psycho-social model. “Biopsychosocial” is really a very poor compound- term which points to a certain “laziness of thinking.” Anything that we experience is happening in the brain, and psychiatry needs to understand and show how brain circuitry makes this happen.
We will also move away occasionally from purely psychiatric considerations and explore social sciences that are often highly relevant to psychiatry such as urbanization (and city planning).Did you know that if you take a walk in a green pasture and have you brain activity evaluated after your walk, that a critical area of your brain that has been implicated in depression, is calmed down and is functioning in a way that is correlated with a less fearful and more relaxed state of mind?
So, the environment talks to the brain. In fact, anything that we experience talks to the brain. For example, psychotherapy does not happen in a vacuum. Rather, psychotherapy has been shown to change brain circuitry

To summarize this line of thought-you may have already detected our viewpoint as quite materialistic. We do not believe in any other universe outside the one that is studied by the physical sciences. The mind and consciousness live in the same home it shares with electromagnetism, gravity, atoms, molecules, plants and animals.

Please click the images below to review videos by Dr. Stephen Greenblatt (on the poem by Lucretius. This poem, written about 50 B.C., describes a materialistic description of the universe, and discounts an idea of a non-materialistic theory of the mind) and by Dr. Sean Carrol on the standard model of physics.

Psychiatrists needs to be educated in the sciences and understand genes, evolution, proteins, brain circuits but also social psychology
Neuroscience is in an explosive growth period with a knowledge base doubling every few years. Psychiatric residents face a difficult task in confronting what is known already and what will be known when they finish their training.
Without a solid understanding of the brain functions supporting a healthy
"mind" and the abnormal brain activity in psychiatric disorders.
For psychiatrists trained in our current paradigm will produce produce psychiatrists who are like the man in the "Chinese room."

This is a person who does not read Mandarin. He is being fed a string of Chinese characters through a slot in the room and uses an elaborate rule book to compose an answer, also in Chinese characters, which he drops into the output slot. He has not understood anything, but the recipient of his answer may be fooled, because the rule book and quite comprehensive and produces coherent answers. A psychiatrist functioning in this way will burn out quickly and never wake up to drama of mind/brains trying to find a way in this world.



The brain is wider than the sky

Emily Dickinson (1830-86)

The brain is wider than the sky,
For, put them side by side,
The one the other will include
With ease, and you beside.

The brain is deeper than the sea,
For, hold them, blue to blue,
The one the other will absorb,
As sponges, buckets do.

The brain is just the weight of God,
For, lift them, pound for pound,
And they will differ, if they do,
As syllable from sound.

John Milton (1608-1674)

"The mind is its own place, and in it self/ Can make a Heav'n of Hell, a Hell of Heav'n."
– John Milton, Paradise Lost

Frontiers in Neuroanatomy May 2011 | Volume 5 | Article 29 | 1

The mind–body problem.

Left: Fray Pedro de San Dionisio, painted by Francisco de Zurbarán (1598–1664). © Fundació Institut d'Art Hispanic Amatller. Arxiu Mas. Right: Don Quixote, Museum of Arte Moderno in Mexico. These images are examples of the separation between the mental and the physical worlds. The saint levitates while praying, and his head is separated from his body; Don Quixote appears reflective, with an empty head.

THE BRAIN is wider than the sky

The purpose of this course is to clarify and demystify a set of ideas and assumptions, which pervade the field of psychiatry and cause confusion and unfortunate consequences for the practice and teaching of psychiatry. These crystalize in the so-called mind/body problem or mind/body dualism.

Mind/Body dualism has adverse consequences for psychiatry, such as stigmatization of mental illness, restricted funding for research and patient care, discrimination against patients with psychiatric or addictive disease in the insurance market place and leads to cognitive distortions affecting the training and practice of psychiatry. This paper attempts to deconstruct a set of ideas, which tend to under girth our intuitive mind/body dualism and proposes that neuroscience is increasingly capable of describing human cognition, emotion and psychopathology as the manifestations of brain activity.

Psychiatry operates in a border region of the neurobiology of the brain and mind. Mind is the overarching concept incorporating notions of consciousness, phenomenological experience, free will and the idea of the soul. Psychiatric practice involves modifying brain functions by the use of medications and other means, as well as interventions broadly described as psychotherapy. Psychiatry as a medical discipline has an ambivalent and uneasy relationship with the idea of mind/brain. In this paper, we attempt to trace this tension to the pervasive, intuitive mind/body dualism that lay people as well as scientists tend to adopt. A rapidly growing empirical literature is eroding the idea of mind/ brain dualism. We will review claims that consciousness, first person phenomenological experience or "qualia," and free will are ontologically beyond the grasp of empirical study. A growing number of neuroscientific research results are placing increasing constraints on these claims. We suggest an alternative view based on the philosophy of pragmatism, which we believe would recommend a critical reappraisal of our intuitive beliefs, by means of an empirically responsible stance.

The literature on these topics is extensive. We restrict our review to very recent results from neurobiology.

Introduction

The mind is disembodied. It consists of mental substance, while the body consists of

> *"It ought to be generally known that the source of our pleasure, merriment, laughter, and amusement, as of our grief, pain, anxiety, and tears, is none other than the brain. It is specially the organ which enables us to think, see, and hear, and to distinguish the ugly and the beautiful, the bad and the good, pleasant and unpleasant. Sometimes we judge according to the perceptions of expediency. It is the brain too which is the seat of madness and delirium, of the fears and frights which assail us, often by night, but sometimes even by day; it is there where lies the cause of insomnia and sleep-walking, of thoughts that will not come, forgotten duties, and eccentricities. All such things result from an unhealthy condition of the brain."*
>
> Hippocrates

physical substance (Descartes, 1970).

There is nothing inherently dehumanizing or "stigmatizing" about a psychiatric diagnosis. Ironically, such inflammatory charges only worsen society's animus and prejudice toward those with mental illness, by implying that having a psychiatric disorder is grounds for shame. Diagnoses in other medical specialties rarely provoke such a reaction…I believe that psychiatric diagnoses are castigated largely because society fears, misunderstands and often reviles mental illness (Pies, 2013).

*Inevitably there term 'mental" carries with it connotations of etiology—mental and not physical, mind and not brain, functional and not organic. The problem with this approach, which remains embedded in our vocabulary and way of thinking, is that it assumes a discontinuity in the human mind/brain system that does not exist in nature. The influence of this dualistic view of psychiatry derived from a 'perfect storm' of Cartesianism,nineteenth century neuropathology and computer functionalism (hardware vs software), are legion (**Kendler, 2012**).*

There has been systematic discrimination against patients with mental illness for many decades by the general public (Stuart et al, 2012) and by insurance companies. The coverage for psychiatric disorders was "carved out" from the coverage for other illnesses and payments for psychiatric services were declined or denied. The Mental Health Parity

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Act of 1996 (expired September 2001) had only limited effect and its provisions were easily circumvented (Frank et al, 2001). The Surgeon General declared that "equality between mental health coverage is an affordable and effective objective" in 1999 (Mental Health: a report of the Surgeon General. Rockville, MD: DHHS, 1999).The report finds that mental disorders can be reliably diagnosed, impose an enormous burden, and can be effectively treated. The Mental Health Equitable Treatment Act of 2001 has not delivered a fundamental change in the treatment of patients with mental illness. State parity statutes vary and continue to restrict access to care (Frank et al, 2001).

The persistent stigma of mental illness (Pescosolido et al, 2000) is an important factor driving such discriminatory policies. Public acceptance of a neurobiological concept of mental illness has increased in recent years, however, stigma among the American public appears to be surprisingly fixed (**Pescosolido et al, 2010**). A review of 33 studies showed that "biogenetic" causal attributions of mental illness do not result in increased tolerance but were in fact related to stronger rejection in most studies examining schizophrenia (**Angermeyer et al, 2011**). The increasing scope of neuroscience's presence in public consciousness has fostered three frequently encountered claims about neuroscience's societal influence: that neuroscience fosters a conception of the self that is based in biology, that neuroscience promotes conceptions of individual fate as predetermined, and that neuroscience attenuates the stigma attached to particular social categories. Participants in focus groups report an interest in neurobiological explanations but discount their relevance for self perception (Pickersgill et al, 2011).An empirical review concludes that many neuroscientific ideas have assimilated in ways that perpetuate rather than challenge existing modes of understanding self, others and society (**O'Connor and Joffe, 2013)**. It has been suggested that presenting physicians with knowledge of the physiological components of mental illness might be an effective strategy in combating stigma among this professional group (**Ungar and Knaak, 2013**), however, a recent study of American clinicians reading descriptions of patients whose symptoms were either attributed to biological or psychosocial problems yielded a surprising and counterintuitive result. Biological explanations decreased clinician's empathy towards their patients (**Lebowitz and Ahn, 2014**). This result is troubling as empathy is an important aspect of psychotherapy (Elliot et al, 2011). Biological *e*xplanations of mental illness appear to activate the tendency of psychological essentialism attributing unique and immutable "essences" to patient's DNA or brain, which make them categorically different from "normal people". Psychological Essentialism has pervasive effects on how people categorize members of groups (Gelman, 2009) and may be considered a functional human universal (**Dar-Nimrod and Heine, 2011**). Patients may be perceived as acting from deterministic mechanism rather than their own "agency" resulting in a dehumanizing attitude toward them (Haslam, 2006).

Psychiatry has failed to effectively address the stigmatization of mental illness (Stewart et al, 2012).This failure may be traced to lack of clarity about the fundamental issue facing the field, the mind/body dualism pervasive in our culture. Dualism has

consequences for defining what psychiatry is and what it aspires to become. Psychiatry is in an increasingly severe crisis as a result. It is a discipline built on a fault line straddling the tectonic plate of neuroscience, which includes neuro-psychopharmacology and other biological treatments on the one hand, and the tectonic plate of the "psychosocial "which includes a host of psychotherapies and social systems interventions.

The unfortunate divorce of psychiatry from neurology occurred many decades ago. Psychiatry left the home of the brain and got involved in a long-lasting affair with psychoanalysis and other disciplines that emphasized the notion that there was more to the human mind and its afflictions than a reductionist "bag of enzymes (Ghaemi, 2006)." With the ascent of biological psychiatry, the tension between psychological and medical approaches increased and the synthesis of the "biopsychosocial" model (**Engel, 1977**) became the official philosophy and "standard model "of the American Psychiatric Association and codified in its diagnostic manual, the Diagnostic and Statistical Manual of Mental Disorders (DSM), now in its 5th edition. Engel was a Consultation/Liaison psychiatrist with particular interest in ulcerative colitis, psychogenic pain and the psychological effects of gastrointestinal fistulae in children and tried to *understand the psychological aspects of medical illness (Ghaemi, 2003, pp. 6-7)*. He reacted to what he perceived as a deleterious biomedical reductionism in psychiatry. The biopsychosocial model has ben described as a "list of ingredients rather than a recipe…it is silent as to how to understand those (bio-psycho-social) under different conditions and circumstances …and becomes eclecticism where the clinician essentially does whatever he wants to do …the model has become transformed into an excuse for intellectual laziness "(Ghaemi, ibid. 8) and has been judged to be heuristically sterile
(McHugh and Slavney, 1998).

DSM-5 has little utility in guiding research and drug development. The NIMH has proposed an alternative approach to diagnostic classification (Research Domain Criteria (RDoC)) because the DSM-5 is not informed by recent breakthroughs in genetics; and cellular and systems neuroscience). Novel data about genomic factors and the role of particular brain circuits are reported almost monthly. However, new findings on mental disorders have had limited clinical impact, partly because they map only moderately onto current diagnostic categories for mental illness (**NIMH website, 2015, Insel, 2014**). The RDoC versus DSM debate has received a great deal of public attention (**Pickersgill, 2013**).
The DSM-5 was not influenced by more than 15,000 MRI studies listed in PubMed (**Gabrieli et al, 2015**) or by a large number of studies using electroencephalography (EEG), magnetoencephalography (MEG) or positron emission tomography (PET).

Despite the exponentially increasing literature supporting a "reductionist and materialistic" model of the mind /brain, most of us remain intuitive dualists. A study of 250 students at Edinburgh University and 1858 healthcare workers and members of the lay public studied at the University of Liege (Demertzi et al., 2009) found that the majority of participants regarded mind and brain as separate entities. A similar study of

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136 mental health faculty members at McGill University showed that mental health professionals continue to employ a mind/ brain dichotomy when reasoning about clinical cases, despite attempts to adopt an integrated biopsychosocial model in psychiatry (**Miresco and Kirmayer, 2006**).

A number of psychiatrists have attempted to lay a foundation for a non-dualist approach to psychiatry. **Kenneth Kendler (2005**), cutting through ambivalence, announced that "no philosophical concept has been as widely influential in our fields or as potentially pernicious in its effects as that of Cartesian dualism." He declared, "Cartesian dualism is false". He experienced difficulties, however, in sustaining a thorough monistic physicalist viewpoint by accepting the notion of "mind- to - brain causality." He "commits himself to the concept of mind- to- brain causality. In ways we can observe but not yet fully understand subjective, first-person mental phenomena have causal efficacy in the world. They affect our brains and our bodies and through them the outside world." However, he denies reintroducing dualism "through the back door" by invoking a philosophical position of "nonreductive materialism". We will attempt to show in subsequent sections of this paper that this position is not empirically supportable and incoherent.
Nancy Andreasen (1997) proposed that, "Mental illnesses have historically been distinguished from other medical illnesses because they affect the higher cognitive processes that are referred to as "mind." The relationship between mind and brain has been extensively discussed in contemporary philosophy and psychology, without any decisive resolution. One heuristic solution, therefore, is to adopt the position that the mind is the expression of the activity of the brain and that these two are separable for purposes of analysis and discussion but inseparable in actuality."
Eric Kandel (1998) discussed the expansion of psychoanalytically oriented psychiatry which eventually claimed medical illnesses such as hypertension, gastric ulcers, asthma and ulcerative colitis for its treatment domain under the banner of "psycho"-somatic theory and advocates for a thorough grounding of psychiatrists in genetics and neuroscience. However, he stays clear of the mind/brain dualism by suggesting that "the relationship between brain and mental processes is understood poorly and, and only in outline". Kandel's influential paper has been carefully analyzed with the summary judgement that parallel to the ambiguity Kandel's theoretical framework, there is a clear gap between psychiatry as a clinical discipline (with a strong emphasis on a broad, biopsychosocial conceptualization of mental illness) and contemporary psychiatric research where a neurobiological paradigm is explicitly or at least implicitly dominant. As a result, most research in psychiatry tries to ground clinical practice almost exclusively in neurobiology, although strikingly little of the massive amount of neuroscientific insight gained over the past 20 years have been able to truly change clinical psychiatric practice (**Oudenhove and Cuypers, 2010**).
Kandel's paper is a case study of the confusion in psychiatry about its self-understanding and ontological status.
We will try to show that a great deal of progress has been made since Kandel wrote these words in 1998.

Side Bar Mind Body Dualism

Further Reading:

Stigmatization of mental illness

Paradigms Lost-Fighting Stigma and the Lessons learned. H. Stewart, Julio Arboleda-Flores, Norman Sartorius; Oxford University Press 2012.

Concepts in Psychiatry

The Concepts of Psychiatry-A Pluralistic Approach to the Mind and Mental Illness. SN Ghaemi; Johns Hopkins University Press, 2003.

The Perspectives of Psychiatry. PR McHugh, PR Slavney;Johns Hopkins University Press, 1998.

The Problem with Language

Mind is embodied

The human body is the best picture of the human soul.
Wittgenstein (2015)

The mind is inherently embodied.
Thought is mostly unconscious.
Abstract concepts are largely metaphorical.
These are three major findings of cognitive science. More than two millennia of a priori philosophical speculation about these aspects of reason are over. Because of these discoveries, philosophy can never be the same again.
When taken together and considered in detail, these three findings from the science of the mind are inconsistent with central parts of Western philosophy (Lakoff and Johnson, 1999).

In the compound word [psycho-physical]. the prefix "psycho" denotes that physical activity has acquired additional properties, those of ability to procure a peculiar kind of interactive support of needs from the surrounding media. Psychophysical does not denote an abrogation of the physico-chemical; nor a peculiar mixture of something physical with something psychical (as a centaur is half man and half horse); it denotes the possession of certain qualities and efficacies not displayed by the inanimate (Dewey, 1925)

Language and Metaphor
*People not only talk about abstract concepts in terms of concrete ones but also appear to think about them in those terms. People think and talk about time in spatial metaphors, about affection in terms of warmth (Williams and Bargh, 2008) .The insular cortex is implicated in processing both the physical and the psychological versions of warmth information (Meyer-Lindenberg, 2008).Likewise, loneliness is experienced as feeling cold (**Zhong and Leonardelli, 2008**), and threatened morality as dirt and contamination (**Zhong and Liljenquist, 2006**).*

In the compound word [psycho-physical]. the prefix "psycho" denotes that physical activity has acquired additional properties, those of ability to procure a peculiar kind of interactive support of needs from the surrounding media. Psychophysical does not denote an abrogation of the physico-chemical; nor a peculiar mixture of something physical with

something psychical (as a centaur is half man and half horse); it denotes the possession of certain qualities and efficacies not displayed by the inanimate (Dewey, 1925)

*Subjects were asked to look at a cartoon face (**Fig. 1**) and answer the question, "How aware is Kevin of the object next to him? Subjects were asked to attribute states of awareness to a cartoon face. Activity associated with this task was found bilaterally within the temporoparietal junction (TPJ) among other areas. Second, the TPJ was transiently disrupted us- ing single-pulse transcranial magnetic stimulation (TMS). When the TMS was targeted to the same cortical sites that had become active during the social* ***attribution task, the subjects showed symptoms of visual neglect in that their detection visual stimuli was significantly affected.***

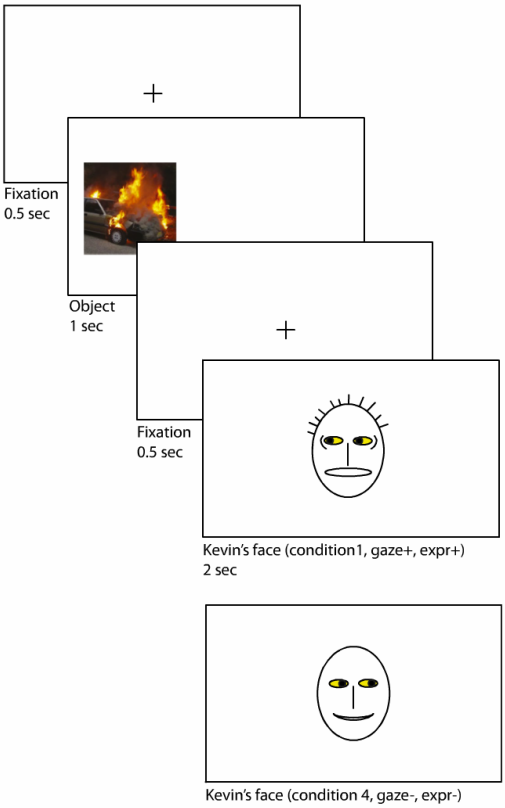


Fig. 1. Social attribution task. Subjects pressed buttons to rate Kevin's awareness of the object on a scale of 1 (not aware), 2 (somewhat aware), or 3 (very aware). Two versions of the face stimulus are shown corresponding to trial condition 1 (gaze and expression both aligned to the object: gaze+, expr+) and condition 4 (gaze and expression both misaligned with the object: gaze–, expr–). Other conditions included condition 2 (gaze+, expr–) and condition 3 (gaze–, expr+).

Fig. 1 *Metaphor "**seeing is believing**."*
*From **Kelly et al (2015)***

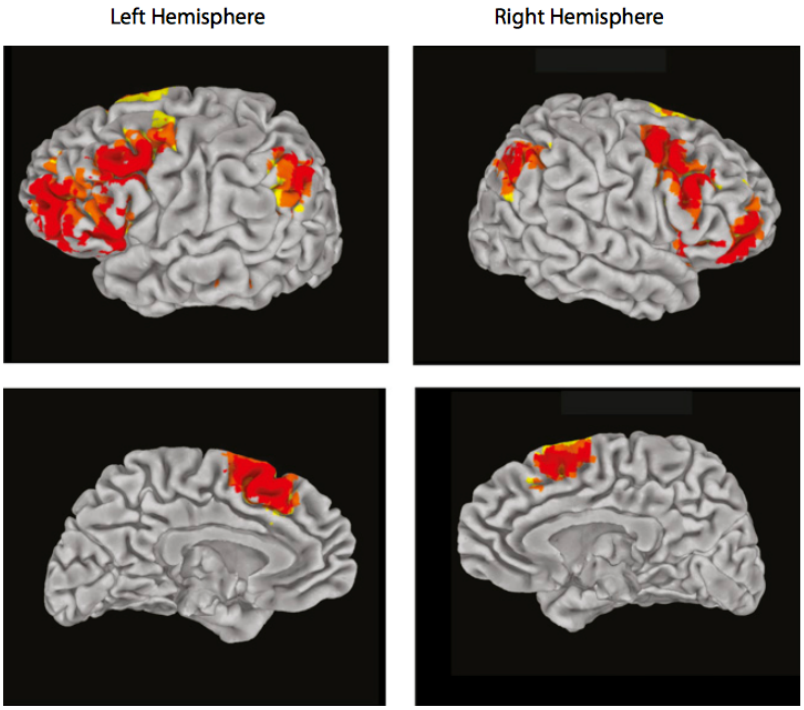


Fig 1a
Involvement of the TPJ in Social awareness
From ***Kelly et al 2015***
Four main areas were found: one in posterior cortex in the TPJ and three in the prefrontal cortex, including a dorsolateral prefrontal region, an anterior ventral prefrontal region, and a region on the medial wall of the hemisphere
Four main areas were found: one in posterior cortex in the TPJ and three in the prefrontal cortex, including a dorsolateral prefrontal region, an anterior ventral prefrontal region, and a region on the medial wall of the hemisphere

The Problem with Language

Understanding of human cognition emphasizes dynamic interaction between cognition and environment through sensorimotor activation, a position supported by converging lines of evidence.
In decision tasks, before asserting their preference for faces or similarly valued snack foods people look more toward the alternative they are going to choose.

The attentional drift-diffusion model (aDDM) proposes that a computational mechanism underlying choices whereby gaze direction biases the decision-including moral judgements.

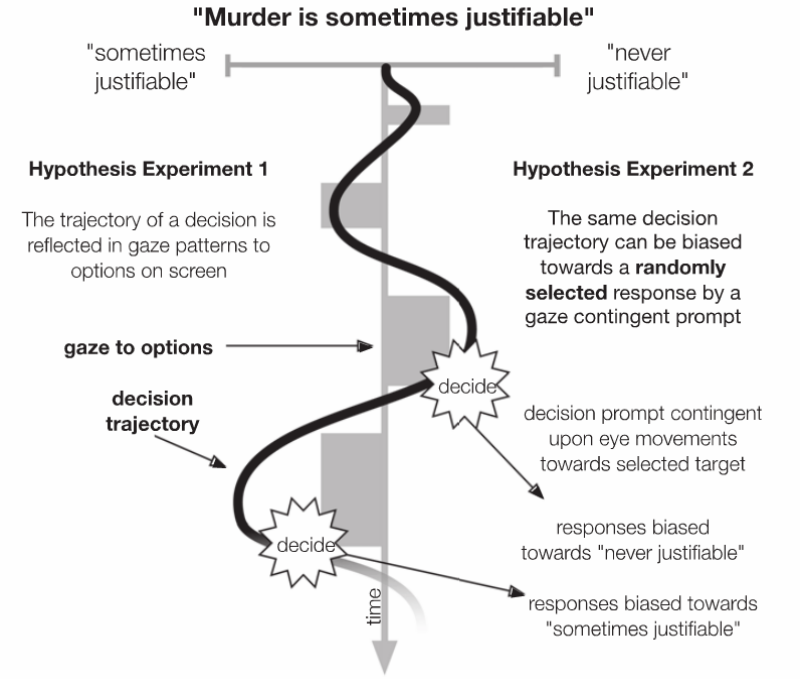


Fig. 2 It is hypothesized that **participants' eye gaze reveals their decision process owing to general coupling between sensorimotor decision processes.**
By using a gaze-contingent probe and selecting when a decision is prompted the resulting choice can be biased toward a randomly predetermined option ***(Fig. 2)****.*
*Moral decision making, like other cognitive processes attributed to a self/soul can be influenced without awareness o the part of the subject. Information derived from eye gaze can be used to change the course of individuals' decisions, even when they are reasoning about high-level, moral issues (****Pärnamets et al, 2015****).*

The Problem with Language

Embodied Mathematics

Reason is evolutionary, in that abstract reason builds on and makes use of forms of perceptual and motor inference present in "lower" animals. The result is a Darwinism of reason, a rational Darwinism: Reason, even in its most abstract form, makes use of, rather than transcends, our animal nature .
*(*George Lakoff. Philosophy In The Flesh (Kindle Locations 73-74, Kindle Edition).

*A disposition to map numerical magnitudes onto a left -to -right -oriented MNL exists independently of cultural factors and can be observed in animals with very little non symbolic numerical experience, supporting a nativistic foundation of such orientation.Spatial mapping of numbers from left to right may be a universal cognitive strategy available soon after birth. Experience and, in humans, culture and education (e.g., reading habits and formal mathematics education) may modulate or even be modulated by this innate number sense. Number-space mapping is implemented through a topographical representation in the right posterior parietal cortex. Such topography has not yet been found in neurons responding to number in animals. Because nonverbal numerical cognition is shared by many animal classes , we suggest that a similar predisposition to map numbers onto space is embodied in the architecture of the animal neural systems (**Rugani et al, 2015**).*

It *is virtually impossible to conceptualize the mind without metaphor. Therefore, it should not be surprising that there is a long history in philosophy in which ontological commitments about the nature of mind are a consequence of common conceptual metaphors.*
What emerged from Descartes' philosophy was a new metaphoric view of mind as representing in some "inner" realm the objects existing in the "external" world.
But Descartes reaches conclusions beyond this: first, that being able to think constitutes our essence; second, that the mind is disembodied; and third, therefore, that the essence of human beings, that which makes us human, has nothing to do with our bodies. These three elements of Cartesian philosophy have had a profound effect on the character of much contemporary philosophical thinking.
An embodied concept is a neural structure that is actually part of, or makes use of the sensorimotor system of our brains. Much of conceptual inference is, therefore, sensorimotor inference.
(George Lakoff. Philosophy In The Flesh (Kindle Locations 273-274) Kindle Edition

The Problem with Language

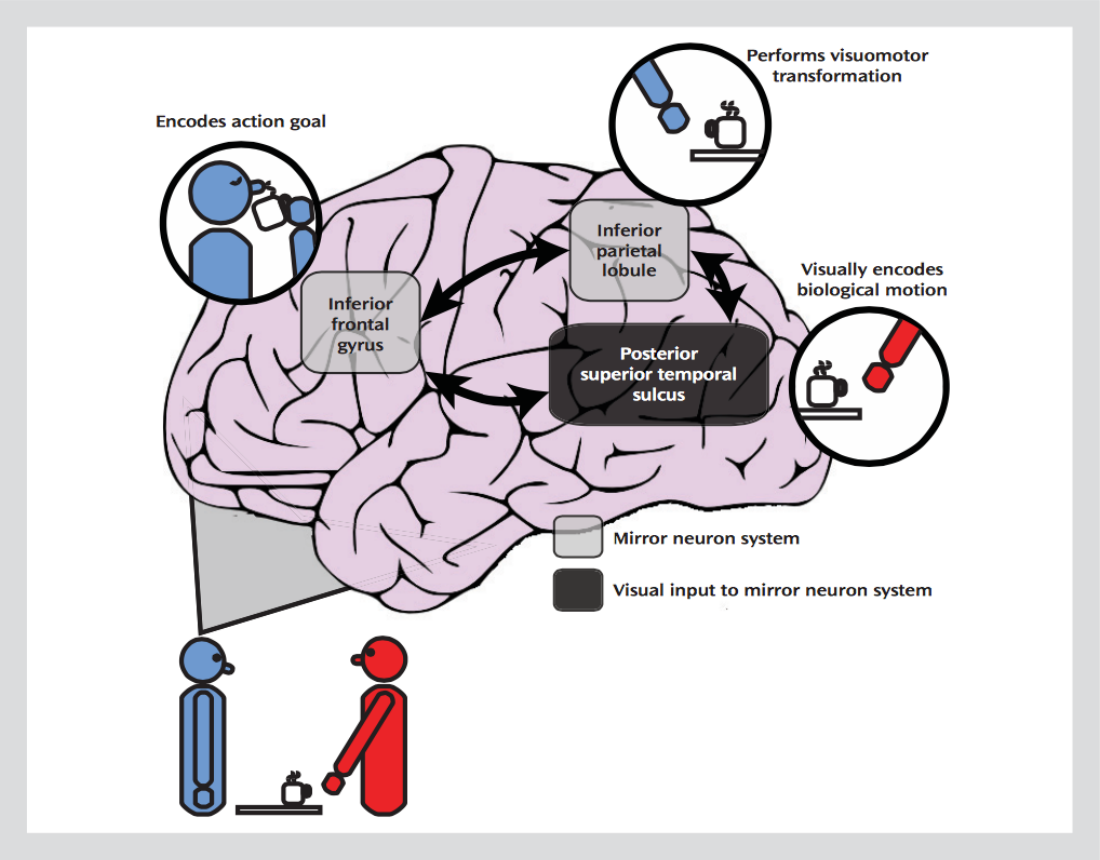
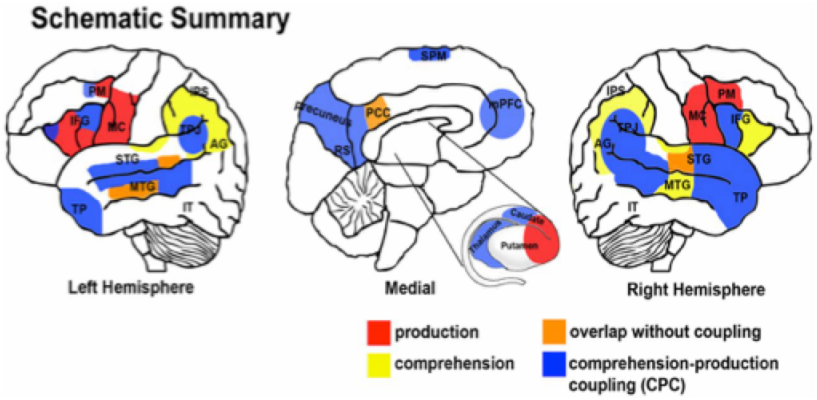


Fig 3. The mirror neuron system *(Thakkar et al, 2014)*
Language is processed in the brain by simulation in the visual-motor system
*Subject nouns or main verbs can trigger visual imagery, but only when used in literal sentences about real space—metaphorical language does not yield significant effects—which implies that it is the comprehension of the sentence as a whole and not simply lexical associations that yields imagery effects (Bergen et al, 2007). People processing sentences automatically construct perceptually detailed embodied simulations of described objects (*Rizzolatti and Craighero, 2004).
Gallese (2007)suggests that the premotor system is the basis of different aspects of the faculty of language and introduces the 'neural exploitation hypothesis', according to which a single functional mechanism , embodied simulation, is probably at the basis of various and important aspects of social cognition (see slide set ***Mirroring People).***
Recruitment of the motor system is fundamental for sentence comprehension (Chersi et al, 2010).
Activation in the mirror neuron system is less specific for imitation in schizophrenia. Relative to healthy subjects, patients had reduced activity in the posterior superior temporal sulcus during imitation and greater activity in the posterior superior temporal

*sulcus and inferior parietal lobe during nonimitative action. Patients also showed reduced activity in these regions during action observation. Mirror neuron system activation was related to symptom severity and social functioning in patients and to schizotypal syndrome in comparison subjects (**Thakkar et al, 2014**)*
Recruitment of the motor system is fundamental for sentence comprehension (Chersi et al, 2010).
In conclusion, there is now hard evidence that at least five brain regions of the human cortex contain mirror neurons: The ventral and dorsal premotor cortex , the supplementary motor cortex , the inferior parietal lobe, and the temporal lobe (Keysers and Gazzola, 2009).

When people communicate verbally. wide areas of their brains exceeding the territory allocated to speech production and perception are synchronized.
A real-life narrative is not localized to the left hemisphere but recruits an extensive bilateral network, which overlaps extensively with the comprehension system.
Moreover, by directly comparing the neural activity time courses during production and comprehension , areas coupled across the speaker's and listener's brains during production and comprehension of the same narrative were detected *(***Fig. 3a***)*.
Widespread bilateral coupling between production- and comprehension-related processing within both linguistic and nonlinguistic areas exposed a surprising extent of shared processes across the two systems *(* **Silbert et al, 2014***)*
These areas include comprehension related areas as well as extra linguistic areas, such as the precuneus and the mPFC. In fact, the most extensive production–comprehension coupling is seen in the mPFC and precuneus, areas important in social cognition, first person perspective taking, and the experience of agency, theory of mind, and empathy (**Silbert et al, 2014***)*.

Schematic summary of the networks of brain areas active during real-life communication.



Lauren J. Silbert et al. PNAS 2014;111:E4687-E4696

Fig. 3a *Areas that exhibited reliable time courses only during the production of speech are marked in red and include the right and left motor cortex, right premotor cortex, left anterior section of the IFG, right anterior inferior temporal (IT), and the caudate nucleus of the striatum. Areas that exhibited reliable time courses only during the comprehension of speech are marked in yellow, and include the right and left IPS, the left and right posterior STG, and the right anterior IFG. Areas that exhibited reliable time courses during both the production and comprehension of speech (overlapping areas) but in which the response time courses during the production and comprehension of speech did not correlate are marked in orange. These areas include sections of the left and right MTG, sections of the left and right IPS, and the PCC. Areas in which the response time courses during the production and comprehension of speech are coupled are marked in blue. These areas include comprehension related areas along the left and right anterior and posterior STG, left anterior and posterior MTG, left and right TP, left and right AG, and bilateral TPJ; production-related areas in the dorsal posterior section of the left IFG, the left and right insula, and the left premotor cortex; and a collection of extra linguistic areas in the precuneus and medial prefrontal cortices.*

Similarly, during non-verbal communication, such as gesturing (the game of charades) brain activity in the gesturer triggers muscle movements (gestures, **Fig. 3b**) that are seen by the receiver and which trigger activity in brain regions of the observer that are similar to those that caused the gestures in the gesturer. Brain-to-brain Granger causality can map such information transfer by calculating how much brain activity in the gesturer helps predict brain activity in the viewer (**Hasson et al, 2012**).
Furthermore, the extent of understanding and comprehension on the part of the listener is reflected quantitatively in her brain activity.
The observed alignment of production-based and comprehension based processes may serve as a mechanism by which brains convey information (Stephens et al, 2010). Neural coupling during communication occurs in Broca's area (production) and Wernicke's area and the TPJ as well as high-order extra linguistic areas such as the precuneus and the mPFC *(* Stephens et al, 2010*)*.

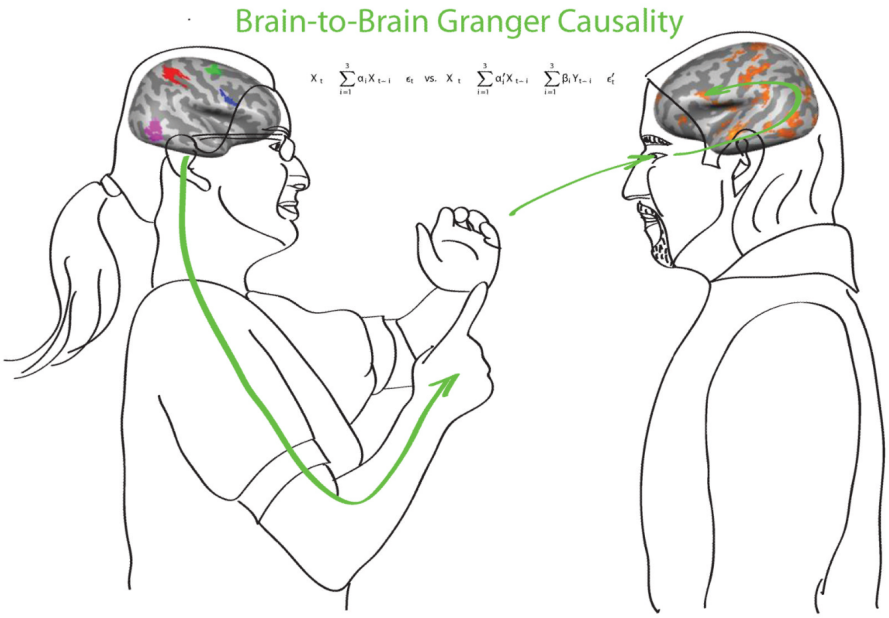


Fig. 3b *During gestural communication, in the game of charades, brain activity in the gesturer triggers muscle movements (gestures), that are seen by the receiver and which trigger activity in brain regions of the observer that are similar to those that caused the gestures in the gesturer. Brain-to-brain Granger causality can map such information transfer by calculating how much brain activity in the gesturer helps predict brain activity in the viewer (**Hasson et al, 2012**)*

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The Problem with Language

The brain can be viewed as an inferential machine following Bayesian principles that continuously brings forth predictions about the causes of sensory input and elicits actions that seek to confirm them.
This scheme is embodied in a complex cortical hierarchy where higher level assemblies compute prediction errors and issue modification signals to the generative model, implemented at a lower level. Minimization of free-energy occurs in the brain via adjustment of three neural aspects: (i) synaptic activity, during the process of perception, (ii) synaptic gain (precision), accounting for the modulatory effect of attention on perception, and (iii) synaptic efficacy, implementing learning processes.

SIDE BAR 1 THE BAYESIAN BRAIN (clickable)

Example: Hemilateral neglect; a failure of the basic , a priori categories without which no can occur.

Schizophrenia:
So-called "positive" symptoms include auditory hallucinations, paranoid delusions and disorganized speech, while "negative" symptoms comprise affective flattening,memory and attention impairment. Preliminary data suggesting an **overactive DMN in schizophrenia** have recently been reported (Garrity et al., 2007; Harrison et al., 2007; Zhou et al., 2007), on the basis of the typically blurred boundary between inner mentalized scenarios and stimuli from the external environment, as well as between self and other (Buckner et al., 2008).

Meditation: The cognitive activity about the world that is generated in performing adjustments to the internal probabilistic model on the basis of sensory data during everyday life,becomes cognitive activity about the self, a perspective that affords some intriguing speculations.

Garrison K, Santoyo J, Davis J, Thornhill T, Kerr C, andBrewer J. (2013a). Effortless awareness:using realtime neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators self- report. Front.Hum.Neurosci. 7:440. doi: 10.3389/fnhum.2013.00440

The Bayesian Brain

visit this website before reading further.

https://www.youtube.com/watch?v=sKa0eaKsdA0

The rotating mask illusion

Despite you best efforts, you are unable to see the "hollow" aspect of the mask. Why is that? Because you know that faces (noses) stick out and the contours of the face are pointing out into the world rather than going inside. This notion, this experience, this conviction is encoded in the brain, reinforced by the millions of times of seeing faces, and is cemented and hard-wired into our neurons.
In Bayesian terms, the is a so called "prior", something that is already there before you gather new experiences
Bayes was a man in the 1700's who came up with a new way of statistical thinking.
The next figures summarize how Bayesian thinking has ben applied to understanding how the brain manages perceptions by using the strategy of constructing inferences.
For examples, photons strike your retina, photoreceptors interact with these photons, and action potentials are generated which are relayed to the visual cortex, starting at V1 to V2 etc., until the image is "recomposed" in higher visual cortices and come to awareness in your "mind's eye."
An immediate problem arises because of something called "bandwidth." You accumulate a tremendous amount of sensory data every second you interact with the world, such as visual, auditory, tactile, olfactory, and proprioceptive stimuli. This may well be an overload for our brain's processing power. The brain invented a workaround, reinvented by man in signal processing. For example video imaged can be compressed; the same is true for audio files (mp3, mp4). You don't hear the entire full spectrum of frequencies. Files are edited in such a way that the nearest neighbor of the data point of interest is "guessed at." Most likely, its value will be close in value to the point you want to encode. All you have to collect is the error term, i.e., the degree of deviation from the inferred value; how for away is the pixel-value from the "central pixel" you are interested in?
Error terms require less bandwidth in terms of coding.
Evolution has optimized our bandwidth utilization.
Bayesian statistics are using the error terms.

In the example of the hollow face illusion, the error terms get totally overwhelmed by what we call the "prior."
You may have noticed a sense of surprise or even a somewhat creepy feeling when watching the hollow face video. You expected to look into the hollow convex area of the face when you brain "corrected you" and defied your expectations.
This eerie feeling is the collision of your prior expectation with error terms that the brain was computing. This collision is experience emotionally as a sense of surprise.

Rather than processing the raw data coming in from the world, the brain compares them with notions as to how things should be according to prior experience. You have a vast set of experiences you can fall back on for interpreting incoming data.
All you have to do is to compare the incoming data against the prior expectations and compute the error terms.

The brain as a black box

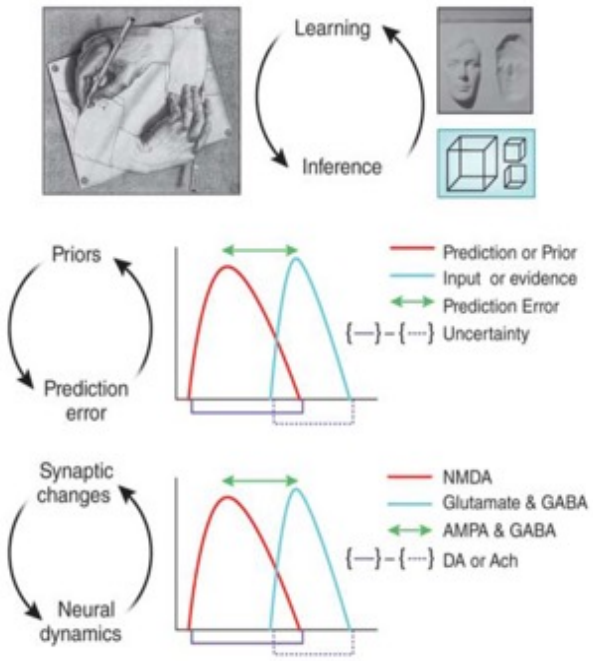
> The task of the brain, when viewed from a certain distance, can seem impossible: it must discover information about the likely causes of impinging signals without any form of direct access to their source. Thus, consider a black box taking inputs from a complex external world. The box has input and output channels along which signals flow. But all that it "knows", in any direct sense, are the ways its own states (e.g., spike trains) flow and alter. In that (restricted) sense, all the system has direct access to is its own states. The world itself is thus off-limits (though the box can, importantly, issue motor commands and await developments). **The brain is one such black box.**

> Perception thus involves "explaining away" the driving (incoming) sensory signal by matching it with a cascade of predictions pitched at a variety of spatial and temporal scales. These predictions reflect what the system already knows about the world (including the body) and the uncertainties associated with its own processing. Perception here becomes "theory-laden" in at least one (rather specific) sense: What we perceive depends heavily upon the set of priors (including any relevant hyper-priors) that the brain brings to bear in its best attempt to predict the current sensory signal.

The brain is constantly "*explaining away*" incoming signals by comparing them to against already existing models of the world (*minimizing the error terms*).

Here is an application of Bayesian thinking to psychiatry, specifically to schizophrenia. We have the dopamine hypothesis of schizophrenia, which rests upon the two key findings: flooding the dopamine system by administering amphetamine will produce psychotic symptoms and blocking the dopamine D2 receptor with neuroleptic drugs will attenuate these symptoms. Why, however, are delusions so long lived and often resistant to antipsychotic drugs.

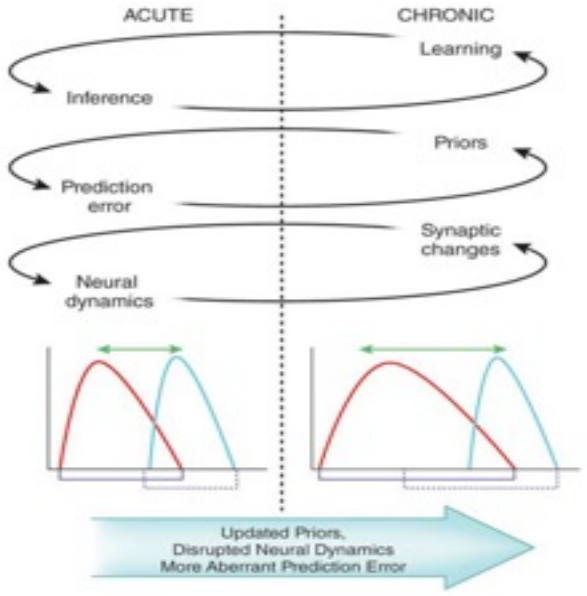
This proposal was inspired by the finding that ketamine, a glutamate receptor antagonist can produce psychotic symptoms.



A model of the reciprocal relationships between inference and learning, priors and prediction error, synaptic plasticity and neural dynamics. Inference is encapsulated in the bistable percepts of the Necker Cube, that is, when faced with ambiguous inputs, the brain entertains multiple hypotheses and makes an inference as to the best candidate. The powerful effect of learning on perception is captured by the **hollow mask illusion**, wherein, as a result of our overwhelming experience with faces as convex, we perceive a hollow, concave, inverted mask as convex. *All predictions, or hypotheses that we entertain, have a likelihood distribution, which we compare with the inputs, computing: a prediction error; a degree of uncertainty associated with that prediction error.* We speculate that fast neurotransmitters (GABA and glutamate) may code the prediction error and slower neuromodulators (eg, dopamine and acetylcholine, depending on the task and underlying circuitry) may compute the uncertainty.

Neuropsychopharmacology REVIEWS (2011) 36, 294–315

The circuits are no longer able to respond to new information, thus favoring priors over new learning. Delusions are solidified prior resistant to modifications. Note that the role of dopamine is diminished in the later stages of this process, providing a possible explanation for the failure of dopamine blocking drugs to attenuate delusions.



The putative effects of acute and chronic ketamine treatment within the Bayesian model. We predict that, with repeated ketamine exposure, aberrant learning (due to deranged synaptic plasticity) and subsequent inappropriate inferences (based on perturbed neural dynamics) lead to maladaptive and inaccurate representations of the world; delusional beliefs.

Uncertainty is encoded in the brain by dopamine.

This proposal is supported by finding that dopamine may be involved in encoding the *precision* of the error term computation.

Dopamine in in the business of error detection. There is an entire literature in the field of Neuroeconomics involving this role of dopamine
Powerful heuristic models can be derived from Neuroeconomics which illuminate possible mechanisms of psychiatric disorders.

In recent work, effects of the neurotransmitter dopamine are presented as one possible neural mechanism for encoding precision (see Fletcher & Frith [2009, pp. 53–54] who refer the reader to work on prediction error and the mesolimbic dopaminergic system such as Holleman & Schultz 1998; Waelti et al. 2001). Greater precision (however encoded) means less uncertainty, and is reflected in a higher gain on the relevant error units (see Friston 2005; 2010; Friston et al. 2009). Attention, if this is correct, is simply one means by which certain error-unit responses are given increased weight, hence becoming more apt to drive learning and plasticity, and to engage compensatory action.
Here is an example of dopamine in action. This is a recording of a dopamine neuron in the process of responding to expectation, in this case the expectation of *reward*. In this experiment a conditioned stimulus (CS) predicts reward (see next page)

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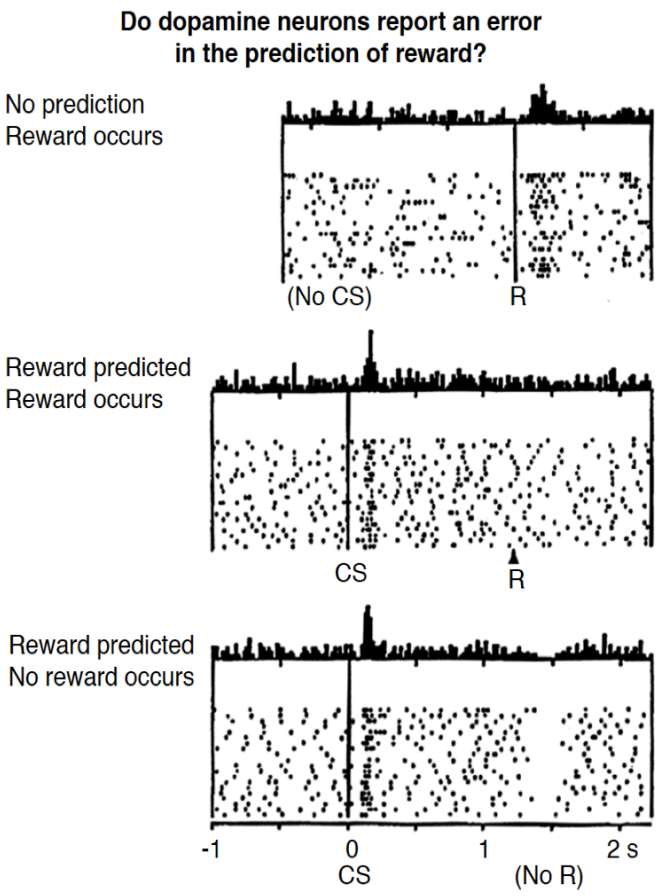

Changes in dopamine neurons' output code for an error in the prediction of appetitive events. (**Top**) Before learning, a drop of appetitive fruit juice occurs in the absence of prediction—hence a positive error in the prediction of reward. The dopamine neuron is activated by this unpredicted occurrence of juice. **(Middle**) After learning, the conditioned stimulus predicts reward, and the reward occurs according to the prediction—hence no error in the prediction of reward. The dopamine neuron is activated by the reward-predicting stimulus but fails to be activated by the predicted reward (right). **(Bottom**) After learning, the conditioned stimulus predicts a reward, but the reward fails to occur because of a mistake in the behavioral response of the monkey. The activity of the dopamine neuron is depressed exactly at the time when the reward would have occurred. The depression occurs more than 1 s after the conditioned stimulus without any intervening stimuli, revealing an internal representation of the time of the predicted reward. Neuronal activity is aligned on the electronic pulse that drives the solenoid valve delivering the reward liquid (top) or the onset of the conditioned visual stimulus (middle and bottom). Each panel shows the perievent time histogram and raster of impulses from the same neuron. Horizontal distances of dots correspond to real-time intervals. Each line of dots shows one trial. Original sequence of trials is plotted from top to bottom. CS, conditioned, reward-predicting stimulus; R, primary reward. **Science 275:1593-1599 (1997**).

What is the key role of the brain?

It should make decisions in the face of uncertainty.

Sensory motor learning, for example in playing tennis, is a typical example of a Bayesian activity involving predictions in the context of uncertainty. You have prior experience where your opponent usually places his forehand shot. That is the prior here outlined in green. But you are also observing the trajectory of the ball as it is approaching you, and you integrate those 2 items and predict the most likely bounce location to determine where to place your racket.

Fig. shows the temporal evolution of your belief where the ball will most likely land. You have prior experience where your opponent usually places his forehand shot. That is the *prior* here outlined in green. But you are also observing the trajectory of the ball as it is approaching you, and you integrate those 2 items and predict the most likely bounce location to determine where to place your racket racket.

Fig. x shows the temporal evolution of your belief where the ball will most likely land.

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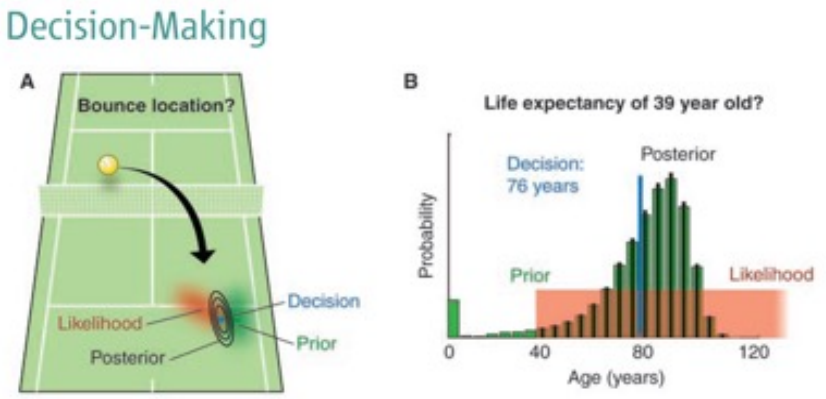


Fig. 2. (**A**) In the example of tennis, people need to combine what they know from before (prior, green) with what they currently see (likelihood, red). That way we can estimate the posterior (black contour lines) to make an optimal perceptual decision (blue). (**B**) Similarly if we estimate the life expectancy of a person who is 39 years old, we need to combine what we know from before (prior, histogram of lifetimes, green) with our new information (person survived 39 years, likelihood, red) to come up with an optimal estimate.

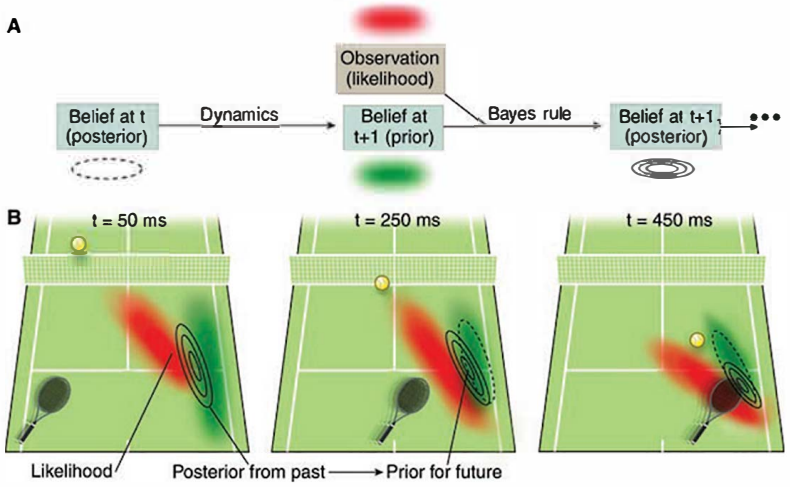


Fig. 3. Integration of information over time. (**A**) A diagram of a Kalman filter is shown. At any point of time *t*, the person has a belief about the state of the world. The person then updates this belief with a model of the dynamics of the world (e.g., gravity) to calculate the belief at the next point of time. This belief (prior) is then combined with new sensory information (likelihood) using Bayes's rule to calculate the belief at the next time step. The ellipses indicate probability distributions sketched in (B). (**B**) To estimate the position of a ball hitting the ground, people continuously update their beliefs with incoming sensory information, yielding precise estimates. The posterior of the previous time step is the prior for the new one: The dashed line indicating the previous posterior is identical to the one standard deviation line of the prior (green).

Integration of priors and likelihoods.
To calculate probabilities of outcomes, it is often necessary to update our belief from the past (prior) with new knowledge (likelihood). For example, when we play tennis it is helpful to estimate where the ball will land. The visual system, although noisy, still provides us with an estimate or a likelihood of where the ball will land (sketched in red in Fig. 2A). This knowledge may be combined with information obtained from experience; the positions where the ball may land are not uniformly distributed over the court. The locations may be clustered near the boundary lines, where it is most difficult to return the ball. This distribution of positions is called the prior (sketched in green in Fig. 2A). Bayes's rule states that how the probability of the ball landing at position x given our observation o (posterior) needs to be estimated as

$$\underbrace{p(x|o)}_{\text{posterior}} = \underbrace{p(x)}_{\text{prior}} \underbrace{p(o|x)}_{\text{likelihood}} / p(o)$$

Brains need to learn but also draw inferences about what is going on in the world from prior experience. The Bayesian formula captures the notion that prior believes can be incorporated into statistics.

Regular statistics is “frequentist”, meaning that we count the occurrence of events and determine the frequency distribution of these events and then contrast them with other observations that we want to differentiate and assign a significance level to the difference in the frequency of observations.

Bayesian statistics is different because it takes into account what has already been “laid down” in experience and assigns a value to characterize the belief already formulated before inferences are being made about what the brain is dealing with in the world.

Bayesian statistics is useful in understanding how sensory=motor integration works. For example, in tennis you know your opponents style from having observed his prior strokes, you have a prior believe where his forehand may land the ball, and can adjust your strategy accordingly. Rather than computing all the raw data in estimating the trajectory of the last stroke, the brain can compute the error term from the prediction already “on file”, thus minimizing bandwidth utilization.

Bayesian statistics plays a role in decision making by utilizing the error detection activity of dopamine neurons.

Review of Bayes’ formula:

Step 1
A central assumption is that degrees of belief can be represented as probabilities: that our conviction in some hypothesis h can be expressed as a real number ranging from 0 to 1, where 0 means something like \h is completely false" and 1 that \h is completely true."

Step 2

These assumptions turn the mathematics of probability theory into **an engine of inference**, a means of weighing each of a set of mutually exclusive and exhaustive hypotheses H to determine which best explain the observed data. Probability theory tells us how to compute the degree of belief in some hypothesis hi, given some data d.

Step 3
Computing degrees of belief as probabilities depends on two components. One, called the **prior probability** and denoted **P(hi), captures how much we believe in hi prior to observing the data d**. The other, called ***the likelihood and denoted P(d/hi)***, captures the probability with which we would expect to observe the data d if hi were true. These combine to yield the **posterior probability of hi**, given via Bayes' Rule

$$P(h_i|d) = \frac{P(d|h_i)P(h_i)}{\sum_{h_j \in \mathcal{H}} P(d|h_j)P(h_j)}.$$

Step 4

The denominator in Equation 1 provides a normalizing term which is the sum of the probability of each of the possible hypotheses under consideration; this ensures that **Bayes' Rule will reflect the proportion of all of the probability that is assigned to any single hypothesis hi, and (relatedly) that the posterior probabilities of all hypotheses sum to one.**

$$\frac{}{\sum_{h_j \in \mathcal{H}} P(d|h_j)P(h_j)}.$$

law of conservation of belief

This captures what we might call the "**law of conservation of belief**": a rational learner has a fixed "mass" of belief to allocate over different hypotheses, and the act of observing data just pushes this mass around to different regions of the hypothesis space. If the data lead us to strongly believe one hypothesis, we must decrease our degree of belief in all other hypotheses. By contrast, if the data strongly disfavor all but one hypothesis, then (to paraphrase Sherlock Holmes) whichever remains, however implausible a priori, is very likely to be the truth.

The central assumption is that degrees of belief can be represented as a number between 0 and 1, where means that the hypothesis is clearly false and 1 means that it is completely true. Our beliefs, by using probability theory, can now drive an engine of inference. Probability theory allows us to compute the degree of belief in some hypothesis hi *P(hi)* is the prior probability, the degree of belief, that he hypothesis is true. *P(d/hi)* is the likelihood of the data fitting the hypothesis. *P(hi/d)* is the "posterior", the likelihood of the hypothesis being true given the observed data.

The denominator is an expression to normalize the data such that the probabilities assume values between 0 and 1. This has been called (tongue in cheek) the **Law of Conservation of Belief.** This is a riff on the Law of conservation of energy, or momentum in physics. What this phrase encapsulates is the fact that we cannot hold all beliefs at the same time. A rational learner has a fixed "mass of belief" to allocate over different hypotheses and the act of observing data pushes the mass around to different regions of the hypothesis space. If the data lead us to belief strongly one hypothesis, we must decrease our belief in the other hypotheses. By contrast, if the data disfavor all but one hypothesis, then, to paraphrase Sherlock Holmes, whatever remains, however implausible a prior may seem, is likely to be the truth.

This concludes our short review of the Bayesian formula.

The Bayesian approach has been used to understand a very challenging finding related to the syndrome of depression.

There is a relationship of depression to various other conditions such as obesity, inflammation and other medical conditions, which are in some way to the stress response as encoded by the hypothalamic-pituitary-adrenal axis.

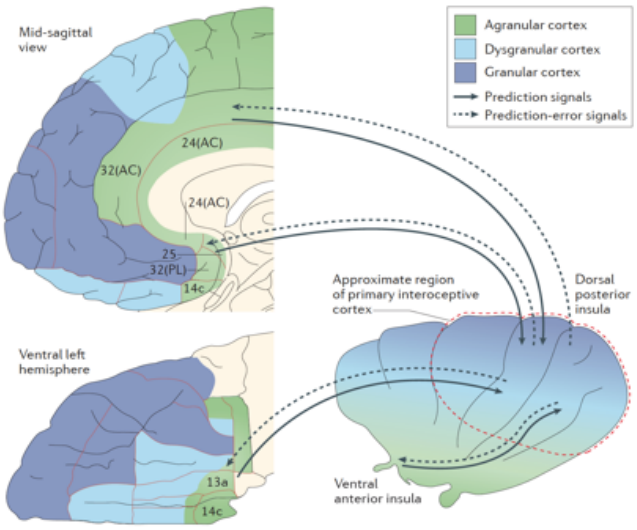
There is often a bidirectional relationship of medical illness to depression. In other words, depression is a risk factor for some medical conditions and medical illnesses such as diabetes, for example are risk factors for depression. A possible explanations is proposed in the paper "Interoreceptive predictions in the brain " (Barret and Simmons,).

We believe that perception follows sensation, but, as this paper suggest, it is possible that prior interoceptive experiences, already encoded in particular brain areas as "priors" and what we respond to is an "error term" which measures the deviation from our expectations.

According to this active inference account,
the brain forms neural representations that are constructed from previous experience. These function as a generative model of how stimuli in the environment cause sensations. Rather than neurons simply lying dormant until information arrives via the external sensors
the body (that is, the eyes, ears and taste receptors, among others), the brain anticipates incoming sensory inputs, which it implements as predictions that cascade throughout the cortex. As predictions propagate across cortical regions –following their roughly **centrifugal** connections–

they modulate the firing of neurons within cortical columns in anticipation of these regions receiving actual sensory sensation –that is, the "prediction error"

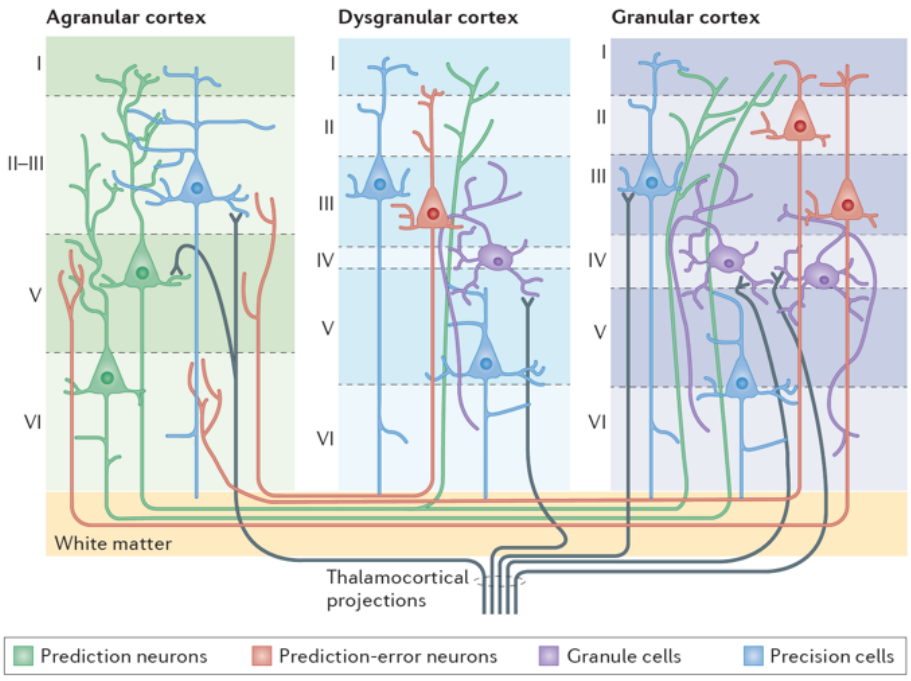
In this active inference framework ,perception and action are tightly coupled, with both arising from the brain's hypotheses about the world and constraint by sensory input from the world. By this account, **action drives perception to reduce prediction error.**



According to this model, we suggest that **agranular visceromotor cortices** — including the cingulate cortex (Brodmann area 24 (BA24), BA25 and BA32), the posterior ventral medial prefrontal cortex (BA14c), the posterior orbitofrontal cortex (BA13a) and the most ventral portions of the anterior insula — **estimate the balance between the autonomic, metabolic and immunological resources that are available to the body, and the predicted requirements of the body, based on past experience.**

visceromotor cortices simultaneously issue predictions of the interoceptive signals that are expected to arise as consequences of those allostatic visceral changes to the primary interoceptive sensory cortex (see the figure)

The granular cortex in primary interoceptive sensory regions of the mid- and posterior insula are architecturally well suited for computing and transmitting prediction error and for propagating prediction-error signals back to visceromotor regions to modify predictions.



Please review these video lectures for a detailed presentation of the Bayesian (predictive) Brain

Video Lecture 3: The Bayesian Brain, Part 1
Video Lecture 4: The Bayesian Brain, Part 2
Video Lecture 5: The Bayesian Brain, Part 3
Video Lecture 5.1: The Bayesian Brain_Update 1

Consciousness

Phenomenal First Person Experience, Qualia, Free Will, and the Soul.

All conscious states are caused by lower level neurobiological biological processes in the brain, and they are realized in the brain as higher level features. Consciousness is a feature of the brain in a way, for example, that the liquidity of the water is a feature of the system of H2O molecules… why is it so hard for people to accept a naturalistic conception? ***(Searle, 2013)***

*T*he conscious mind, its ability to have phenomenological experiences (so called "qualia"), its apparent exercise of free will and its expansion into concepts such as the self and the soul is intuitively felt to be non-reducible to biological terms (Popper and Eccles, 1977). Qualia have frequently been cited as evidence for an "explanatory gap" which ontologically separates the physicalist/ materialistic account of reality and the individual (first person) experience. Qualia lie at the core of the so-called "hard problem" of consciousness (Chalmers, 1996). An empirical physical theory of consciousness has to be consistent with evolution and reject any explanatory ideas outside of the physical universe such as dualism. Frameworks for such an approach to consciousness have been formulated (Mountcastle, 1982; **Edelman, 2003**; **Edelman et al, 2011**; Metzinger, 2000; **Crick and Koch, 2003**). Searle answers his above quoted question in this way:

We are the victims of two traditions that appear to be in consistent with each other, but in fact they trade off on each other. One is the tradition of God, the soul, and immortality that says consciousness is not a part of the natural world. Consciousness is not even a property on the body or the brain. The second tradition is usually mistakenly described as "materialism," and often its adherents simply deny that consciousness as qualitative, subjective states really exists.

We will attempt to deconstruct the claim that consciousness, and phenomenological experience, cannot be studied in neuroscientific terms; we will examine empirical constraints on the concept of free will and examine the idea of the soul and its possible function in the human animal. Our focus will be on very recent results from the neurosciences which in the aggregate suggest that physicalism provides an adequate account of the mind/brain with its emergent manifestations.

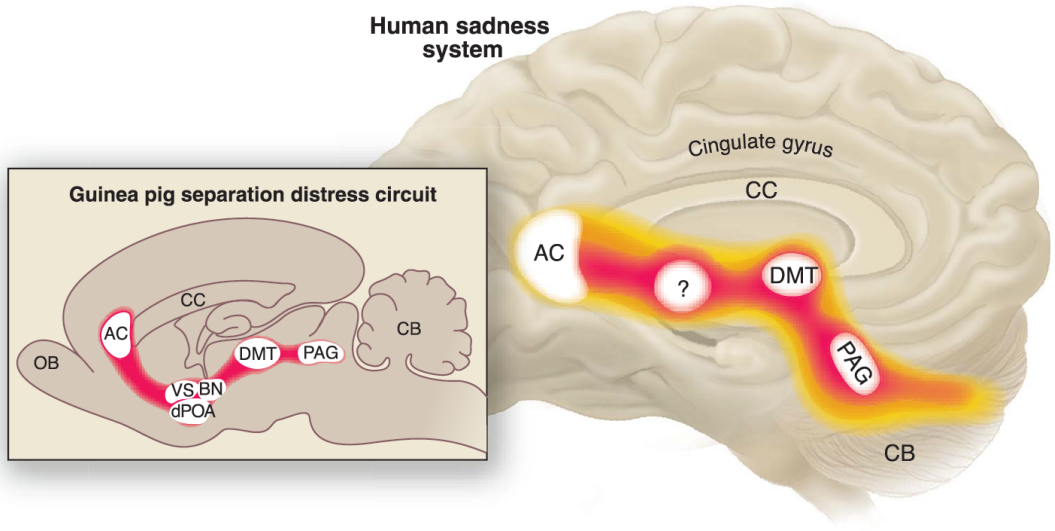
function in the human animal. Our focus will be on very recent results from the neurosciences which in the aggregate suggest that physicalism provides an adequate account of the mind/brain with its emergent manifestations.

Evolution

Mind/Brain is a product of Evolution

*Consciousness must have a point of emergence during evolution and that point likely occurred before Homo sapiens. "How," Darwin questioned, "does consciousness commence?" His post-Beagle research on this question evidently caused him violent headaches (**Mashour and Alkire, 2013**).*

The brain and its sensory organs are adapted to the environment the animal inhabits and implement the behaviors necessary for survival and reproductive success**.** The evolution of the brain is a demonstration of the conservation of structural and functional features linking the human brain to distant relatives in profound ways. It is difficult to identify an entry point for non-physical entities such as the soul in this continuous chain of evolutionary adaptations. There is a vast literature in this field. We will highlight only some very recent findings that serve as examples of the profound connectedness of neuronal function and the circuitry implementing behaviors throughout evolution. Darwin was first to highlight how commonalities in emotional expression across different species likely reflected similar states of mind that only made sense within a theory of evolution (Darwin, 1872). The evolutionary roots of consciousness of affective experiences we share with other animals probably involve areas in the upper brainstem (**Panksepp, 2005**; 2011; 2012).



The emotional pain of social loss. There are remarkable similarities between regions of the guinea pig brain that when activated provoke separation distress and areas of the human brain that are activated during feelings of sadness. During separation distress in guinea pigs, the most responsive brain areas are the anterior cingulate (AC), the ventral septal (VS) and dorsal preoptic areas (dPOA), the bed nucleus of the stria terminalis (BN), the dorsomedial thalamus (DMT), and the periaqueductal central gray area of the brain stem (PAG) (*18*, *19*). In humans experiencing sadness (*17*), it is the anterior cingulate that is most responsive, but other areas that are also activated include the DMT, PAG, and insula. The correspondence between the brain regions activated during human sadness and those activated during animal separation distress suggests that human feelings may arise from the instinctual emotional action systems of ancient regions of the mammalian brain. OB, olfactory bulb; CC, corpus callosum; CB, cerebellum.

Fig. 4 (Panksepp, 2005)

The neurobiological structures needed to support consciousness not uniquely human (Low, 2012) suggesting that the capacity for consciousness likely very early in evolutionary terms, and those processes that support consciousness in in humans are likely characteristic of many living creatures. We even share highly evolved social cognitions such as empathy with our primate relatives (**de Waal, 2012**).
The evolutionary links become even more compelling from a molecular perspective. Dopamine is the neurotransmitter involved in the reward circuits (Dayan et.al.2002; Wise, 2004) from C. elegans to the drosophila nervous system to the human brain (**Wolozin, 2011**; **Liu et al, 2012**); **Burke et al, 2012**). In C. elegans 6 neurons are found in the head of the animal, 4 CEP and 2 ADE neurons, which mediate locomotion behavior in response to the presence of food (**Fig. 5**) foreshadowing the role of dopamine in the

control of movement and in reward circuitry in mammals across many millions of years of evolutionary time.

An oxytocin/vasopressin-like signaling system has been discovered in Caenorhabditis elegans, consisting of a peptide and two receptors that are expressed in sexually dimorphic patterns. Males lacking the peptide or its receptors perform poorly in reproductive behaviors, including mate search, mate recognition, and mating, but other sensorimotor behaviors are intact (**Garrison et al, 2012**).

Stress-induced avoidance behavior in crayfish exhibits striking homologies with vertebrate anxiety. Crayfish anxiety like behavior is sensitive to systematically applied benzodiazepine anxiolytics that modulate vertebrate GABA type A receptors. 5HT can also induce anxiety like behavior in crayfish suggesting that an invertebrate analog of mammalian emotion dates to the time of metazoan evolution (**Fossat et al, 2014**).

Neurocircuits have been conserved throughout evolutionary time.

The amygdala is a brain region that is important for emotional processing, the circuitry and function of which has been well-conserved across evolution (Figure). Even non-mammalian species such as reptiles, birds and fish have an amygdala-like brain region with similar circuits and functions to the amygdala in mammals (**Janak and Tye, 2015**).

There are converging genetic data pointing to a deep homology of vertebrate basal ganglia and the arthropod central complex, suggesting that the circuits essential for behavioral choices have been conserved through deep evolutionary time (Strausfeld and Hirth, 2013). A recent review examined the utility of zebrafish, an organism which has high DNA homology (70% or higher) in genes homologous to corresponding human genes and glutamate, γ-aminobutyric acid (GABA), acetylcholine and the aminergic neurotransmitters dopamine (DA), noradrenaline (NA), serotonin (5-hydroxytryptamine, 5-HT) and histamine (HA) key mediators implicated in multiple psychiatric disease, as a model system for biological psychiatry (Stewart et al, 2014)

Likewise, neurocircuits have been conserved throughout evolutionary time.

The amygdala is a brain region that is important for emotional processing, the circuitry and function of which has been well-conserved across evolution (Figure). Even non-mammalian species such as reptiles, birds and fish have an amygdala-like brain region with similar circuits and functions to the amygdala in mammals (**Janak and Tye, 2015**).

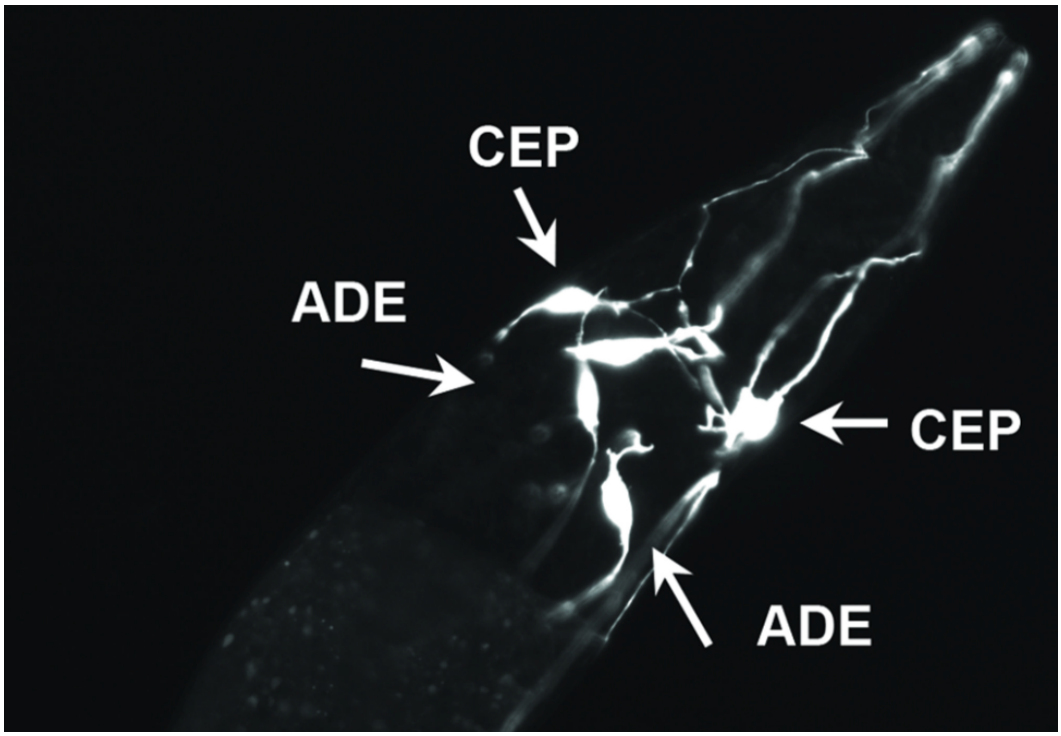


Fig. 5 Localization of dopaminergic neurons in C. elegans shown using GFP driven by the dopamine transporter promoter. C. elegans has 6 dopaminergic neurons in the head; 4 neurons are termed CEP and 2 are termed ADE (arrows).
From Wolozin et al (2011)

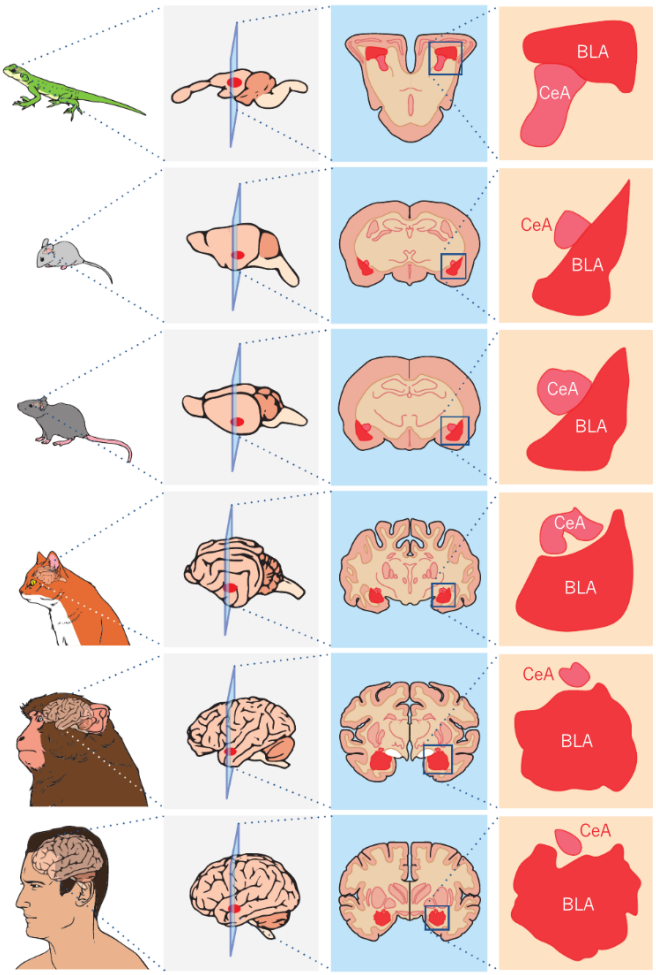


Fig. 5a Primary amygdalar nuclei and basic circuit connections and function are conserved across species. An enlarged image of the basolateral complex of the amygdala (BLA) and central nucleus of the amygdala (CeA) or analogues are shown next to a coronal section from the brains of a lizard, mouse, rat, cat, monkey and human (**Janak and Tye, 2015**)

The default mode network (**Raichle et al, 2001**) in humans, which supports self referential cognitive functions such as recollection, conceptual processing and conscious awareness (**Buckner et al, 2008**; Binder et al, 1999; Horovitz et al, 2009), is found both in other primates (**Mantini et al, 2011**; Rilling et al, 2007) and in the evolutionarily distant rodent brain (Burke et al, 2012; **Lu et al, 2012**).

The evolutionary roots of consciousness of affective experiences we share with other animals probably involve areas in the upper brainstem (Panksepp, 2012). We share highly evolved social cognitions such as empathy with our primate relatives **(de Waal, 2012**). Recently, an evolutionary molecular mechanism has been found that may drive the expansion of cognitive complexity in vertebrates involving gene duplications (**Belgard and Geschwind, 2013**; Ryan et al, 2013; **Nithianantharajah et al, 2013)**. Also, the genetic basis of heritable complex behavioral adaptations in rodents affecting distinct behavioral modules has been identified (Weber et al, 2013), providing first direct evidence for the "extended phenotype" postulated by Dawkins (1982). Complex behavioral responses to social challenge provoked by territory intrusions in such divergent species as mice, stickleback fish and honeybees (phylogenetic distance that spans ~650My of evolution) have been shown to employ deeply conserved mechanisms. These involve metabolism, chromosome organization as well as transcriptional regulation of seven homologous transcription factors identified as putative "toolkit genes" for social behavior (Rittschof et al, 2014).

Consoling con-specifics in need is observed in humans and our great apes relatives, suggesting that advanced cognitive mechanisms may be involved in empathic behaviors. However, a recent study (**Burkett et al, 2016**) describes the presence of consolation behavior in prairie voles, demonstrating that this behavior is not based on cognitive capacities but rather on a deep homology in the underlying neural substrates conserved in rodents and homo sapience.

Further Reading:

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R Dawkins , The Blind Watchmaker, WW Norton 1987

Consciousness is not beyond the scope of science

The study ... of the distribution of consciousness shows it to be exactly such as we might expect in an organ added for the sake of steering a nervous system grown too complex to regulate itself (William James, 1890/1984)

Phasic cycling of internally generated activity, accessing first primary sensory but then successively more general and abstract processing units of the homotypical cortex, should allow for continual updating of the perceptual image of self and self-in –the-world as well as matching functions between that perceptual image and impinging external events. This internal readout of internally stored information, and its match with the neural replication of the external continuum, is thought to provide an objective mechanism for conscious awareness. That mechanism is not beyond the reach of scientific inquiry (Mountcastle, 1982).

*The cognitive neuroscience of consciousness aims at determining whether there is a systematic form of information processing and a reproducible class of neuronal activation patterns that systematically distinguish mental states that subjects label as conscious, from other states (***Dehaene and Naccache, 2001***).*

T*he neurobiological structure of the vertebrate central nervous system is evolutionarily ancient and highly conserved across species and that the basic neurophysiologic mechanisms supporting consciousness in humans are found at the earliest points of vertebrate brain evolution (***Mashour and Alkire, 2013***).*

*The study of consciousness has long been avoided by neuroscience because of the "mistake of supposing that the subjectivity of consciousness made it beyond the reach of an objective science" (***Searle, 2000**).

I think, therefore I am (Descartes,1970)
I feel therefore I am (Damasio, 1994)
*I feel that I am (*Craig, 2015)

Consciousness emerges as a result of the coordinated activity of brain networks spanning many scales of space and time. These networks have "small world" architecture (Watts and Strogatz, 1998) and enable high efficiency information processing, particularly at higher frequencies (**Bassett et al, 2009**). Neuroscience is responding to the challenge of modeling how functionally distinct brain states emerge from interactions of a large number of brain regions, each containing millions of neurons, by rapid, real-time integration without the supervision of an executive controller (**Sporns and Honey, 2006; Sporns, 2014**). These networks, while providing long range connectivity of cortical regions which may facilitate sensory-motor integration, preserve a fractal small world topology which allows for correlated high frequency (gamma band) oscillations. These in turn provide the substrate of temporal binding and permit rapid state- related changes

(**Bassett et al, 2006**). The function of neural circuits in bringing about mental states is emergent, arising from complex and constantly changing interactions of many neurons (**Alivisatos et al, 2012**).
A number of strategies have been used to identify brain states that are required for consciousness. Basic consciousness can be studied by observing the brain as it emerges from anesthesia or deep sleep. Emerging consciousness from sleep is associated with recovered midline arousal structures of the thalamus and brainstem function well before cortical connectivity resumed. Thus, the core of human consciousness appears to be associated primarily with phylogenetically ancient structures involved in arousal and primitive emotions.

The thalamocortical system plays a critical role in the breakdown and re-emergence of consciousness as shown in studies using anesthesia (**Hwang et al, 2012**). The conscious state requires the coupling of subcortical and limbic regions with parts of the frontal and inferior parietal cortex (**Langsjo et al, 2012)**. Loss of consciousness induced by the anesthetic propofol is associated with a rapid change in cortical network dynamics and a resultant decrease of communication between distant cortical areas (**Lewis et al, 2012**). Loss of consciousness at the onset of sleep is also associated with a breakdown of connectivity between cortical regions (Massimini et al, 2005).
Coherent oscillations of distributed cortical networks are the physical substrate for perceptual, motor and cognitive representations in the brain, with gamma phase synchrony as a possible mechanism for large scale cognitive integration (Rodriguez et al, 1999). A possible mechanism for binding information across brain regions, through the synchronized activity of neurons, as proposed by Singer (**Engel et al, 2001**).
Dehaene and Changeux (2011) *summarize a number of studies which show that converging neuroimaging and neurophysiological data, acquired during minimal experimental contrasts between conscious and nonconscious processing , point to objective neural measures of conscious access:late amplification of relevant sensory activity, long distance cortico -cortical synchronization at beta and gamma frequencies, and ignition of large scale prefronto -parietal networks.*
*A recent study showed that awareness of a visual target is associated with a degradation of the modularity of the brain's functional networks and an increase in inter-modular functional connectivity and thus strengthening the case for global changes in connectivity driving awareness (***Godwin et al, 2015***).*

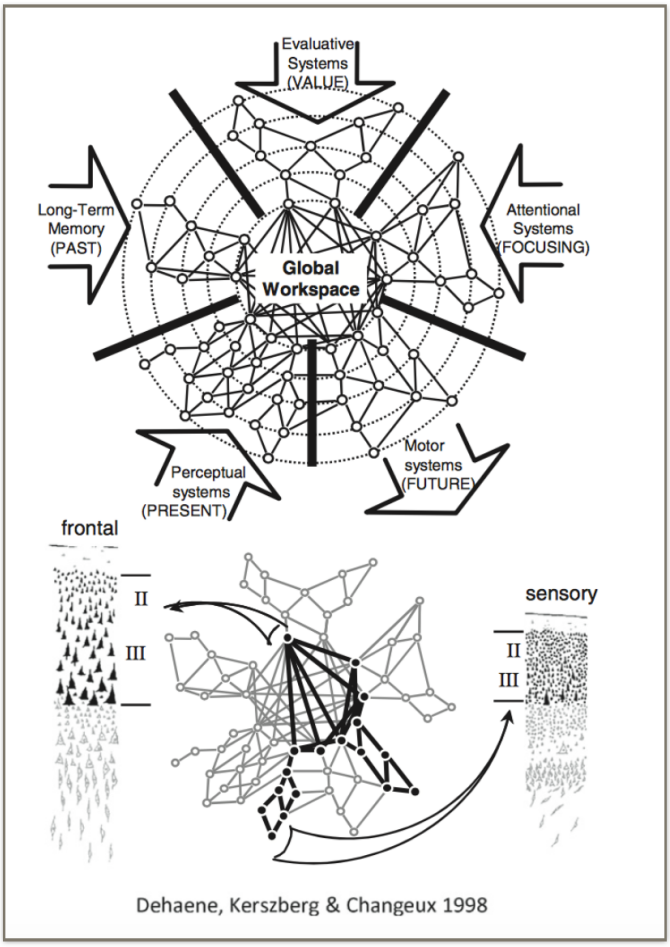


Fig. 6a Global Neuronal Workspace Model
*T*he global neuronal workspace (GNW) hypothesis (right) proposes that associative perceptual, motor, attention, memory, and value areas interconnect to form a higher-level unified space where information is broadly shared and broadcasted back to lower-level processors. The GNW is characterized by its massive connectivity, made possibly by thick layers II/III with large pyramidal cells sending long-distance cortico-cortical axons, particularly dense in prefrontal cortex (**Dehaene et al., 1998**)

These studies are consistent with theoretical models of conscious processing, including the Global Neuronal Workspace (GNW) model according to which conscious access occurs when incoming information is made globally available to multiple brain systems.

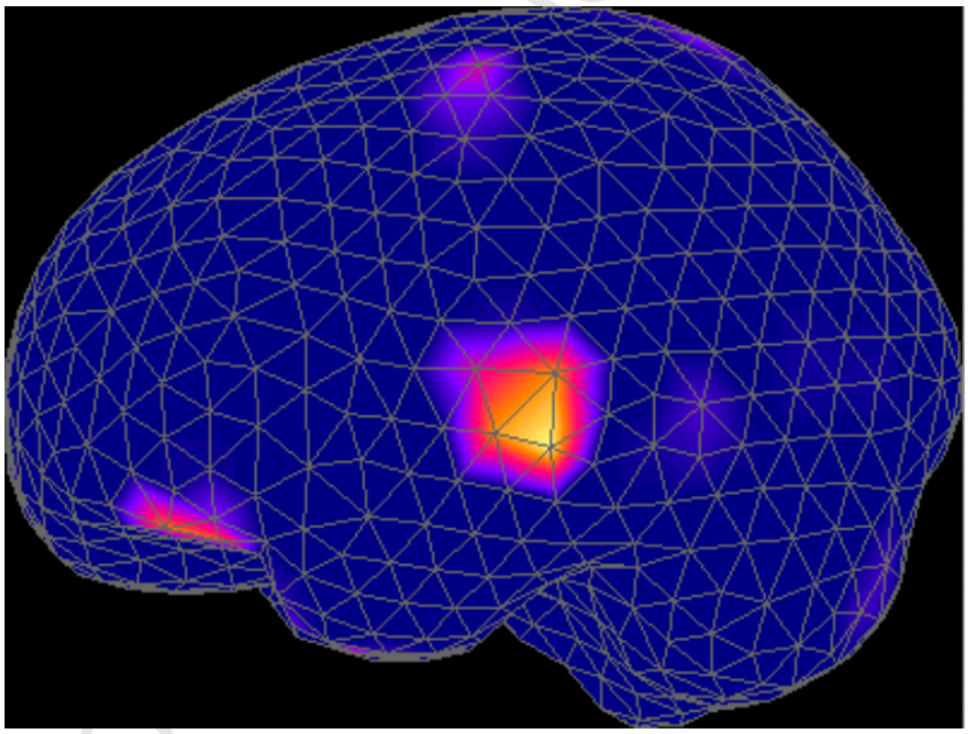


Fig. 6b The Global Access Hypothesis:
conscious contents evoke widespread brain activation, as proposed by Global Workspace Theory
From Baars and Franklin (2007)

There is now a sizable body of evidence to support the GWT hypothesis that conscious, but not unconscious, brain events evoke widespread cortical activity related to the reportable content1 (Baars 2002; Dehaene, 2002).

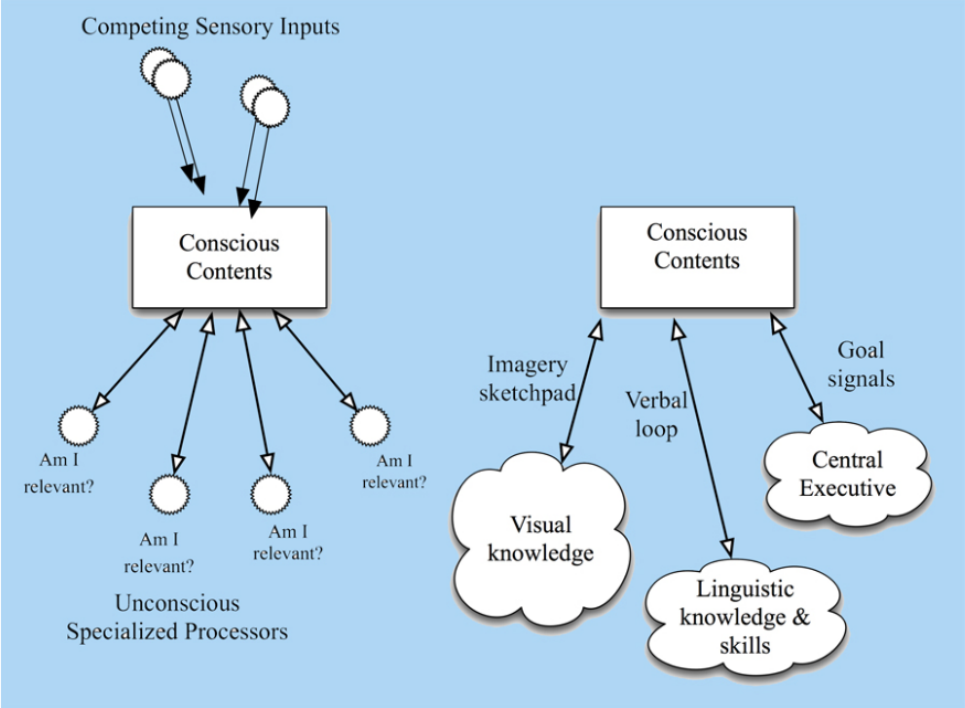


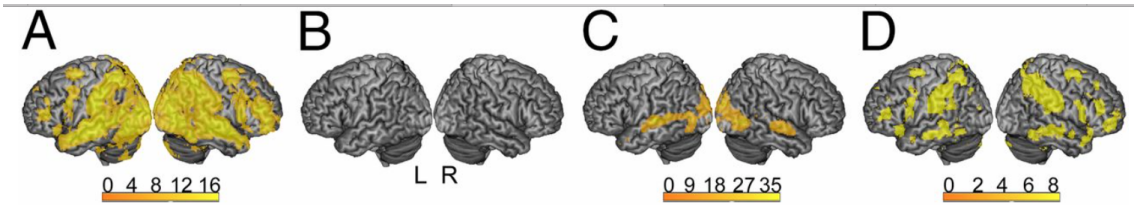
Fig. 6c Global Workspace Theory integrates conscious contents with unconscious distributed expertise in the brain. Notice the radically distributed nature of the architecture, with the exception of functions supported by consciousness, including action planning. On the left is a simplified GWT model from Shanahan (2006). Notice that the small white circles, representing unconscious processors, constantly search conscious for (globally distributed) messages that are relevant to them, somewhat like humans listening for air flight announcements. The right side shows how GWT suggests that cognitive Working Memory may be mobilized by brief conscious access to perceptual input, rehearsed words or digits, output decisions, and other conscious events. Notice that WM components like verbal rehearsal have both conscious and unconscious aspects. The details of language, perceptual processing and storage are handled "off line" by unconscious distributed processors. Only the contents of the GW need to be conscious, as assessed by accurate reportability. (Baars, 1988, 2002)

The Global Workspace Theory was originally formulated by **Baars (1997)** and has been able to accommodate an increasing number of empirical findings. Dehaene's group has recently compared resting- state brain activity and dynamical functional connectivity with functional MRI under conditions of anesthesia and wakefulness. Under anesthesia, the more frequent functional connectivity patterns inherit the structure of anatomical connectivity, exhibit fewer small-world properties and lack negative correlations (**Dehaene and Changeux, 2011**).

Conversely,wakefulness is characterized by the sequential exploration of a richer repertoire of functional configurations, often dissimilar to anatomical structure, and comprising positive and negative correlations among brain areas (**Barrtfeld et al, 2015**). They conclude that these results reconcile theories of consciousness with observations of long-range correlation in the anesthetized brain and show that a rich functional dynamics might constitute a signature of consciousness, with potential clinical implications for the detection of awareness in anesthesia and brain-lesioned patients. Experiments on visual perception using binocular rivalry show that the onset of a new conscious percept coincides with the emergence of a new gamma-synchronous neuronal assembly locked to an ongoing theta rhythm, suggesting that oscillatory networks linking relevant cortical regions are critical for furnishing consciousness for the percept (Doesburg et al, 2009). The "perception" and monitoring of one's own cognitive metacognition), a hallmark of conscious awareness, has been shown in an error detection paradigm to involve brain mechanisms distinct from more automated and unconscious mental processes (**Charles et al, 2013**). Recently, differential oscillatory coupling of prefrontal, parietal and parahippocampal cortices has been shown to mediate temporal versus spatial components of episodic memory (**Watrous et al, 2013**).

The conscious processing of mathematical expressions has been traced with fMRI and Magneto-Encephalography (MEG) suggesting that mathematical syntax becomes compiled into visual-spatial areas in trained mathematicians (Maruyama et al, 2012). Watching an engaging movie and following a suspenseful plot requires brain areas supporting executive functions as the current features of the movie are compared with

stored knowledge of the world, which are synchronized across individuals (**Fig. 7**) and can be probed without relying in verbal ("first person") reports or behavioral observations (**Naci et al, 2014**). When participants attended to naturalistic stimuli evolving meaningfully over time, akin to real-world events—such as those present in a plot-driven movie they displayed highly synchronized brain activity in supramodal frontal and parietal regions, which support executive functions. The movie's executive demands drove brain activity in in frontal and parietal regions and, further, that the synchronization of this activity across individuals underpinned their similar experience.
The awareness of a visual target is associated with a degradation of the modularity of the brain's functional networks brought about by an increase in inter modular functional connectivity. This result has been interpreted as evidence that awareness is associated with global changes in brain functional connectivity (**Godwin et al, 2015**) and may be



consistent with the Global Neuronal Workspace (GNW) model (Newman and Baars,

Fig. 7 ***Synchronizing Brains during Shared Conscious Content***

Brain-wide synchronization of neural activity across subjects. (*A*) Movie viewing elicited significant ($P < 0.05$; FWE cor) cross-subject correlation across the brain. (*B*) No cross-subject correlation was observed in the resting state. (*C*) The scrambled movie elicited significant ($P < 0.05$; FWE cor) cross-subject correlation only within primary and association visual and auditory cortex; none was observed in higher-order, supramodal cortex. (*D*) The intact movie elicited significantly ($P < 0.05$; FWE cor) more cross-subject correlation than the scrambled movie bilaterally in parietal, temporal, motor, and dorsal/ventral frontal/prefrontal cortex. Warmer colors depict higher *t* values of cross-subject correlation.

Naci et al (2014)

Please review these lectures for a detailed discussion of theory of consciousness.

Video Lecture 18.1: Consciousness: Where In The Brain
Video Lecture 18.2: Consciousness: Ignition in the Global Workplace
Video Lecture 18.3: Consciousness: Consciousness during Dream States
Video Blog 10: Consciousness and Psychedelics

Other theories of consciousness

1. The "attention schema theory"

(Graziano and Kastner, 2011; **Kelly et al, 2014**; Graziano, 2013; **Graziano, 2014**; Graziano and Webb. 2014)

Hypothesis: Awareness is a perceptual model of attention.
There three components to consider in this theoretical approach:
1. ***Attention*** *is a selection process by which some signals in the brain are enhanced in strength at the expense of other, competing signals. The boosted signals have a bigger impact on downstream systems. Those signals are more deeply processed, more likely to be stored in memory for later use and more likely to alter behavioral output. Selective signal enhancement has evolved for 520 to 600 million years (Graziano and Webb, 2014).*
2. ***Internal Model*** *, for example a control model constructed by the brain is the body schema. Regions of the brain spanning the somatosensory system, the visual system, and the motor system, integrate many sources of information to construct an internal model or simulation of the body. The body schema in intrinsically inaccurate , like a cartoon sketch. The same principles evident in the body schema are theoretically transferrable to an attention schema. Because a brain has a need to control its own attention, theoretically it aught to construct a model of attention, or an attention schema.*
That model should be a constantly updated description of what attention is, what it means for a brain to attend to something, what the possible consequences of attention are, and what signals in particular are the focus of attention at the moment.
To control attention, in control theory, there aught to be an internal model of it, or an attention schema. That attention schema would necessarily leave out the physical details. It would depict a state of knowing that is non-physical, without mechanism. And higher cognition would be captive to that internal model. The creature would be certain that it has subjective awareness and would have no basis for understanding the true source of that certainty. The theory explains how a brain can arrive at the conclusion that it is aware of something without ever knowing that is has arrived at a conclusion or that the conclusion conclusion derives from computation.
3. **Social cognition and self awareness :** *Humans have neuronal machinery that apparently contributes to constructing models of other people's minds. In this hypothesis, consciousness is not an emergent property, or a metaphysical emanation, but is itself information computed by an expert system. If consciousness is associated with a global workspace, or a bound set of information that spans many cortical areas then in the*

*present proposal the awareness ingredient added to that global information set is provided by the machinery for social perception (**see* **Fig. 1**). *In specific, awareness is proposed to be a rich descriptive model of the process of attention.*
Like most informational models in the brain, it is not a literal transcription of the thing it represents. It is a caricature. It exaggerates useful, need-to-know information. Its purpose is not to provide the brain with a scientifically accurate account of attention, but to provide useful information that can help guide behavior.

2. The Insula : a critical structure mediating human awareness?
(Craig, 2011; **Craig, 2009**; **Craig, 2010)**

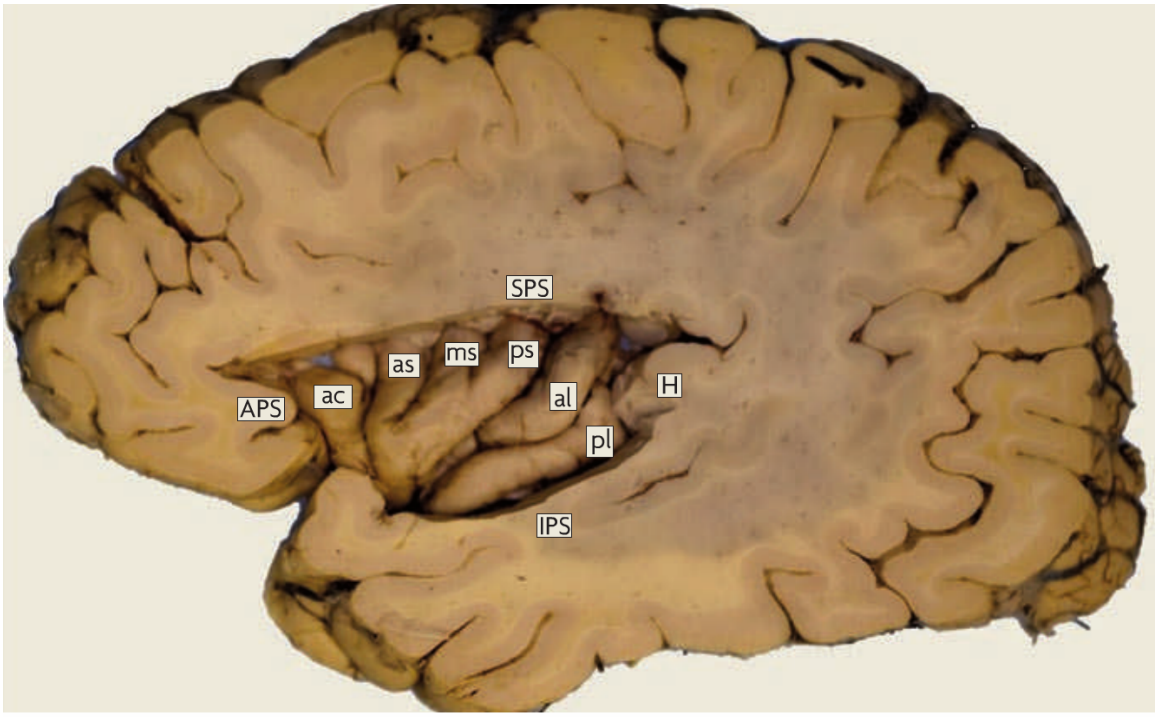


Fig. 8 Left Insular Cortex
APS; anterior peri-insular sulcus; **H**, Heschl's gyrus; **IPS**, inferior peri-insular sulcus, **ms,** middle short insular gyrus; **ps**, posterior short insular gyrus; **pl**, posterior long insular gyrus; **SPS,** superior peri-insular gyrus.
Craig (2009) noted in the most cited review article for the year 2009 in Nature Neuroscience Reviews *(* **Luo et al, 2010***)* that hundreds of functional imaging studies reported the activation of the anterior insula (and the anterior cingulate) and proposed that the *anterior insular cortex is implicated in a wide range of conditions and behaviors, from bowel distentions and orgasm, to cigarette craving and maternal love, to decision making and sudden insight* and suggested a role for the AIC (and the von Economy neurons in this area) in awareness and as a correlate of *and sudden insight* and suggested a role for the AIC (and the von Economy neurons in this area) in awareness and as a correlate of consciousness.

This paper was an extension of a highly cited review (Craig, 2002) describing a phylogenetically novel pathway to the primate insular cortex that provides a homeostatic sensory representation of the physiological conditions of the body and that leads to re-representation in the anterior insula that underlie human awareness.

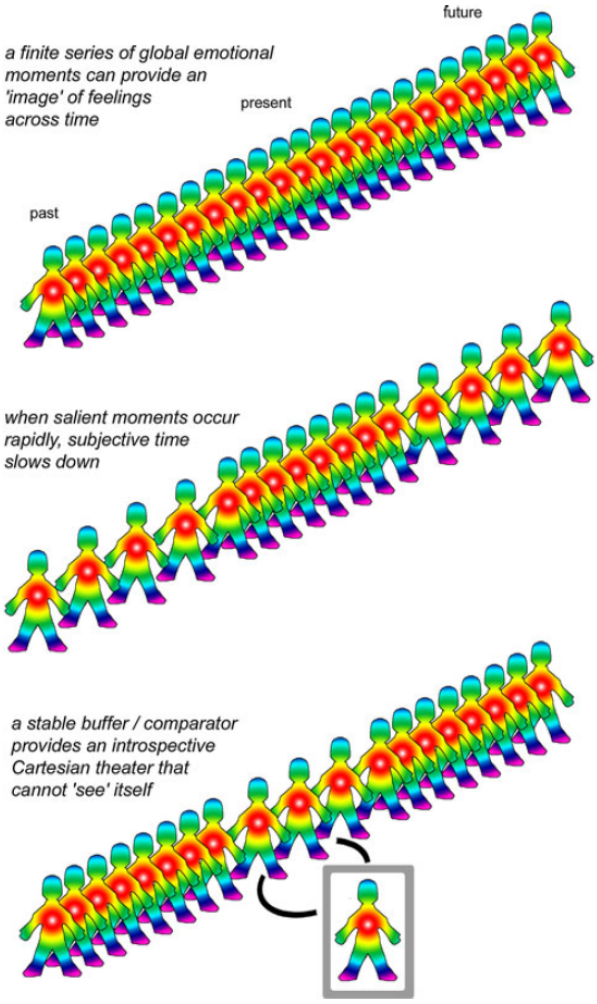


Fig. 9 (Craig, 2010)
A cartoon illustrating the cinemascopic model of awareness on time-shifting global emotional moments (top), which can subjective dilation of time (middle), and which provides a possible basis for subjectivity with a comparator buffer (bottom) that be loaded with the present global emotional moment for with any other from the past or future, but which is one tick behind when compared with the present moment compared with the present moment.

The representational image of the body's state provides a neural basis for distinguishing self from non-self, and re-representations of this image enable the behavioral neural agent to project the effects of possible actions onto the state of the body, as well as the resultant changes in such feeling states due to interactions with other (external) agents. This hypothesis posits that degrees of conscious awareness are related to successive upgrades in the self-representational maps (Churchland, 2002). **The anatomical features of Damasio's (Damasio, 1994) hypothesis include a central role for the anterior insular cortex in the representation of such feeling states.**

Dr. Grazino discusses his "Attention Schema Theory" of consciousness

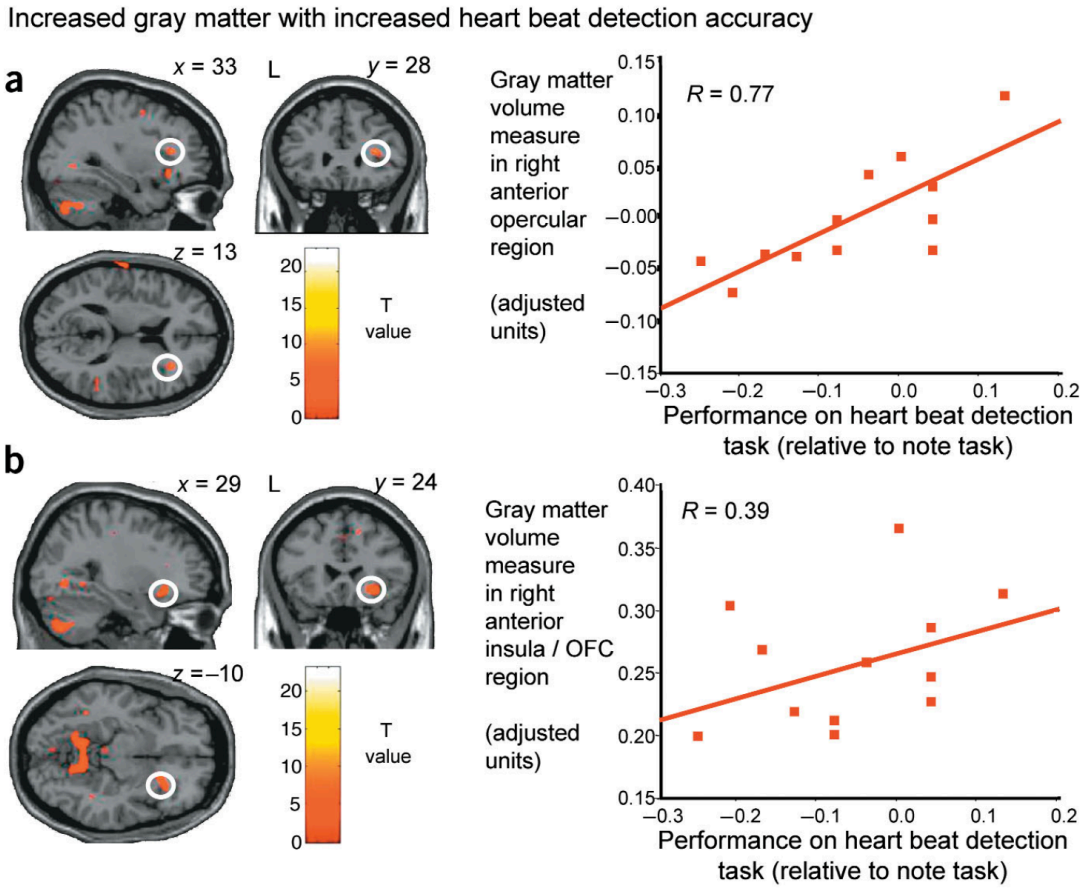
The Integrated Information Theory of Consciousness

Giulio Tononi discusses his ITT theory of consciousness

Morphometric (gray matter) correlates of interoceptive sensitivity.

(a, b) Voxel-based morphometry was used to determine the relationship between regional grey matter volume and interoceptive sensitivity (relative to heart beat detection accuracy),highlighting effects in

(a) right anterior insula operculum and (b) right orbitofrontal cortex



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Constraints on the concept of Free Will

My first act of free will shall be to believe in free will (William James)

*Whereas Cartesian duality, at least superficially, provides a nice mechanism whereby one could entertain the concept of free will, belief in this mechanism among scientists has ostensibly disappeared. However, if we no longer entertain the luxury of a belief in the "magic of the soul," then there is little else to offer in support of the concept of free will (**Cashmore, 2010**).*

Many of our intuitive common- sense ideas and strongly held beliefs have proven to be wrong or inadequate in describing nature and our place in it. The human brain is adapted to process only a very limited spectral bandwidth of electromagnetic radiation and sound waves. Our experience of space and time is limited by our embodied cognition (Lakoff and Johnson, 1999). For example, the findings of Special and General Relativity are not intuitively obvious to us. Likewise, the results of quantum mechanics, a theory empirically verified to unprecedented precision, demonstrate deeply counter-intuitive events such as entanglement ("spooky action at a distance"), and events traveling backwards in time, among others, which can be captured by mathematical formalisms but not visualized or truly understood by the human mind/brain. The philosophical interpretation of the implications quantum mechanics remains unsettled since the Copenhagen interpretation of Niels Bohr (1935), and Feynman (1965) has claimed that "nobody understands quantum mechanics". However, our lack of capacity to "understand" these issues did not prevent us from building the electronics industry, which is based on the foundation of quantum mechanics, or using GPS satellites, which would be quite inaccurate without invoking the concepts and mathematics of Einstein's relativity. empirically verified to unprecedented precision, demonstrate deeply counter-intuitive events such as entanglement ("spooky action at a distance"), and events traveling backwards in time, among others, which can be captured by mathematical formalisms but not visualized or truly understood by the human mind/brain. The philosophical interpretation of the implications quantum mechanics remains unsettled since the Copenhagen interpretation of Niels Bohr (1935), and Feynman (1965) has claimed that "nobody understands quantum mechanics". However, our lack of capacity to "understand" these issues did not prevent us from building the electronics industry, which is based on the foundation of quantum mechanics, or using GPS satellites, which would quite inaccurate without invoking the concepts and mathematics of Einstein's relativity.

The subjective experience of Free Will is deeply imbedded in our concept of ourselves, and how we function in the world. The increased penetration of neuroscience into the

culture has done little to change this. In fact, the suggestion that the diffusion of neuroscience will erode belief in free will therefore appears unsubstantiated.

Deterministic ideas collide with deeply entrenched cultural understandings of Individual responsibility and self-control, and as yet little evidence suggests that these values will buckle under the pressure. Indeed, it seems more likely that neuroscientific information is being co-opted into these value systems, rejuvenating them and driving them forward within superficial reframings (O'Connor and Joffe, 2013) People are quite invested in the idea of free will and generally believe that the tenets of free will apply more in their own lives than in the lives of others (Pronin and Kugler, 2010) An exaggeration of the sense of personal agency may even be a hallmark of mental health (Taylor and Brown, 1988) but may also lead people to illusions of control and magical beliefs that their will is influencing the outcome of events (Langer, 1975; Matute, 1996; Pronin et al, 2006). Wegner has suggested an explanation for the apparent mental causation based on the idea that Free Will is an experience arising from interpreting one's thoughts as the cause of actions whether or not a causal relationship exists (Wegner, 2002; Ebert and Wegner, 2011).The philosophical debate about free will is ongoing.

Neuroscience places significant constraints on the common sense notion of free will. We will present the viewpoint that in a physicalist model of reality Free Will as commonly understood may well an illusion created by our brain. Haynes (2011) offered this:*the subjective experience of Free Will is deeply imbedded in our concept of ourselves, and how we function in the world. The increased penetration of neuroscience into the culture has done little to change this. In fact, the suggestion that the diffusion of neuroscience will erode belief in free will therefore appears unsubstantiated.*

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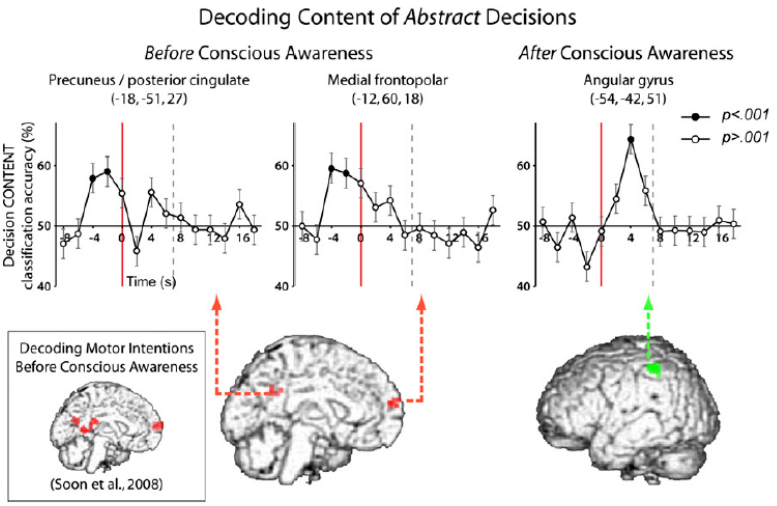
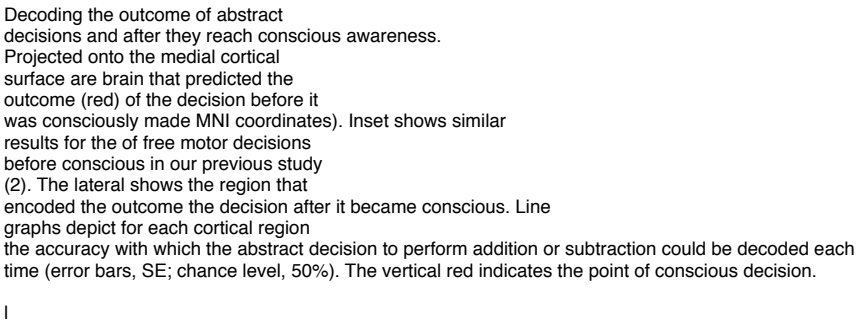


understood may well an illusion created by our brain.

Fig. 10
(Soon et al, 2013)



Decoding the outcome of abstract
decisions and after they reach conscious awareness.
Projected onto the medial cortical
surface are brain that predicted the
outcome (red) of the decision before it
was consciously made MNI coordinates). Inset shows similar
results for the of free motor decisions
before conscious in our previous study
(2). The lateral shows the region that
encoded the outcome the decision after it became conscious. Line
graphs depict for each cortical region
the accuracy with which the abstract decision to perform addition or subtraction could be decoded each
time (error bars, SE; chance level, 50%). The vertical red indicates the point of conscious decision.

I

*This belief in the freedom of decisions is fundamental to our human self-concept. It is so strong that it is generally maintained even though it contradicts several other core beliefs. For example, freedom appears to be incompatible with the nature of our universe. The deterministic, causally closed physical world seems to stand in the way of "additional" and "unconstrained" influences on our behavior from mental faculties that exist beyond the laws of physics. Interestingly, in most people's (and even in some philosophers') minds, the incompatible beliefs in free will and in determinism coexist happily without any apparent conflict (*Haynes, 2011).

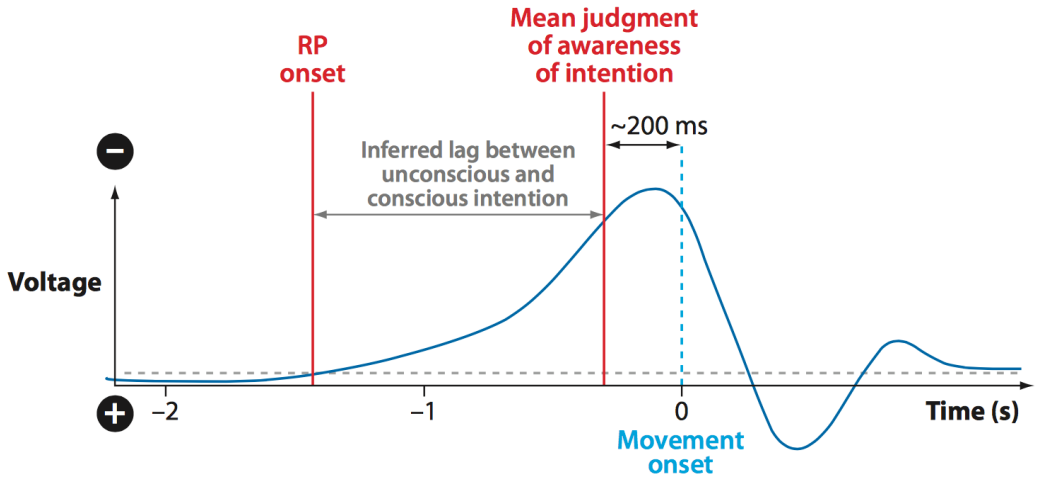


Fig. 11 *Schematic results of Libet's findings (**Libet et al, 1983**). On average, neural signals in the motor areas of the brain preceding finger movement (RP) begin more than 1 s before movement onset, whereas awareness of intending the movement, by contrast, is reported to be only ~200 ms before movement onset.*

(Roskies, 2010)

One reason why most people don't perceive this conflict might be that our belief in freedom is so deeply embedded in our everyday thoughts and behavior that the rather abstract belief in physical determinism is simply not strong enough to compete.

The first landmark study of the brain in the process of engaging in a free will transaction conducted by Libet et al (1983) revealed that the brain initiates preparatory electrophysiological for motor behavior 500 milliseconds before the subject reports first becoming aware of the wish to perform the behavior. The implications of this result proved difficult to accept for many, including Libet (1999) who while admitting that "initiation of the freely voluntary act appears to begin in the brain unconsciously, well before the person consciously knows he wants to act", provides an escape hatch by suggesting that during the 100 msec immediately preceding the motor act, "conscious will might block or veto the process, so that no act occurs." The Libet study has been criticized for its experimental limitations. However, more recent experiments using fMRI scans have confirmed the original findings and demonstrate that the outcome of a decision can be encoded in neuronal activity of the frontal and parietal cortex up to 10 seconds before it enters conscious awareness (**Soon et al, 2008**). This finding was replicated, demonstrating that motor intentions were encoded in frontopolar cortex up to seven seconds before participants were aware of their decisions, and the characteristic patterns became more stable with increasing temporal proximity to the conscious decision. This supported the conclusion that the frontopolar cortex is part of a network of brain regions that shape conscious decisions long before they reach conscious awareness

(Bode et al, 2011). More recently it was shown that the outcome of a free decision to either add or subtract numbers can already be decoded from neural activity in medial prefrontal and parietal cortex 4 s before the subjects reported that they were consciously making their choice (**Fig 7**) indicating that unconscious preparation of "free choices" at multiple scales of abstraction evolve from the dynamics of preceding brain activity (**Soon et al, 2013**).

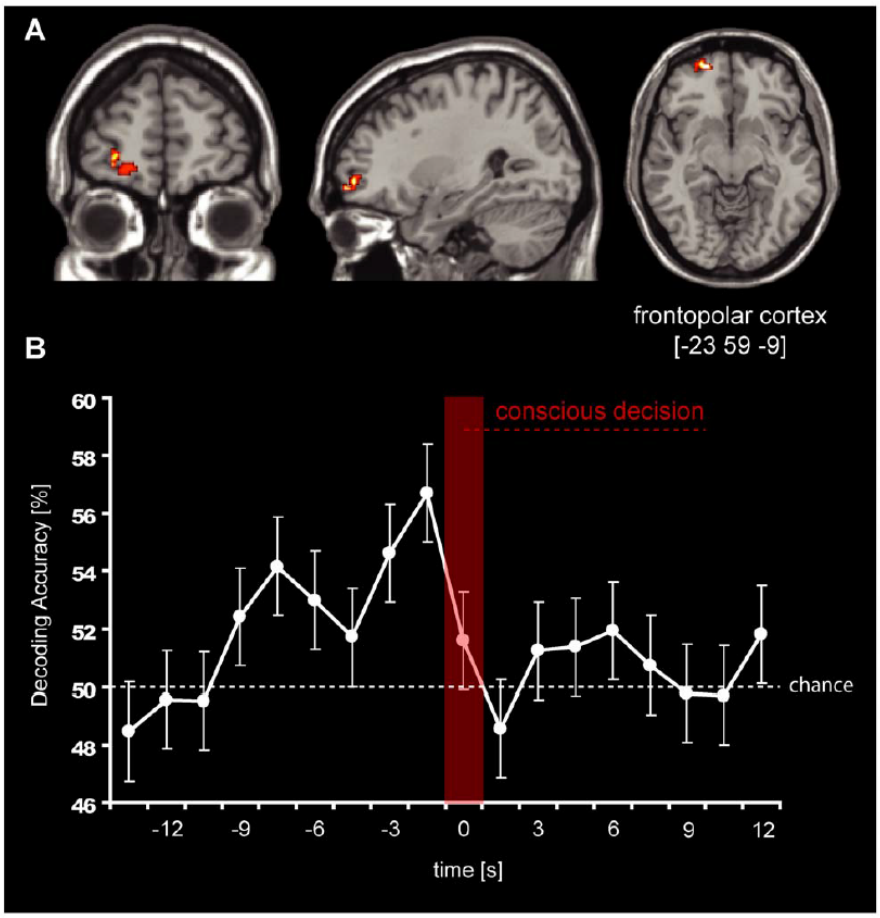


Fig. 12 (Bode et al, 2011)
Decoding of upcoming motor decisions from frontopolar cortex.

A) The figure displays a region in left frontopolar cortex from which decoding was possible significantly above chance (50%) using a threshold of $p<.05$ (FDR corrected; voxel-threshold 5 voxels).
FPC only showed significant decoding accuracies in the time-bins preceding the decision.
B) The graph displays the average time-course of decoding, taken from the central voxel of the searchlight cluster that showed the highest decoding accuracy. Error bars represent standard errors. time-bin of the conscious intention is indicated by the red bar and is labelled as time. Time-points preceding the conscious awareness of the are labelled as negative numbers (units = seconds, relative to decision); time-points following the decision are therefore. One time bin to 1.5 s.

Further Reading:

DM Wegner, The Illusion of Conscious Will. MIT Press 2002

Video Blog 1: The experience of free will: an illusion?

Phenomenal Experience and Qualia

*We also maintain that previously argued categories such as selfhood and phenomenal experience can be explained biologically in terms of patterns of neural activity (**Edelman et al, 2011**)*

Imagine a group of scholars in the early 17th century, debating the process that purifies white light and rids it of all colors. They'll never arrive at a scientific answer. Why? Because despite appearances, white is not pure. It's a mixture of colors of the visible spectrum, as Newton later discovered. The scholars are working with a faulty assumption that comes courtesy of the brain's visual system. The scientific truth about white (i.e., that it is not pure) differs from how the brain reconstructs it.How does the brain go beyond processing information to become subjectively aware of information? The answer is: It doesn't. The brain has arrived at a conclusion that is not correct. When we introspect and seem to find that ghostly thing — awareness, consciousness, the way green looks or pain feels — our cognitive machinery is accessing internal models and those models are

*providing information that is wrong. The machinery is computing an elaborate story about a magical-seeming property. And there is no way for the brain to determine through introspection that the story is wrong, because introspection always accesses the same incorrect information. is captive to those internal models. Such a brain would inescapably conclude it has subjective experience (**Graziano, 2014**).*

Qualia , or "what it is like to have the experience" of the color red, or "of being a bat" **(Nagel,1974**), have long been evoked as the major stumbling block for a physicalist theory of consciousness (Chalmers, 1996). How is it possible to reduce the Qualia of the rich sonority of the Quartetto Italiano playing a Beethoven string quartet into mere physical representation? Consider a digitized recording of this performance of the music on compact disc. It does not reveal the phenomenological content of its information until it is played back on an appropriate system of digital to analog converters, amplifiers and speakers. **Ramachandran and Hirstein (1998)** have pointed out that we will , of course, never have the experience of being a bat , "the qualia produced by the bat's radar system along with everything else in its conscious life, which Nagel claims we cannot know", because our mental life is completely different from that of a bat.

The authors go on to suggest a thought experiment involving a rod monochromat (color blind) scientist who studies the brain of a normal color perceiver and arrives at a complete understanding of physical events from the photoreceptors to that neural activity that generates the report "red." Despite his complete understanding of the molecular and neural events, the scientist will not have the experience of "red" until he connects a cable from the area V4 of a normal color perceiver and connects it to the same area in his brain, bypassing his eyes (which are missing the appropriate cone cells). Therefore, it is in principle possible to experience another person's qualia.

This thought experiment was meant to drive home the point that an appropriate "play back" system is required to instantiate the phenomenal experience of sensory input and was not recommended for experimental verification by the authors. However, we have come a long way since 1997 when this idea was published. Very recently a brain- to-brain interface (BTBI) has been described that enabled behaviorally meaningful real time transfer of sensorimotor information between the brain of two rats (**Pais -Viera et al, 2013**). Patterns of cortical sensorimotor signals coding for a particular behavioral response were recorded by microelectrode arrays from the "encoder" rat and transmitted directly via intracortical microstimulation to the "decoder" rat. Pairs of rats fitted with this BTBI cooperated to achieve a common behavioral goal. The authors observed drastic changes in the behavior of the encoder and decoder rats as soon as they started to work as part of a dyad and concluded that operation of a BTBI by an encoder-decoder rat dyad allowed decoders to rely exclusively on neuronal patterns donated by encoders in order to produce the encoder's behavioral choice. Although we cannot verbally interrogate the rats involved in these experiments, we may hypothesize that the qualia, or "what it is like being a rat involved in the specific sensorimotor behavior" , have been transferred from the encoder rat to the decoder rat by physical means.

Edelman (2003) naturalizes qualia and broadens their range from an evolutionary perspective by invoking the following sequence:1. *consciousness evolved in concert with the evolution of neural systems that are able to integrate a very large number of sensory*

inputs and motor responses occurring in parallel; 2. these systems connect sensory inputs with memory and imagery allowing thereby for learning and optimization future behavior and 3. consciousness consists of qualia, by which I mean not just isolated submodalities of red, warm, etc., but also complex scenes, memories, mages, emotions; indeed, the entire rich panoply of subjective experience. If, as I have suggested, the neural systems underlying consciousness arose to enable high order discriminations in a multidimensional space of signals (Edelman and Tononi, 2000)), ***qualia are those discriminations****. Differences in qualia correlate with differences in the neural structure and dynamics that underlie them. Thus, for example, olfactory neurons and their circuits differ from retinal neurons and circuits, and such differences seem sufficient to account for differences in their respective qualia.*

He counters the complaint that no scientific description can provide the actual phenomenological experience of qualia quite definitively: to expect that a theoretical explanation of consciousness can itself provide an observer with the experience of ''the redness of red'' is to ignore just those phenotypic properties and life history that enable an individual animal to know what it is like to be such an animal. A scientific theory cannot presume to replicate the experience that it describes or explains; a theory to account for a hurricane is not a hurricane.

Qualia have been considered "private" first person experiences and therefore assigned to an ontological class different from phenomena that can be studied with the quantitative methods of science. The experience of pain is often cited as an example of such private phenomenal experience. A recent study using fMRI has extracted a neurological signature primarily derived from thalamus, the insula, anterior cingulate cortex and periaqueductal grey matter that predicts pain intensity at the level of the individual person. It discriminates between pain and non-painful warmth with 93% sensitivity and specificity and between physical pain and social pain with 85% sensitivity and 73% specificity (**Wager et al, 2013**).

Other "private" mental states such as visual perceptions, covert attitudes and lying can also be decoded from multivariate analysis of fMRI data (**Haynes and Rees, 2006**). Continuous and subject- driven free streaming cognitive states (James, 1918) can now be "decoded" using whole brain functional connectivity analysis **(Shirer et al, 2012**). The content of visual imagery during dreams, perhaps the most private phenomenal experience, can be predicted by neural decoding using fMRI in association with machine learning strategies, demonstrating that visual experience during sleep shares brain activity patterns that are generated also by stimulus perception and allowing the uncovering of the subjective content of dreaming (**Horikawa et al, 2013**).

Further Reading:

Graziano MSA, Consciousness and the Social Brain. Oxford University Press 2013

Damasio A, Looking for Spinoza. Harcourt INC

The Self and the Soul

Suppose the mind to be reduced even below the life of an oyster. Suppose it to have only one perception, as of thirst or hunger. Consider it in that situation. Do you conceive of anything but merely that perception? Have you any notion of self or substance? If not, the addition of other perceptions can never give you that notion (Hume, 1888).

*The brain's earliest self-representational capacities arose as evolution found neural network solutions for coordinating and regulating inner-body signals, thereby improving behavioral strategies…Brains manipulate inner models to predict the distinct consequences in the external world of distinct behavioral options. The self thus turns out to be identifiable not with a nonphysical soul, but rather with a set of representational capacities of the physical brain (**Churchland, 2002**).*

The concept of self is used in many contexts, and its meaning covers a wide range of definitions and ideas. Hume (1888) approaches this confusion by atomizing the content of consciousness and in the process eliminating any notion of a reified self
The brain generates at set of illusions, one of which is the experience of the self. Descartes first devised the thought experiment of the "evil demon" that creates a pervasive illusion that we mistake as our experiences and thoughts, anticipating The Matrix motion picture. The experience of the self may be the result of a "self-model" produced by the brain **(Metzinger, 2003**) suggesting that "no such things as selves exist in the world: nobody ever was or had a self."
What we consider to be our Self appears to be the phenomenological manifestation of neuronal networks involved in the regulation of positive vs. negative emotional states which have evolutionary roots. We are able, however, to engage in self referential mental activity.

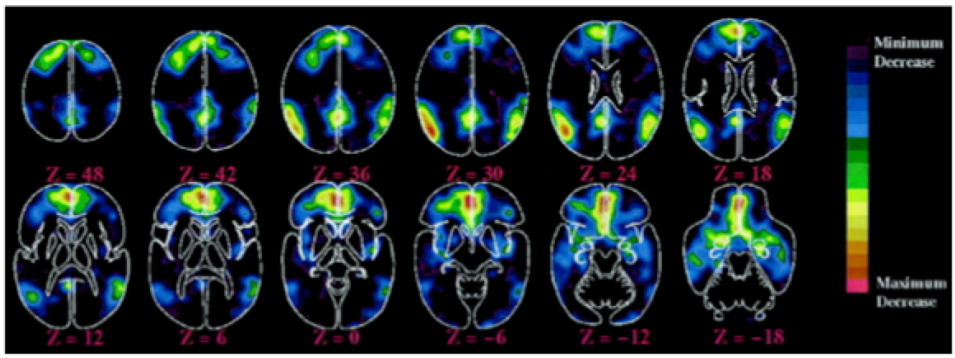
When subjects are asked to evaluate whether a visual scene evoked a pleasant or unpleasant feeling, an increase in metabolic activity (and by inference neuronal activity) in their medial prefrontal cortex (MPFC) is observed (Gusnard et al, 2001). This midline brain region is part of the default mode network (DMN) which is deactivated during non-referential goal-directed tasks (Raichle et al, 2001). Depressed patients show increased stimulus- induced activity in the DMN, and fail to down-regulate this circuit during reappraisal of the stimulus. This suggests that focus on the Self may have adverse consequences for emotional regulation and the ability to engage in cognitive tasks that require a deactivation of the DMN **(Sheline et al 2009**). Conversely, treatment of depressed individuals with antidepressant medication normalizes the DMN (**Posner et al, 2013**).

Mind wandering has been described as a *specific form of mental autonomy loss* and that during t*wo thirds of our conscious life-time we do not possess mental autonomy*

The Self

*The normal conditions, we spend 30–50% or our conscious waking lives mind wandering. It is empirically plausible to assume that a considerable part of our own cognitive phenomenology simply results from a frequent failure of executive control (***Metzinger, 2013***).*

Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks.



Raichle M E et al. PNAS 2001;98:676-682

Fig. 13 ***The discovery of the Default Mode Network (*****Raichle et al, 2001*****)***

Self-evaluation is fraught with illusional distortions which probably are adaptive, such as optimism bias and illusions of control (Taylor and Brown, 1988). The cognitive bias of "superiority illusion", judging oneself as being superior to average people in various desirable traits, may be evolutionarily selected (Johnson and Fowler, 2011) and has been *l*inked to resting-state functional connectivity between MPFC and the striatum regulated by inhibitory dopaminergic neurotransmission (**Yamada et al, 2013**).
The activity of the self-referential network can be down-regulated over time and its connectivity to other brain areas can be modified (**Brewer et al, 2011**) by meditation, a form of meta awareness used in Buddhist practice to loosen the grip of the illusionary self from the functioning of the mind/brain and thereby alleviating suffering. A much more rapid and dramatic decrease in DMN activity can be achieved by administration of psilocybin (**Carhart-Harris et al, 2012**).

Mind wandering in the absence (a) and presence (b) of meta-awareness.

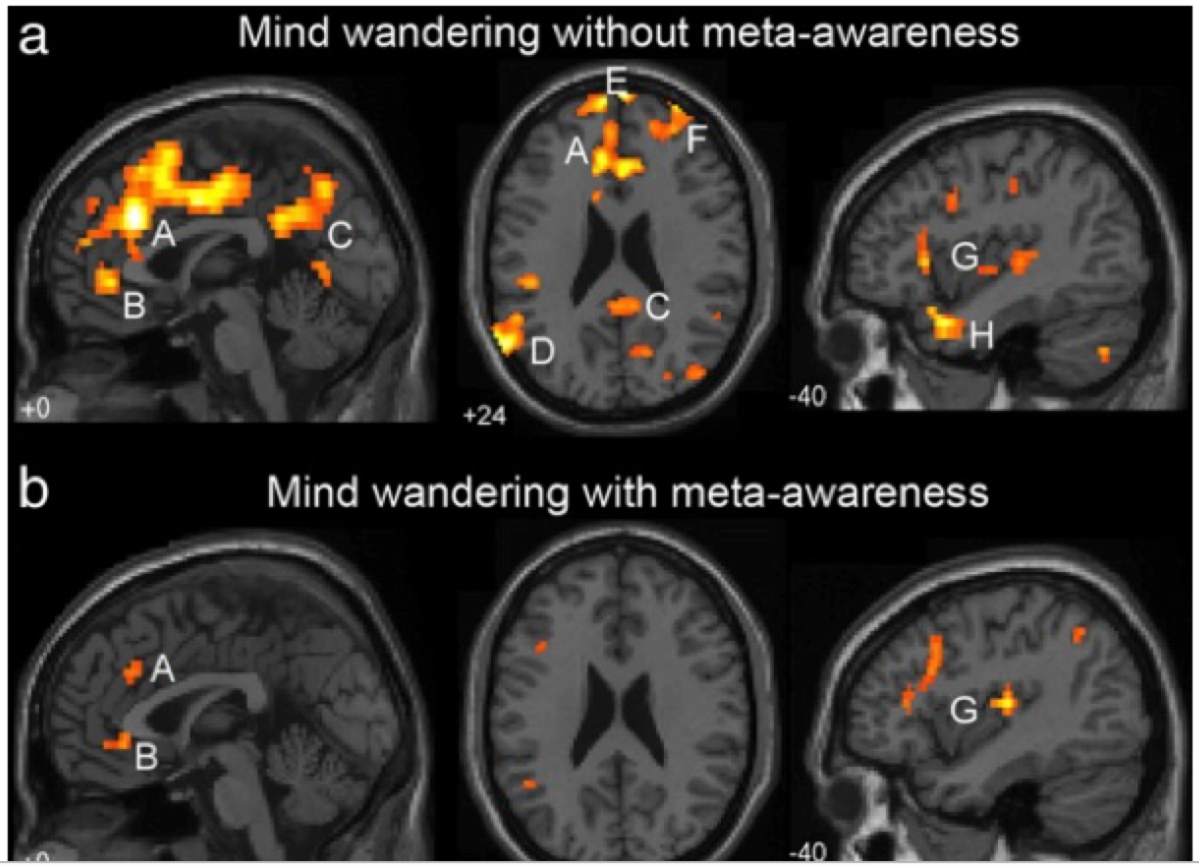


Fig. 13

a) Regions of activation associated with mind wandering in the absence of awareness (intervals prior to off-task unaware vs. on-task awareness (intervals prior to off-task unaware vs. on-task probes) included : (A) Dorsal ACC(BA32), (B)Ventral ACC(BA32), (C) Precuneus (BA 7), (D) Temporoparietal junction (BA39), E) Dorsal Rostromedial PFC (BA 10), (F) Right Rostrolateral PFC (BA 10), (G) Posterior and Anterior Insula, and (H) Bilateral Temporopolar Cortex. (b) Similar regions were activated during mind wandering with awareness (intervals prior to of-tasks vs. on -task probes), but to a lesser degree, including : (A) Dorsal ACC (BA32), (B) Ventral ACC (BA24/32), and (G) Posterior and Anterior Insula.

Functional brain networks defined with resting-state functional magnetic resonance imaging have been recapitulated by using measures of correlated gene expression in a post mortem brain tissue data set. A set of 136 genes, significantly enriched for ion channels showed polymorphisms, which significantly affect resting-state functional connectivity in a large sample of healthy adolescents. Expression levels of these genes were also significantly associated with axonal connectivity in the mouse. The results

provide convergent, multimodal evidence that **resting-state functional networks correlate with the orchestrated activity of dozens of genes linked to ion channel activity and synaptic function** (**Richiardi et al, 2015**).

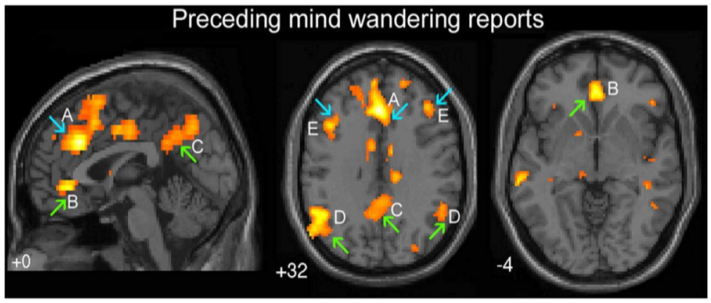


Fig. 14

Activations preceding reports of mind wandering

(intervals prior to off-task versus-task probes). Upward green arrows, default network regions; green arrows, default network regions; downward blue arrows, executive network regions.

Regions of activation: (A) dorsal ACC (BA 32), (B) ventral ACC (BA 24/32), (C) precuneus (BA 7) (D) bilateral temporoparietal junction (BA 39), and (E) bilateral DLPFC (BA 9).

Mind wandering has been described as a *specific form of mental autonomy loss* and that during t*wo thirds of our conscious life-time we do not possess mental autonomy The normal conditions, we spend 30–50% or our conscious waking lives mind wandering. It is empirically plausible to assume that a considerable part of our own cognitive phenomenology simply results from a frequent failure of executive control (***Metzinger, 2013**).

Meditation : ***an open and receptive, nonjudgmental awareness of your present-moment experience***

First they recruited 35 unemployed men and women who were seeking work and experiencing considerable stress. Blood was drawn and brain scans were given. Half the subjects were then taught formal mindfulness meditation at a residential retreat center; the rest completed a kind of sham mindfulness meditation that was focused on relaxation and distracting oneself from worries and stress. At the end of three days, the participants all told the researchers that they felt refreshed and better able to withstand the stress of unemployment. Yet follow-up brain scans showed differences in only those who underwent mindfulness meditation (**Creswell et al, 2016**).

The soul, a concept intimately linked to the notion of the self and its existence, has also been questioned. Greene (2011) says that "we haven;t seen the absence of the soul. Rather, we have inferred its absence, based on our background assumptions about what makes one scientific theory better than another. But to truly deeply believe that we are

The benefits of mindfulness meditation, increasingly popular in recent years, are supposed to be many: reduced stress and risk for various diseases, improved well-being, a rewired brain. But the experimental bases to support these claims have been few. Supporters of the practice have relied on very small samples of unrepresentative subjects, like isolated Buddhist monks who spend hours meditating every day, or on studies that generally were not randomized and did not include placebo-control groups.

This month, however, a study published in Biological Psychiatry brings scientific thoroughness to mindfulness meditation and for the first time shows that, unlike a placebo, it can change the brains of ordinary people and potentially improve their health.

To meditate mindfully demands ''an open and receptive, nonjudgmental awareness of your present-moment experience,'' says J. David Creswell, who led the study and is an associate professor of psychology and the director of the Health and Human Performance Laboratory at Carnegie Mellon University. One difficulty of investigating meditation has been the placebo problem. In rigorous studies, some participants receive treatment while others get a placebo: They believe they are getting the same treatment when they are not. But people can usually tell if they are meditating. Dr. Creswell, working with scientists from a number of other universities, managed to fake mindfulness.

First they recruited 35 unemployed men and women who were seeking work and experiencing considerable stress. Blood was drawn and brain scans were given. Half the subjects were then taught formal mindfulness meditation at a residential retreat center; the rest completed a kind of sham mindfulness meditation that was focused on relaxation and distracting oneself from worries and stress.

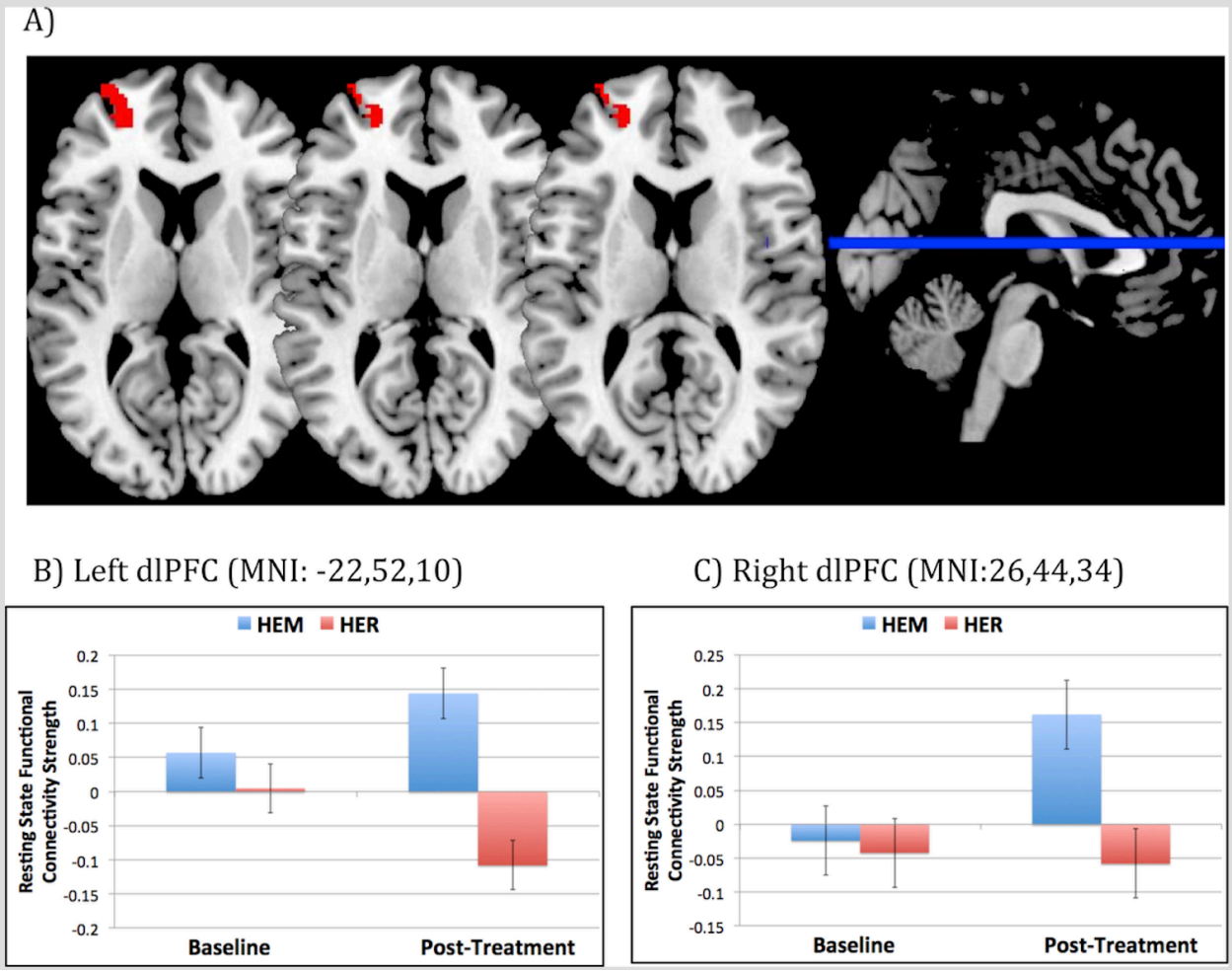
''We had everyone do stretching exercises, for instance,'' Dr. Creswell says. The mindfulness group paid close attention to bodily sensations, including unpleasant ones. The relaxation group was encouraged to chatter and ignore their bodies, while their leader cracked jokes.

At the end of three days, the participants all told the researchers that they felt refreshed and better able to withstand the stress of unemployment. Yet follow-up brain scans showed differences in only those who underwent mindfulness meditation. There was more activity, or communication, among the portions of their brains that process stress-related reactions and other

areas related to focus and calm. Four months later, those who had practiced mindfulness showed much lower levels in their blood of a marker of unhealthy inflammation than the relaxation group, even though few were still meditating.

Dr. Creswell and his colleagues believe that the changes in the brain contributed to the subsequent reduction in inflammation, although precisely how remains unknown. Also unclear is whether you need to spend three uninterrupted days of contemplation to reap the benefits. When it comes to how much mindfulness is needed to improve health, Dr. Creswell says, ‘‘we still have no idea about the ideal dose.”

From the New York Times, 2/18/16



Creswell et al (2016), Biol Psychiatry, doi:10.1016/ j.biopsych.2016.01.008

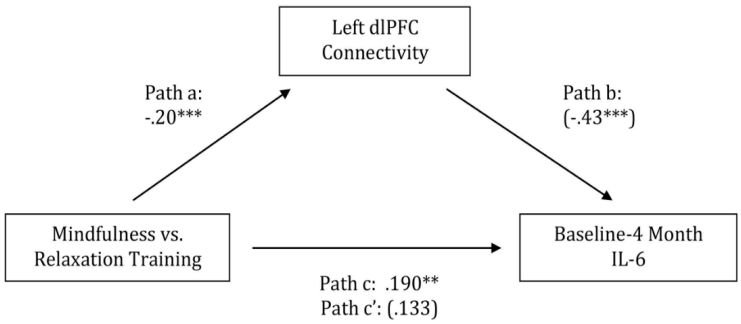
Baseline to Post-Treatment Resting State Functional Connectivity in the Mindfulness and Relaxation

Training Groups.

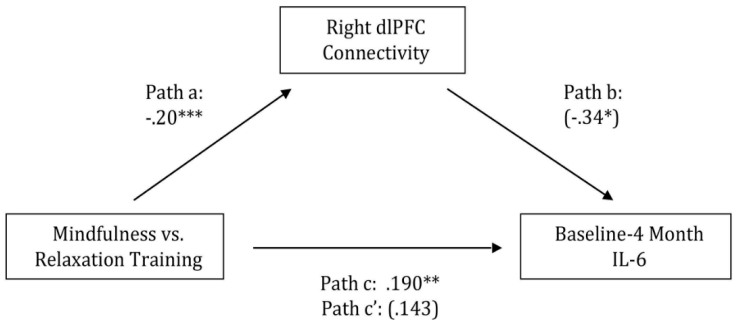
(A) Left dlPFC cluster (MNI: -22,52,10; k=111, p<.05 corrected). that showed increased rsFC with PCC from before to after mindfulness meditation training (HEM) relative to relaxation training (HER). Specifically, a time×condition spreading interaction analysis revealed a significant cluster in left dlPFC (panels A and B). A cluster in right dlPFC (MNI: 26,42,38; k=24) showed the same pattern of effects as the left dlPFC cluster but it did not survive correction, thus the (panel C) right dlPFC rsFC results should be interpreted with caution. .The spreading interaction effects that mediate IL-6 effects are depicted for left (B) and right (C) dlPFC. Specifically, mean connectivity strength is shown for the mindfulness (HEM) and relaxation (HER) training groups at baseline and post- treatment. Error bars depict +/- 1 standard error.

Meditation changes DMN connectivity and mindfulness meditation training functionally couples the DMN with a region known to be important in top-down executive control at rest (left dlPFC), which in turn is associated with improvements in a marker of inflammatory disease risk.

(A)



(B)



IL-6 Mediation analyses. Increases in left dlPFC connectivity (MNI: - 22,52,10) significantly mediate (panel A) the time × treatment interaction on circulating (log transformed) IL-6. Increases in right dlPFC (MNI: 26,42,38) marginally significantly mediate (panel B) IL-6 effects. Numbers represent b coefficients from mixed effect linear models, with parentheses representing b coefficients when the main effect and time × treatment condition interaction terms and dlPFC connectivity parameter estimates are entered in a mixed effect linear model simultaneously. ***p<.05; **p=.05; *p=.06

Creswell et al (2016), Biol Psychiatry,doi:10.1016/ j.biopsych.2016.01.008

machines, we must see the clockwork in action. We have all heard the soul is dead. Now we want to see the body. This is what neuroscience promises to deliver, and it is no small thing." Greene equates the soul's "core competence" with the ability to render moral judgments, while other competencies such as perception, memory and language production and perception have now been mapped onto the activity of specific brain circuits and thereby "outsourced " from the domain on the soul (Greene, 2011). Brain imaging studies argue against the attribution of moral judgments to a "moral faculty" and rather suggest that these judgments are implemented by circuitry which is also involved in self- interested decisions which involve material rewards (Shenshav and Greene, 2010). Moral judgments are not entirely consciously controlled by the individual.

Moral decision making, like other cognitive processes attributed to a self/soul can be influenced without awareness o the part of the subject. Information derived from eye gaze **(Fig. 2)** can be used to change the course of individuals' decisions, even when they are reasoning about high-level, moral issues (**Pärnamets et al, 2015**).

Side Bar The moral brain

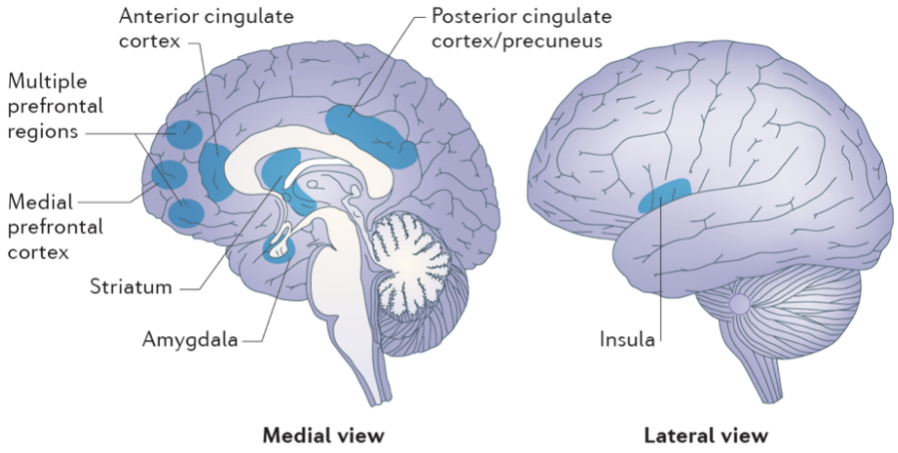
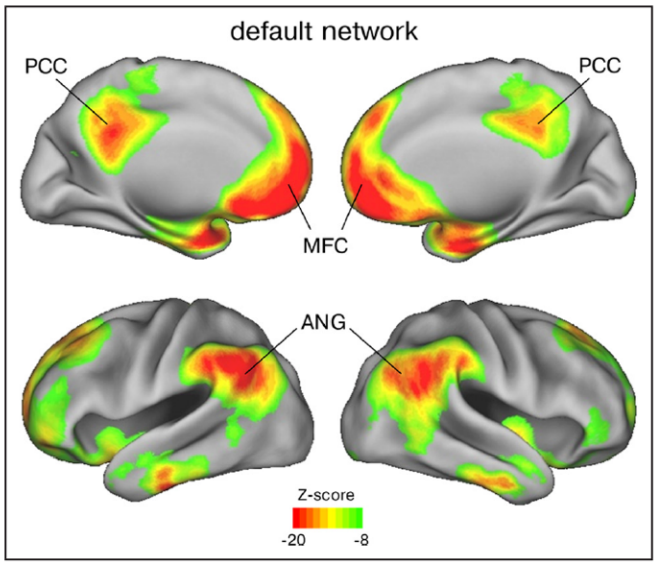


Fig. 15a Emotional control and self-awareness

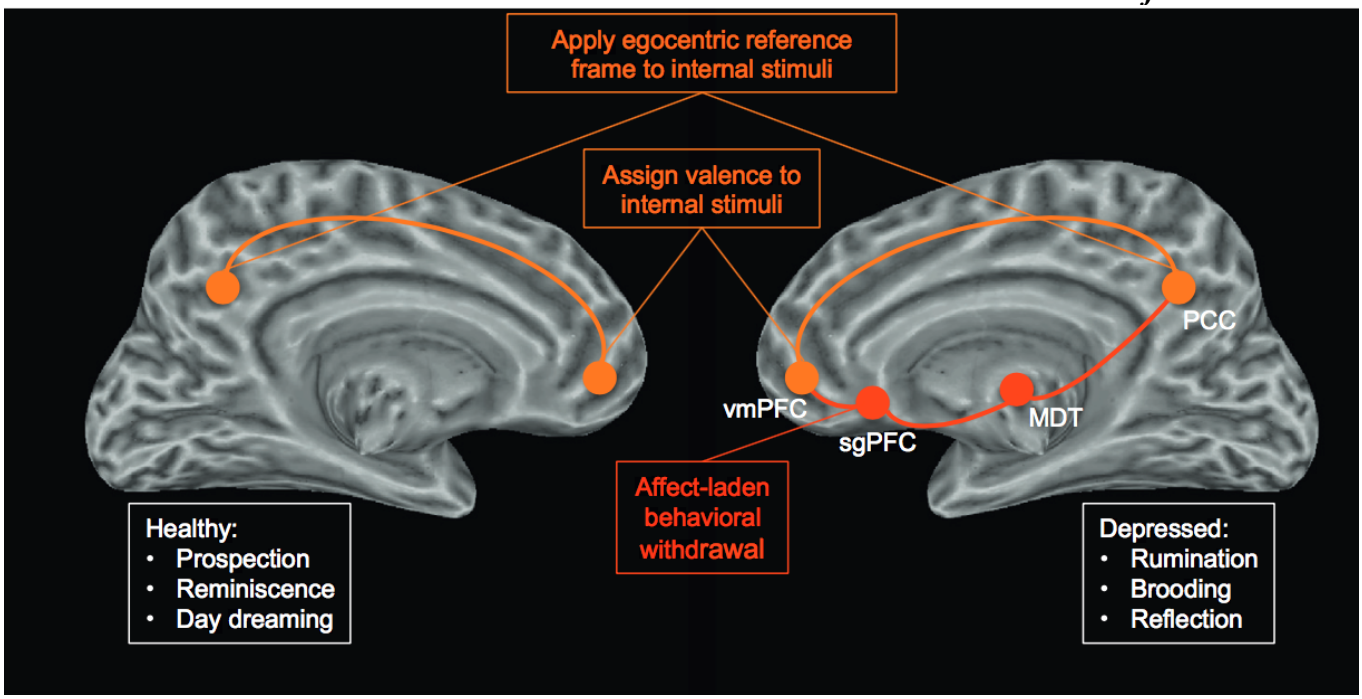
Brain regions involved in the components of mindfulness meditation. Schematic view of some of the brain regions involved in attention control (the anterior cingulate cortex and the striatum), emotion regulation (multiple prefrontal regions, limbic regions and the striatum) and self-awareness (the insula, medial prefrontal cortex and posterior cingulate cortex and precuneus).

Tang et al, 2015



The default network, a set of brain regions showing task-related deactivations across multiple tasks. The network was described by Shulman and colleagues by of a meta- by Shulman and colleagues by of human visual processing (Shulman and others 1997). Images show the medial and lateral surface of the hemispheres using an inflated population-averaged surface representation. The colored areas of the cerebral cortex regions active during active visual tasks relative to passive viewing the same stimulus array. ANG = angular gyrus; MFC = frontal cortex; PCC =posterior gyrus.
Figure is from Shulman and others 1997, Journal of Cognitive Neuroscience.

Fig. 15b *The Default Mode Network* (Mantini and Vanduffel, 2012)



Graphical rendering default-mode network/ cortex (sgPFC) functional integration model of depressive rumination.
Orange nodes and connections normal functionality;
red nodes and connections represent functioning.
MDT, medial dorsal thalamus;, PCC, posterior cingulate cortex;
vmPFC, ventromedial prefrontal cortex.

Fig. 15c (Hamilton et al, 2015)

The DMN- supported process of imbuing internal stimuli with valence and an egocentric frame of reference are united with sgPFC-related that support affectively laden behavioral to a ruminative state that is self-focused, valenced, and withdrawn.

Further Reading

Metzinger T, Being No-One:The Self Model Theory of Subjectivity MIT press 2003

The Brain is not in a Vat

Modification of the brain by interaction with the world and the embodiment of brain/ environment interactions at the molecular, cellular, and neurocircuit level by epigenetics, neuronal plasticity, and network organization.

*The human brain is fundamentally adapted to develop within a social context It is not inserted into the world as a prefabricated apparatus, but rather structured epigenetically by the continuous interaction of an organism and its environment, like a key and its lock ….Subjective experiences …influence the plasticity, the structuring and the functioning of the brain. A 'biographical biology' implies the continuous formation and reconstruction of the brain via subjective experience (**Fuchs, 2009**).*

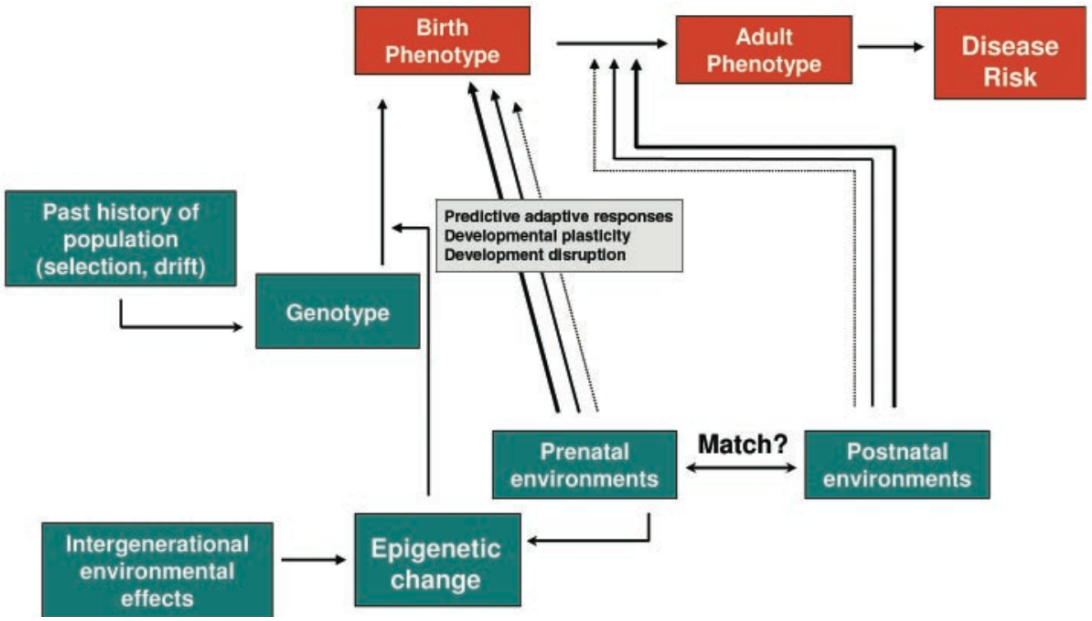


Fig. 16 ***Childhood adversity increases risk*** *for major depression, bipolar disorder, anxiety disorders, substance use disorders, schizophrenia, eating disorders, personality disorders, and suicidality as well as medical conditions such as diabetes and cardiovascular disease*
*(**Gluckman and Hanson, 2004**).*

Side Bar Poverty and the Brain

*There is a long list of difference-makers that alter risk for psychiatric and substance use disorders by impacting on the Human Mind Brain System largely through psychological and social processes. These would include such factors as as poor parenting, childhood sexual abuse, stressful life events, severe trauma exposure, coping strategies, social support and exposure to deviant peers. These risk factors contribute etiologically to most psychiatric disorders (**Kendler, 2012**).*

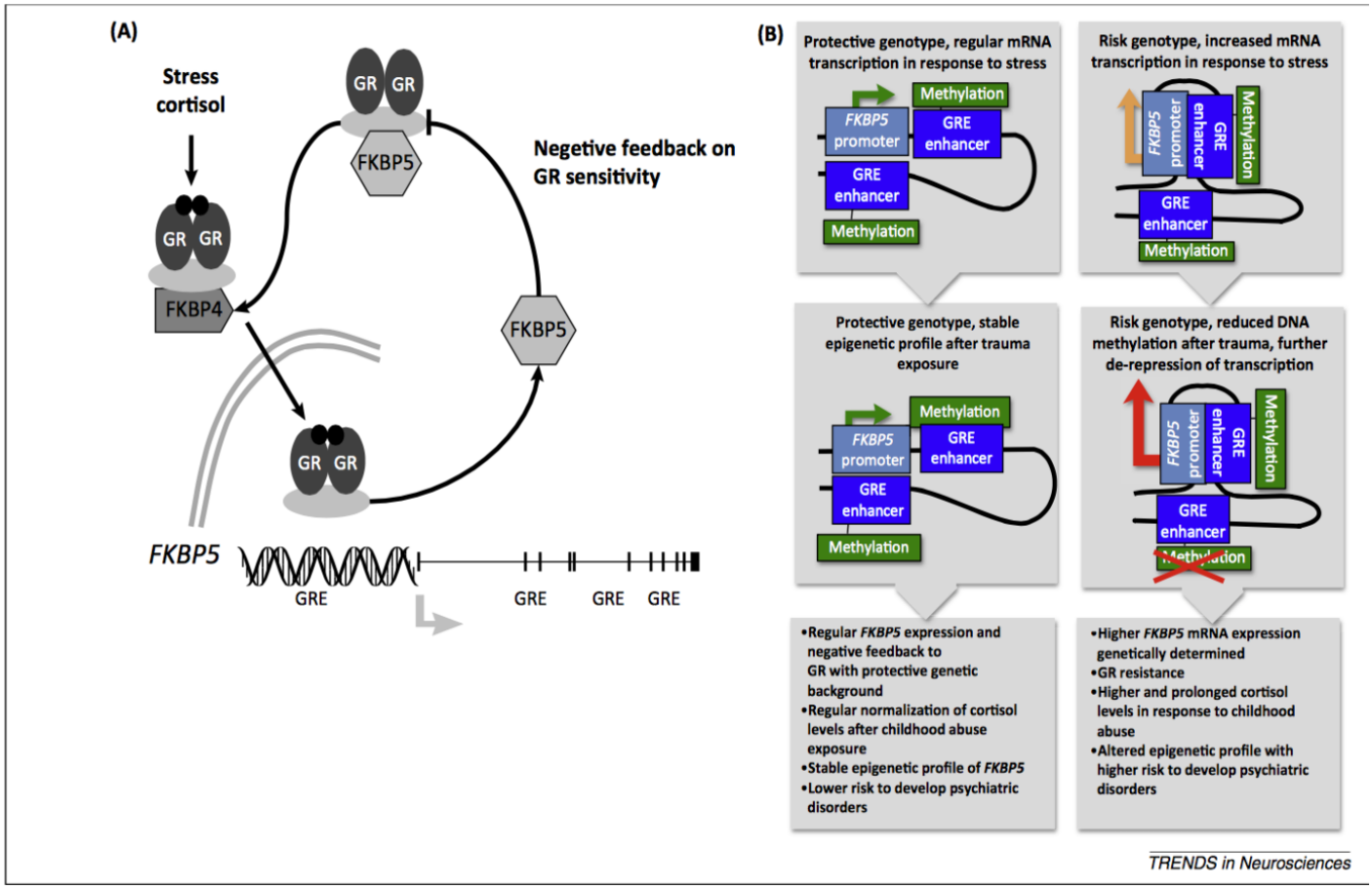
Video Lecture 2: The impact of poverty on brain structure and function
Video Lecture 2.1: Poverty causes Increased Mortality from the Desperation Syndrome

Epigenetics

*Epigenetics not only supplements social neuroscience by highlighting the molecular mechanisms that orchestrate brain plasticity and memory formation, but also seek to blur any residual distinction between biology and social/ecological context. I the first model of the cognitive brain was that of a computing machine, entirely severed from environmental influences, and the brain of social neuroscience still oscillates between plastic change and hardwiring metaphors, with the rise of what can be named the "epigenetic Brain" or neuroepigentics research the reciprocal penetration of the social and the biological reaches a point where trying to establish any residual distinction seems increasingly hopeless (**Meloni, 2014**).*

Fig. 16a

Epigenetics
Fig. 17



Epigenetics and stress responses: example of the FKBP5 (FK506 binding protein 5) gene. FKBP5 regulates the HPA axis and is epigenetically modified by childhood abuse in a genotype-dependent manner. (A) FKBP5 is a co-chaperone of the glucocorticoid receptor (GR), binding via heat-shock protein 90 (hsp90) and reducing its affinity for cortisol thus providing an ultra-short feedback loop to limit hypothalamic–pituitary–adrenal axis (HPA) activation. In response to cortisol binding, FKBP5 is replaced by FKBP4, which facilitates the translocation of the GR complex into the nucleus where the GR binds to glucocorticoid response elements (GREs). Among other stress-responsive genes, FKBP5 transcription and translation is increased via intronic response elements, which confers higher GR resistance, serving as an ultra-short negative feedback loop on GR sensitivity. (B) Epigenetic regulation of FKBP5 in response to childhood abuse. The genetic predisposition in FKBP5 determines the 3D organization of the FKBP5 locus and the stress-dependent transcriptional activation of the gene with higher mRNA expression in risk allele carriers due to the increased interaction of distal GREs. In response to childhood abuse, carriers of the protective genotype maintain a stable epigenetic profile, whereas in risk allele carriers, trauma induces a demethylation in the GRE with further de-repression of FKBP5 transcriptional activation. The resulting HPA axis deregulation contributes to the development of psychiatric disorders.

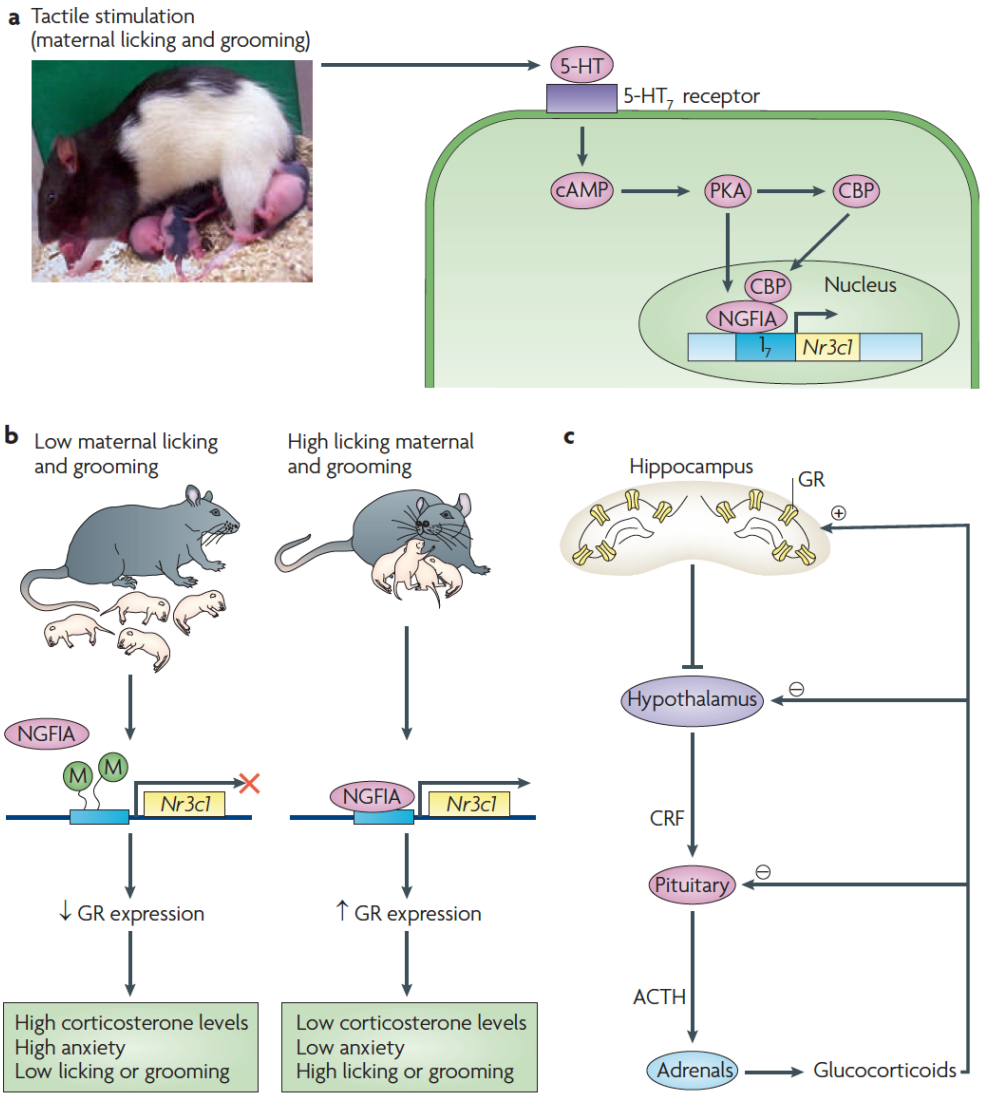


Fig. 18 (Hackman (2010)

a) Working model for the effect of maternal care *(specifically, of licking and grooming pups) on the epigenetic regulation of the expression of Nr3c1, the gene that encodes the glucocorticoid receptor (GR). Licking and grooming of pups activates thyroid hormone-dependent increases in hippocampal serotonin(5-hydroxytryptamine or 5-HT) levels and 5-HT binding to the 5-HT7 receptor. Activation of the 5-HT7receptor leads to the activation of a cyclic AMP–protein kinase A (PKA) cascade that induces the expression of the transcription factor nerve growth factor-inducible A (NGFiA) and cyclic AMP response element-binding (cReB) protein (cBP) expression and their association with the nonspecific exon 17 GR gene promoter.* ***b*** *| in neonates, high levels of licking increases NGFiA and cBP association with the exon 17 promoter by triggering demethylation of a dinucleotide sequence (cpG) that is located within the NGFiA binding region of the exon. This subsequently increases the ability of NGFiA to activate GR gene expression. M, methylation.* ***c*** *| A schematic of the hypothalamic–pituitary–adrenal axis, the pivot of which are the corticotropin-releasing factor (cRF) neurons of the paraventricular nucleus of the hypothalamus. cRF is released into the portal system of the anterior pituitary, stimulating the synthesis and release of adrenocorticotropin (ACTH), which then stimulates the adrenal.*

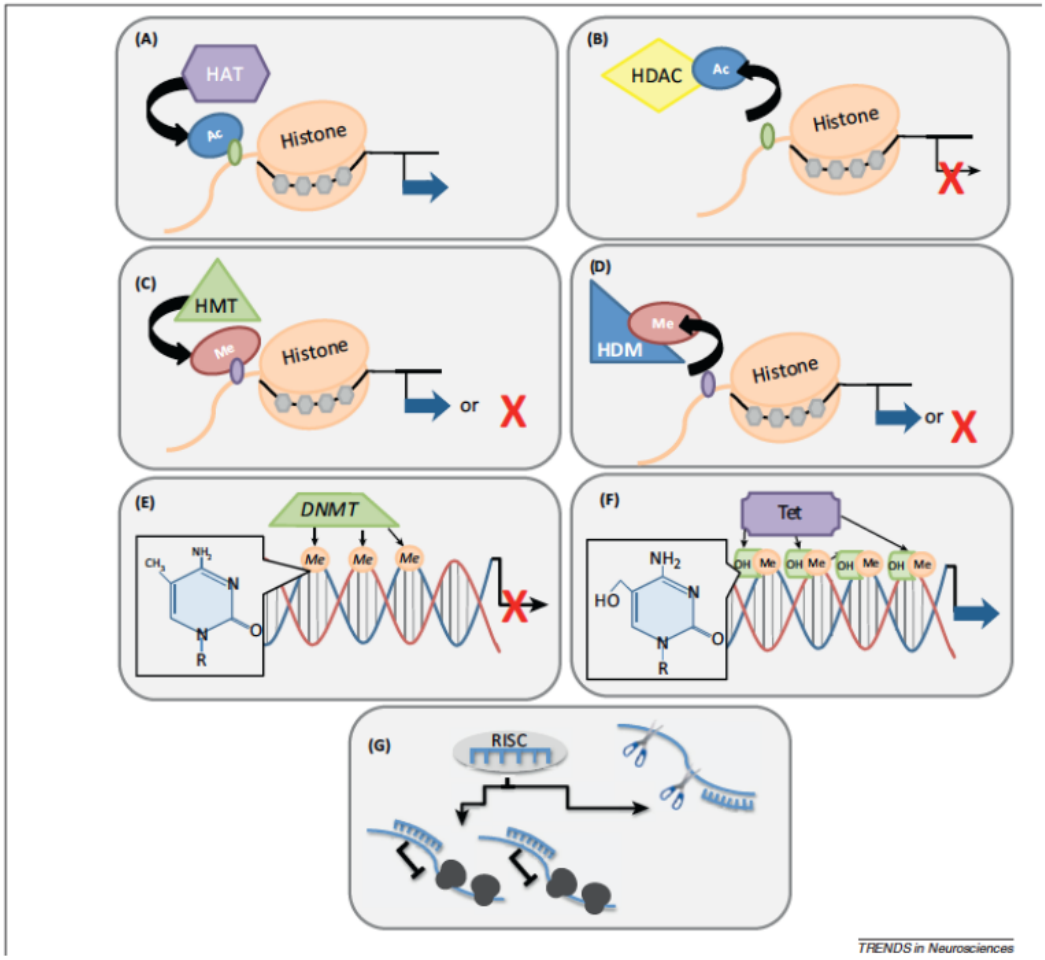


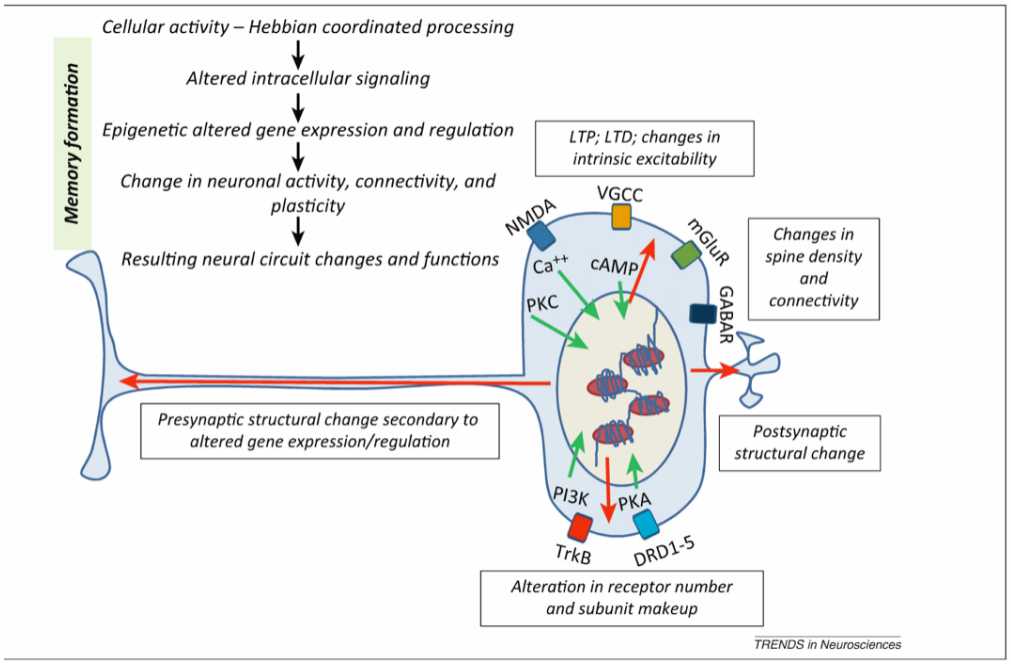
***Fig.* 19**

Overview of epigenetic regulatory mechanisms.

(A) Histone acetyltransferases (HATs) add acetyl groups to lysine residues on histone tails, and are generally associated with relaxing wound DNA and transcription. (B) Histone deacetylases (HDACs) remove those acetyl groups, and inhibit transcription. (C,D) Histone methylation is mediated by histone (HMTs), which add methyl groups to lysine residues on histone tails, and this process is reversed by histone demethylases (HDMs). impact of methylation on transcription largely depends on the lysines and state of methylation (mono-, di-, tri). (E) DNA methyltransferases (DNMTs) add methyl groups to cytosines of CpG islands, resulting in a 5-methylcytosine (5mC) state, and are generally associated with DNA silencing. (F) Active demethylation has recently been with ten-eleven translocation methylcytosine dioxygenase (Tet) protein-mediated hydroxylation of 5mC, resulting in 5- hydroxymethylcytosine (5hmC), and has been found to transcription. (G) A schematic diagram of miRNA-mediated inhibition of gene translation and mRNA degradation via the RNAi Silencing Complex RISC) as examples for epigenetic regulation by small noncoding RNAs.

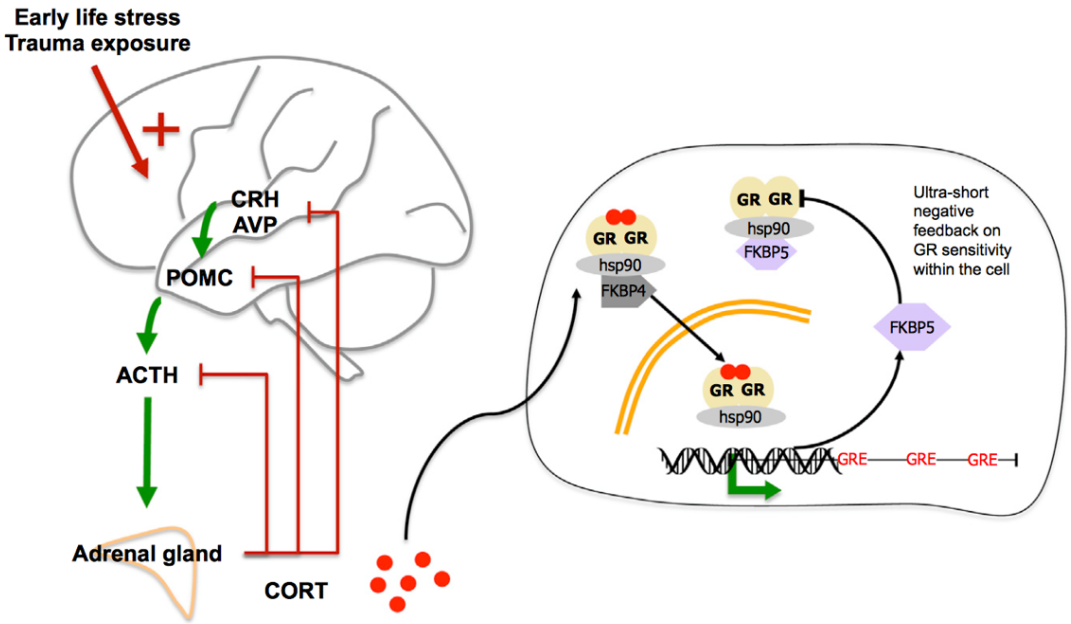
Trends in Neurosciences February 2015, Vol. 38, No. 2 (Dias et al, 2014).

Fig. 20



How epigenetic regulation of neuronal gene expression may alter neuronal plasticity resulting in memory formation. This schematic diagram various mechanisms, supported by published data, by which coordinated cellular activity leads to altered intracellular, with resultant epigenetic at the levels of noncoding RNA, histone regulation, and DNA methylation. Together such changes alter regulation of gene, resulting in changes at the levels of spine density, receptor sensitivity, and intrinsic excitability, etc., as well as providing the substrates for altered presynaptic structural and functional. The changing of the neuronal state at the level of epigenetic gene regulation interacts with local determinants related to synaptic connectivity and circuit activity, together alter neurocircuitry dynamics underlying memory formation. Abbreviations: DRD1-5, dopamine receptor D1-5; GABAR, GABA receptor; LTD, long-term; LTP, long-term potentiation; mGluR, metabotropic glutamate receptor; PI3K, phosphatidylinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; TrkB, tyrosine kinase receptor type 2; VGCC, voltage-gated calcium channel.

From Dias et al (2014)



Stress and, in Particular, Early Life Adversities Activate the Stress Hormone System and May Epigenetically Program the System toward a Lifelong Alteration of the Hormonal Response to Even Minor Stressors

The neuropeptides corticotrophin-releasing hormone (CRH) and vasopressin (AVP), released from the hypothalamus in response to stress, activate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, finally leading to an increased systemic cortisol secretion from the adrenal gland. Cortisol binds to steroid receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), that act as transcriptional activators or repressors in the nucleus through binding to glucocorticoid response elements. This influences the expression of numerous genes involved in the stress response, immune function, and metabolism. Binding of the GR and transcriptional activation of, for example, FKBP5 provide an ultrashort feedback to the GR, terminating the stress response and secretion of cortisol.

From: Klengel and Binder (2015)

Fig. 21

Early life stress (ELS)

Early life stress (ELS) and function of the hypothalamic-pituitary-adrenal axis predict later psychopathology.
The delayed impact of ELS may be mediated by persistent alterations of the amygdala–ventromedial prefrontal cortex (vmPFC) circuitry (**Burghy et al, 2012**).
These alterations are surprisingly resistant to change as evidenced by studies looking at stress related measures in 4.5-year-old children and their predictive impact 13.5 years later (**Fig**. **22**)

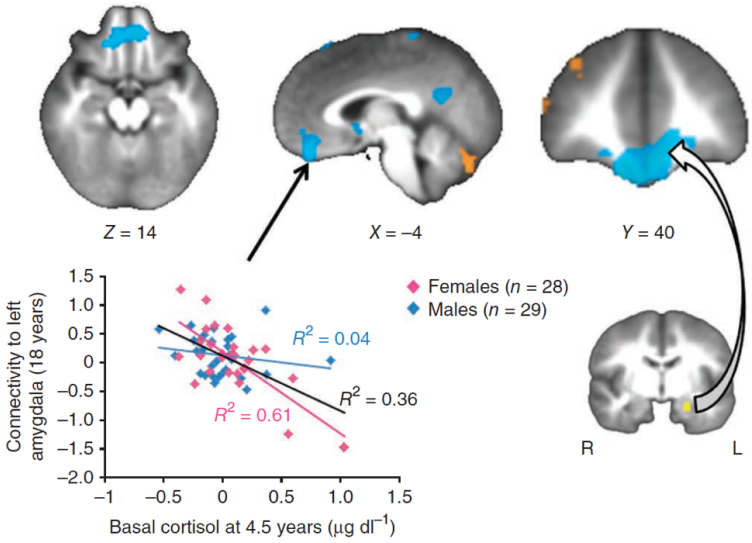


Fig. 22
Correlation between late-afternoon cortisol at age 4.5 years and rs-FC to the left amygdala at 18 years. Connectivity between the left amygdala and vmPFC is significantly negatively associated with childhood cortisol (R2 = 0.36, FDR-corrected P = 0.01). This effect is driven entirely by data for females (R2 = 0.61, FDR-corrected P = 0.01).

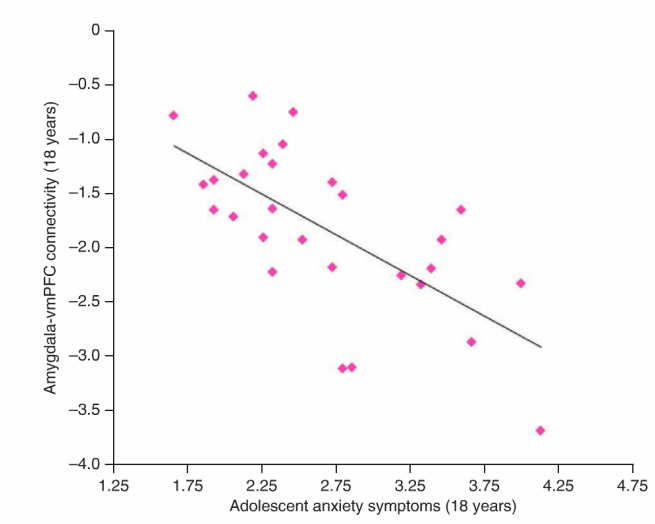


Fig. 22a

Partial correlation between resting-state left amygdala-vmPFC rs-FC and concurrent self-reported anxiety symptoms in adolescent females, controlling for concurrent symptoms of depression and externalizing behaviors (R2 = 0.31, P = 0.004).

TThe upper panels are regions showing a significant association with family income-to-needs ratio at age 9. (*A*) Dorsolateral prefrontal cortex (PFC) (*x*, *y*, *z* = –40, 12, 28; 343 voxels; $P < 0.05$, corrected). (*B*) Ventrolateral PFC, insula, temporopolar area (*x*, *y*, *z* = –46, 10, –8; 672 voxels; $P < 0.05$, corrected). (*C*) Amygdala (*x*, *y*, *z* = –30, –4, –22; 140 voxels; $P < 0.05$, uncorrected). The lower panels depict partial regression plots describing the associations between family income-to-needs ratio at age 9 and parameter estimates of a region in the contrast of Reappraisal vs. Maintain, controlling for adult income level.

The upper panels are regions showing a significant association with family income-to-needs ratio at age 9.

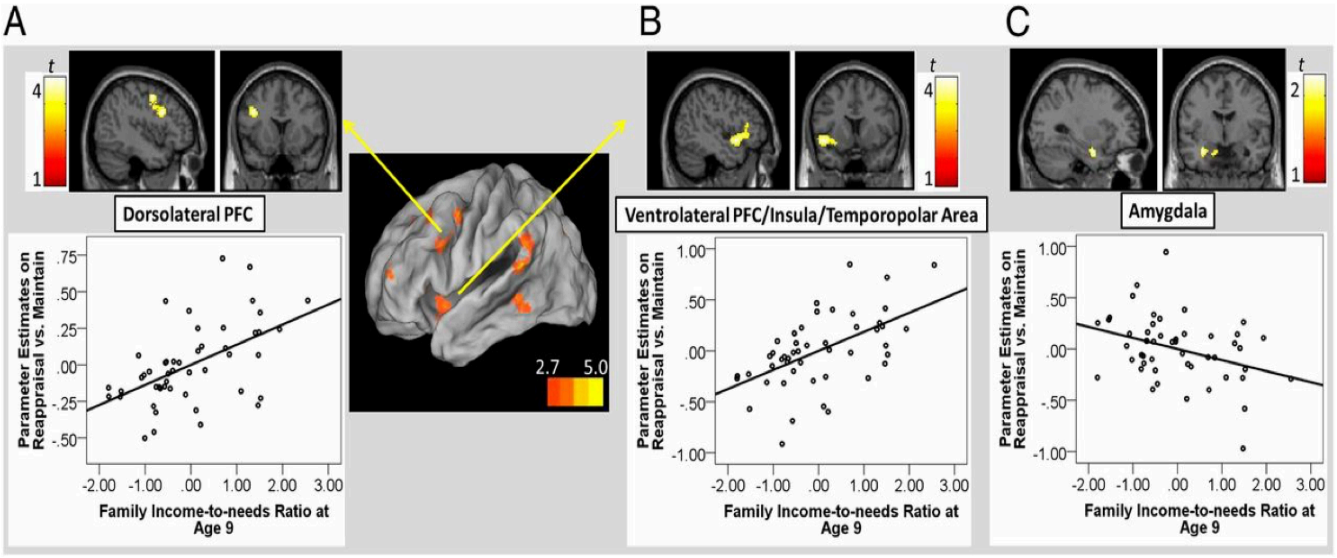
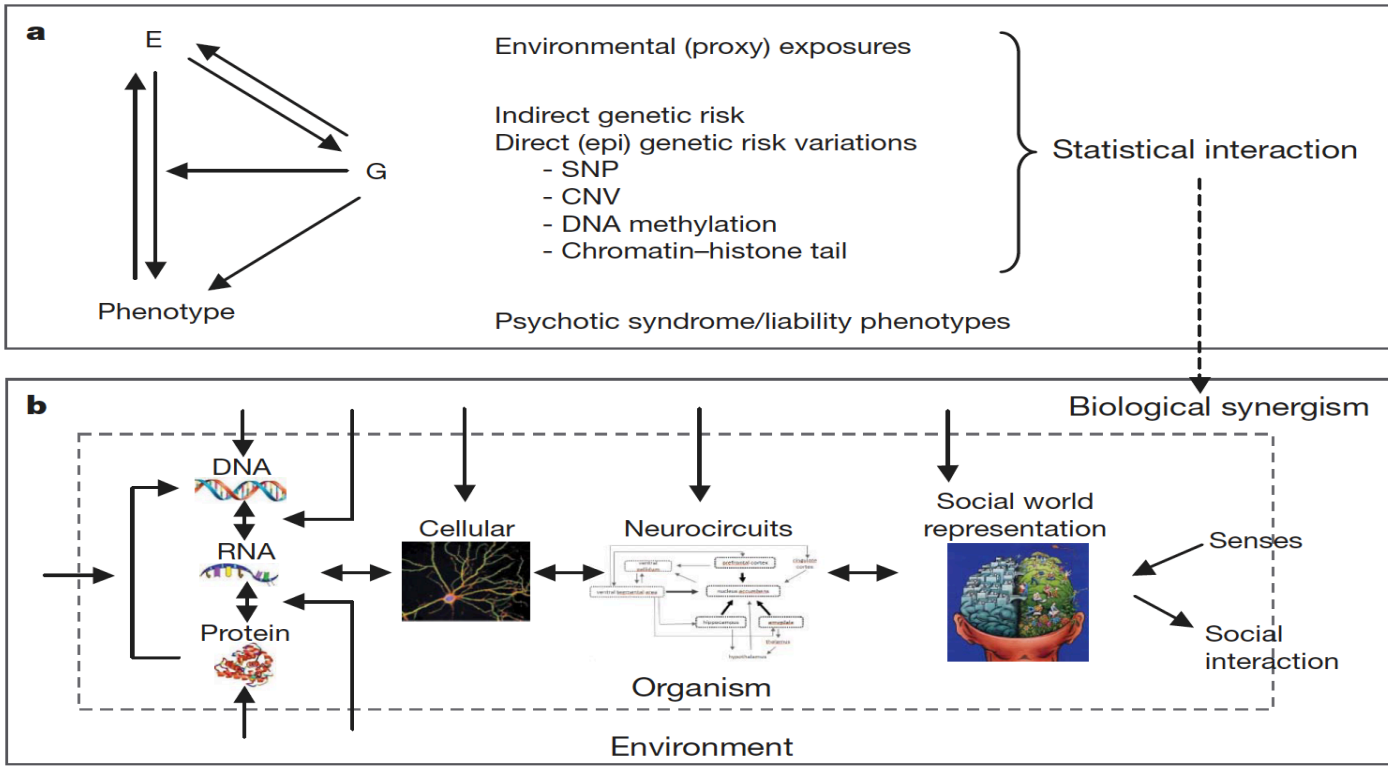


Fig. 22b

Early Life S tress: The Urban vs. Rural Dimension



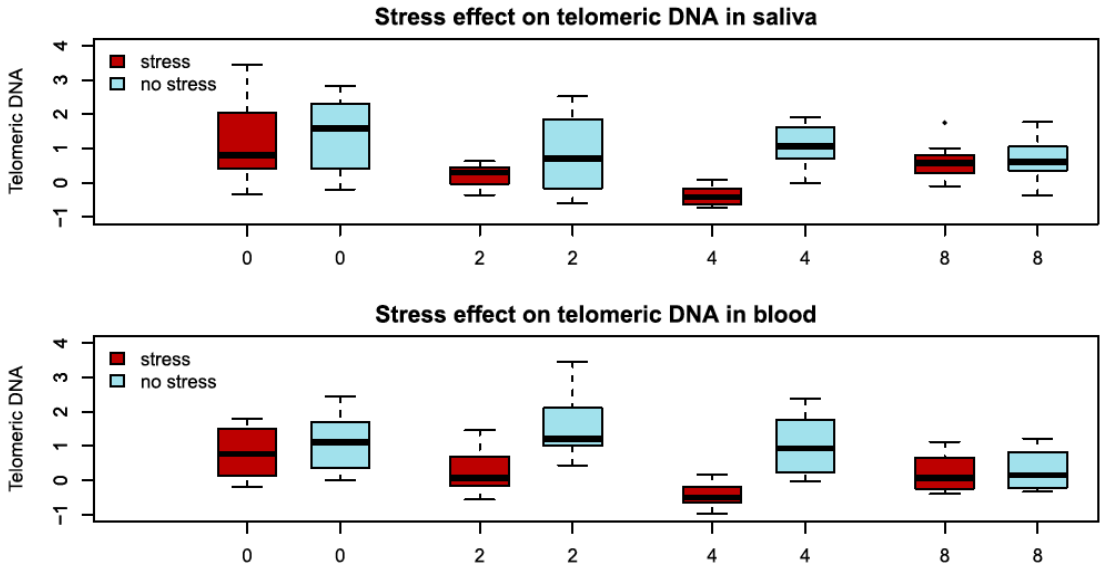
Schematic illustration of gene–environment interplay at the levels of epidemiology and biology.
The left part of **a** represents relationships between environmental exposures (E), genetic liability (G) and the phenotype, that is, psychotic syndrome and related liability phenotypes. Genes may control environmental exposure (arrow from G to E), genes may control environmental sensitivity (arrow from G to arrow E to phenotype), the phenotype may induce reverse causality (arrow from phenotype to E) and the environment may occasion (epigenetic) mutations (arrow from E to G). Measurement of environmental exposures often represent proxies of unknown mediating factors, and measures of genetic risk may be epidemiological (indirect) or molecular (direct). Current genetic and epigenetic variations comprise single nucleotide polymorphisms (SNP), copy number variations (CNV), DNA methylation, chromatin structure and histone tail alterations. Epidemiological studies may focus on the identification of statistically significant marginal effects of individual factors or the statistical interaction between (proxy) environmental exposures and genetic variant(s); evidence for statistical interaction may be pursued to identify biological synergism, or the co-action of genes and environment at the biological level. Panel b illustrates the interrelations between the various levels of biology mediating mental representation of the social world, and the numerous ways that environmental factors may impact on or interact with these. These interactions may be studied in different organisms and model systems using observational and experimental study designs (**van Os et al, 2010**).

Telomeres

Early-life experiences have enduring sequelae and it is now well documented that childhood adversity increases risk for major depression, bipolar disorder, anxiety disorders, substance use disorders, schizophrenia, eating disorders, personality disorders, and suicidality as well as medical conditions such as diabetes and cardiovascular disease
(Gluckman and Hanson, 2004).
By 2008, about 5,000 papers were published on telomeres and by 2013 this number had increased to 14,000 (Price et al, 2013).

Changes in the amount of mtDNA and telomere length are consequences of stress and entering a depressed state.

These findings identify of mtDNA as a molecular markers of MD and have important



implications for understanding how stress causes disease (Cai et al, 2015).
Fig. 23 (**Cai et al, 2015**)

Table 1. Relationship between Childhood Sexual Abuse, Telomere Length, and the Amount of Mitochondrial DNA

CSA Type	Excess Telomeric DNA[a]	t Value[b]	p Value[c]	Excess mtDNA[a]	t Value[b]	p Value[c]	Number Cases[d]	Number Con
Non-genital CSA	0.02	0.35	0.73	0.08	1.37	0.169	186	81
Genital CSA	−0.08	−1.27	0.20	0.11	2.02	0.045	240	47
Intercourse CSA	−0.20	−2.45	0.01	0.38	4.67	3.05×10^{-6}	159	17

Results for analysis of variance in which different forms of childhood sexual abuse (CSA) predict telomere length and the amount of mt
ital CSA refers to sexual invitation, sexual kissing, and exposing; genital CSA refers to fondling and sexual touching; and intercours
attempted or completed intercourse.
[a]Estimated excess of telomeric or mtDNA over mean telomeric DNA or mtDNA in individuals with no CSA.
[b]t statistic of tests of hypotheses that underlying excess is zero.
[c]p value of tests of hypotheses that underlying excess is zero.
[d]Number of MD cases.
[e]Number of controls.
[f]Number of total individuals.

Fig. 23a (Cai et al, 2015)

The new psychiatry

We are aware dispute- ridden character of contemporary psychiatry and intend to forge a conceptual structure on which better research and progressive, coherent practice can arise. We hold that catalogues of diagnostic terms- such as the Diagnostic and Statistical Manual on Mental Disorders (DSM) of the American Psychiatric Association- and the non-specific, all-embracing "biopsychosocial" orientation towards the discipline's elements do not advance such a structure but call attention to its absence.
What do Psychiatrists study?
A natural biosystem called the mind.
It has been suggested that the "mind-brain disjunction plays some role is the factionalism" that plagues psychiatry (McHugh and Slavney, 1998).

Mental disorders are a diverse group of ***brain disorders*** *that primarily affect emotion, higher cognition and executive function (Hyman, 2007)*

While we still lack biomarkers for mental disorders, the tools of basic science are now beginning to change how we approach diagnosis. The discovery of shared genetics, often implicating genes critical for brain development, has supported a new formulation of mental disorders as neurodevelopmental disorders. With functional MR and PET imaging, specific circuits have been implicated in depression, obsessive-compulsive disorder, and posttraumatic stress disorder . A new approach to classification of psychiatric disorders called the Research Domain Criteria (RDoC) project, is based on cognitive domains and circuitry. RDoC attempts to transform diagnosis by building on the findings of neuroscience and cognitive science , rather than relying solely on presenting symptoms, as done for the past century. While this approach is not ready for clinical use, it demonstrates the extent to which ***mental disorders are now addressed as brain disorders, or, more specifically , as brain circuit disorders****.(Insel, 2014; Insel and Landis, 2013).*

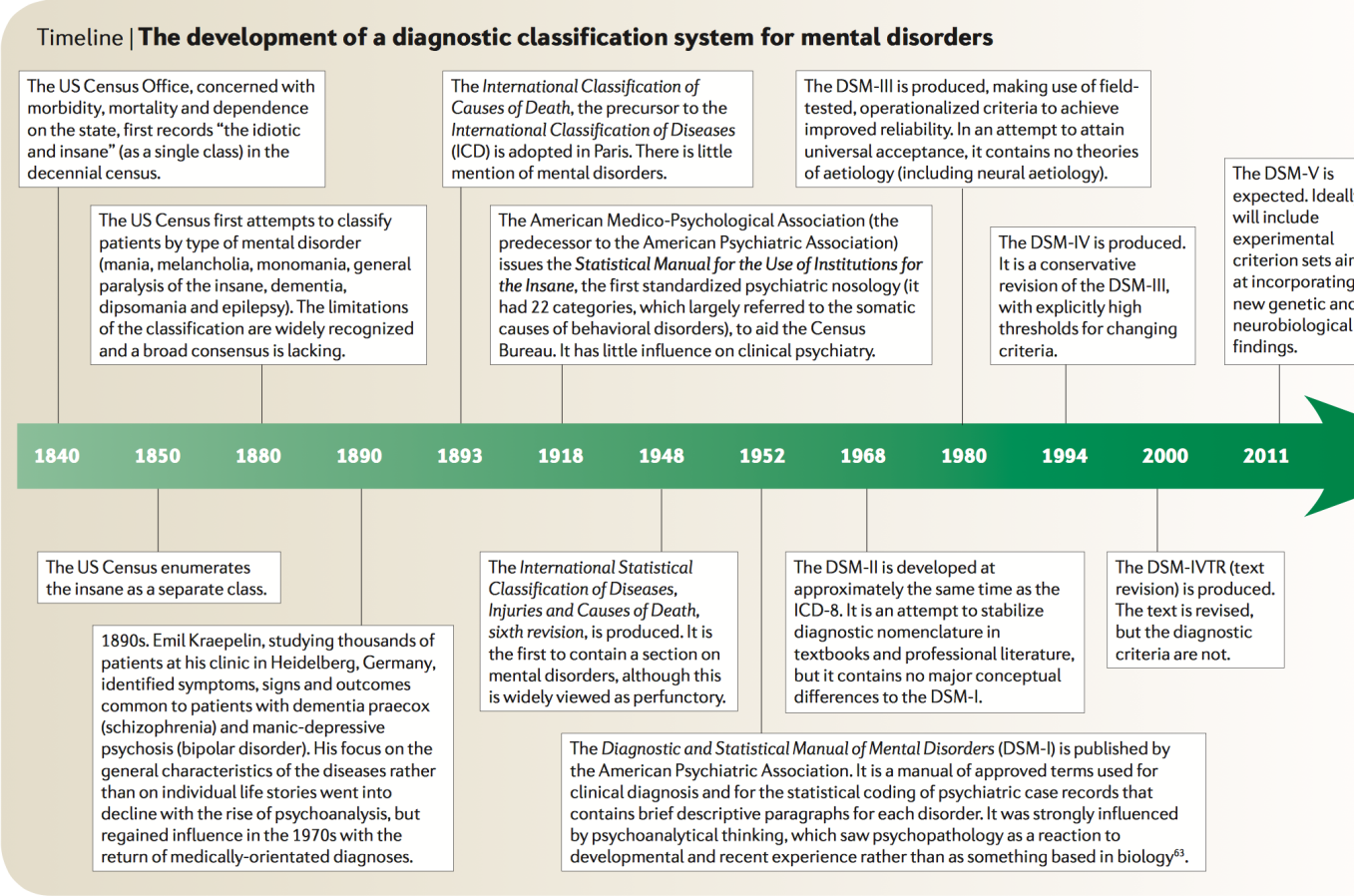
Syndromes once considered exclusively as "mental" are being reconsidered as "brain" disorders-or, to be more precise, as syndromes of disrupted neural, cognitive, and behavioral systems….
Labels like "behavioral health disorders" or "mental disorders" or the awkwardly euphemists "mental health conditions," when juxtaposed against brain science, invite continual recapitulation of the fruitless "mind-body" and "nature-nurture" debates

that have impeded a deep understanding pf psychopathology (Insel and Cuthbert, 2015)

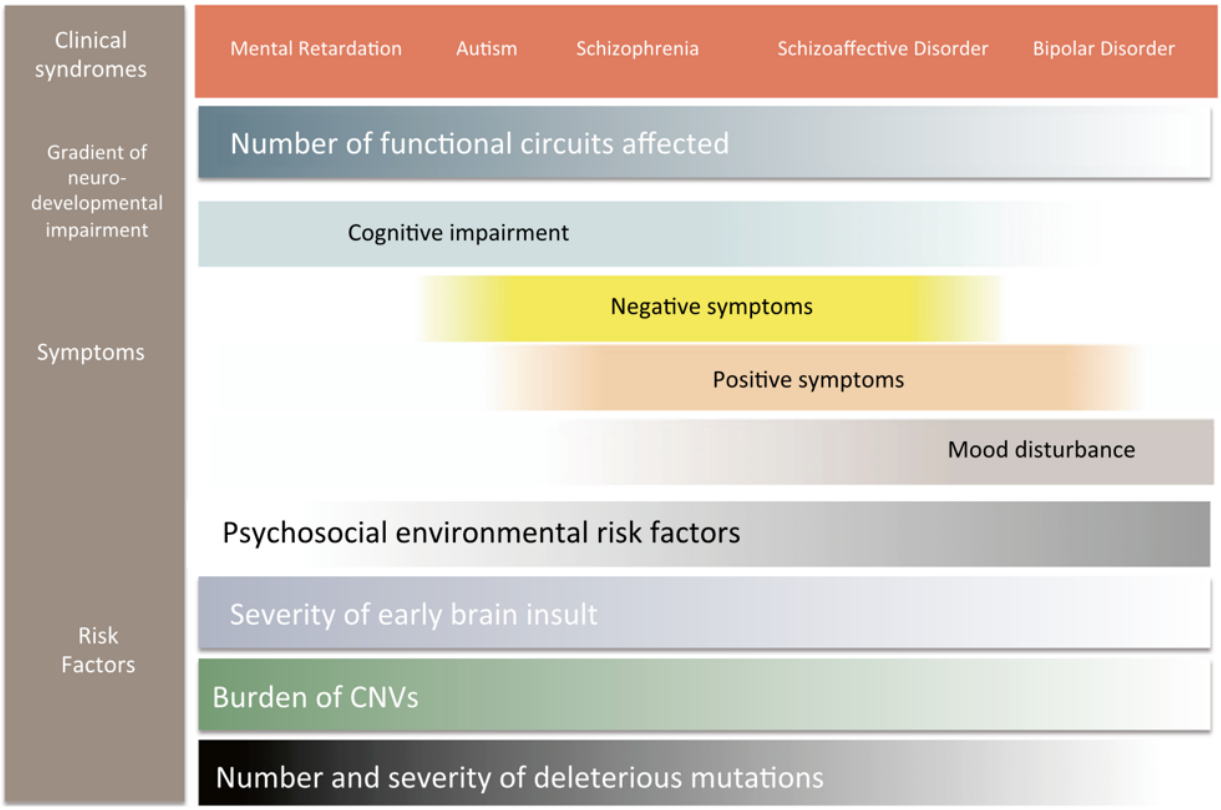
Robins and Guze (1970) established the conceptual frame work for criteria-based syndrome ***categorical*** *classification of psychiatric disorders and the field has been revising its classification scheme ever since.*
The controversies surrounding the latest revision of the DSM-5 and the introduction of an alternative approach to a non-categorical approach to "mental disorders" highlight

the various positions in the philosophy of science that might represent how to think about mental illness ('realist,' 'essentialist,' and so on); categorical versus dimensional approaches to disorders; and the role of reductionism and phenomenology. Any discussion about the ramifications of these various considerations in actually making a *difference on how we we treat our patients(*Cuthbert and Insel, 2013; Nesse and Stein, 2012). A standard textbook of psychiatry comments on the DSM classification system that "there is little reason to believe that these categories are valid" (Grebb and Carlsson, 2009).
Hyman (2007)suggested that " *DSM-V should be* structured *to allow the incorporation of well-replicated findings from neuroscience and genetics as they emerge — without forcing us to wait a decade or more for the DSM-VI"*, and warns that "i*f the current criteria have not effectively 'carved nature at the joints', then there is a risk that genetic, imaging and other disease-related studies will be confounded by there inclusion of heterogeneous populations."*
DSM-5 has now appeared and like its precursors fails to "carve nature at the joints."
Genetic (specific SNPs are associated with a range of psychiatric disorders of childhood and adult onset) and brain imaging studies (concordance across psychiatric diagnoses in terms of the integrity of an anterior insula/dorsal cingulate-based network, which may relate to executive function deficits observed across diagnoses, see ***Fig. 15****) are converging toward an increasingly unavoidable conclusion:*
the DSM system-still impervious to biological data- is a distorted and inadequate attempt to classify psychiatric disorders (Goodkind et al, 2014; Consortium, 2013).
Teachers and trainees in psychiatry are increasingly aware of these problems.
A recent survey, the first of its kind, examined the attitudes towards neuroscience education (Fung et al, 2015). Interestingly, only 9% of psychiatrists randomly selected from the APA membership responded to the survey. By contrast. 53% of department chairs in psychiatry and 18% of psychiatric trainees responded. Almost all respondents (94%) agreed on the need for promoting neuroscience education in psychiatry and 73% believed that advances in neuroscience would lead to new or personalized treatments in 5 to 0 years. However, only 23% of practicing psychiatrists, 13% of trainees and 57% of department chairs report having a "strong neuroscience foundation" (i.e. 43% of department chairs do not!). It is a hopeful sign that all respondents endorsed a transdiagnostic approach, which focuses on the implementation of emotion regulation, attention/cognition and reward by neural circuits. Perhaps this preference reflects the

dissatisfaction with the current obsession with categorical diagnosis denuded of



physiological foundations.
Fig. 24
From: **Hyman, 2007**



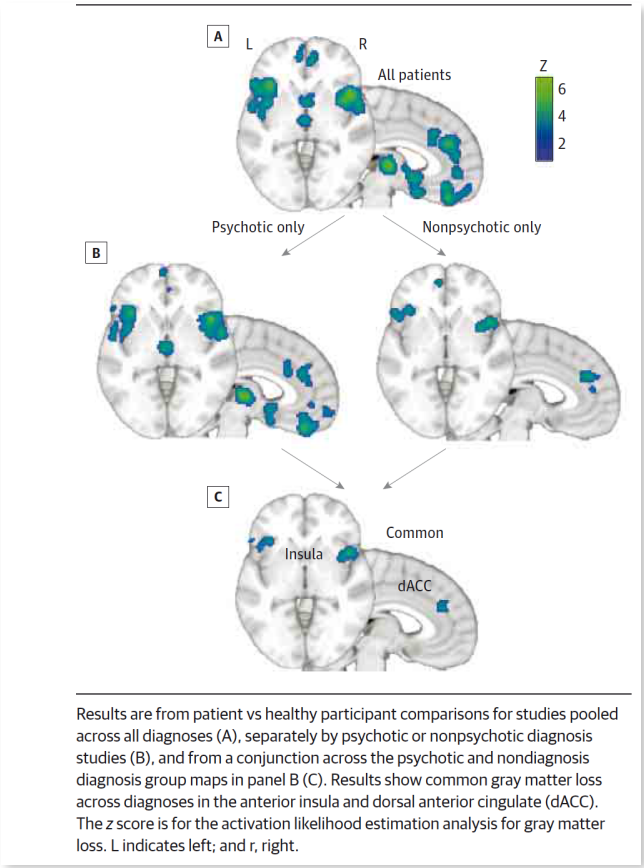
Hypothesized Relationship between Current Diagnostic Categories, Extent of Neurodevelopmental Impairment and Associated Cognitive Dysfunction, Symptoms, and Various Risk Factors
This simple model integrates data from a number of sources (Pasamanick et al., 1956; Craddock and Owen, 2010; Owen et al., 2011; Kirov et al., 2012; Girirajan et al., 2011; Fromer et al., 2014; Grozeva et al., 2010; Girirajan et al., 2011) to propose that psychiatric syndromes as currently classified occupy a gradient with the syndromes ordered by decreasing relative contribution of genetically and/or environmentally induced neurodevelopmental impairment. This indexes the number of structures and circuits that are affected, which in turn is manifest by the extent and degree of associated cognitive impairment. This approach accepts that current diagnostic approaches have some utility in defining groups of cases that are more closely related than chance. A key feature is that it regards current categorical diagnoses as arbitrary divisions of what is essentially a continuous landscape. This model makes predictions about the relative extent of brain dysfunction (number of structures and circuits affected) in the various clinical syndromes and the relationships and likely similarities between disorders. In the interests of clarity, this two-dimensional representation does not show the severity of individual syndromes. These are conceived as being orthogonal and as reflecting the severity, rather than the extent, of damage to structures and circuits. Further details and references are given in the text.
Pasamanick, B., Rogers, M.E., and Lilienfeld, A.M. (1956). Pregnancy experience and the development of behavior disorders in children. Am. J. Psychiatry 112, 613–618.
Craddock, N., and Owen, M.J. (2005). The beginning of the end for the Kraepelinian dichotomy. Br. J. Psychiatry 186, 364–366.

Fig. 25 From: **Owen, 2014**

Depression

Side Bar_A Walk in the Woods

Video Lecture 6: Depression 1 — A Walk in the Woods

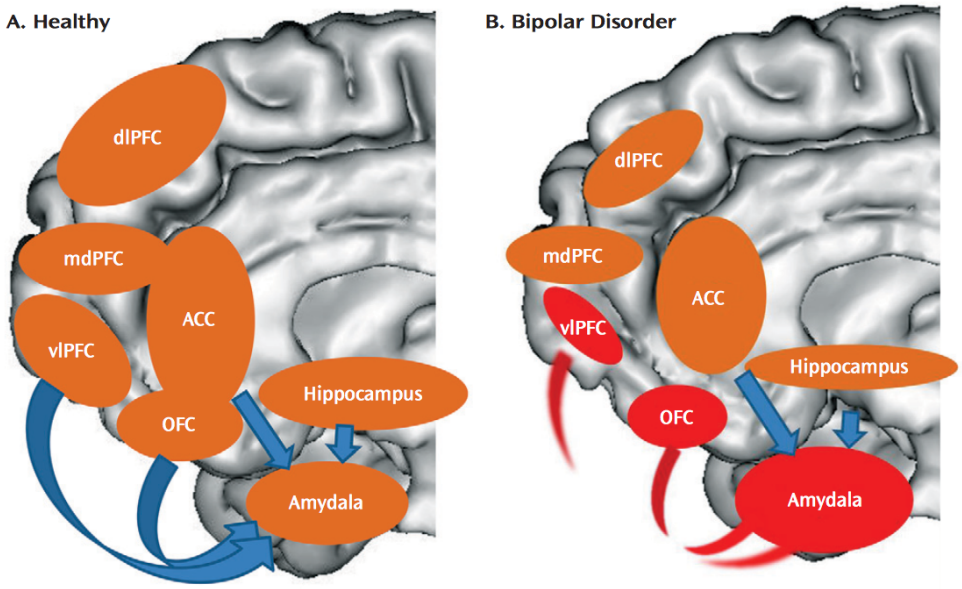


Results are from patient vs healthy participant comparisons for studies pooled across all diagnoses (A), separately by psychotic or nonpsychotic diagnosis studies (B), and from a conjunction across the psychotic and nondiagnosis diagnosis group maps in panel B (C). Results show common gray matter loss across diagnoses in the anterior insula and dorsal anterior cingulate (dACC). The *z* score is for the activation likelihood estimation analysis for gray matter loss. L indicates left; and r, right.

Fig. 26

A recent survey, the first of its kind, examined the attitudes towards neuroscience education (Fung et al, 2015). Interestingly, only 9% of psychiatrists randomly selected from the APA membership responded to the survey. By contrast. 53% of department chairs in psychiatry and 18% of psychiatric trainees responded. Almost all respondents (94%) agreed on the need for promoting neuroscience education in psychiatry and 73% believed that advances in neuroscience would lead to new or personalized treatments in 5 to 0 years. However, only 23% of practicing psychiatrists, 13% of trainees and 57% of department chairs report having a “strong neuroscience foundation" (i.e. 43% of department chairs do not!). It is a hopeful sign that all respondents endorsed a transdiagnostic approach, which focuses on the implementation of emotion regulation, attention/cognition and reward by neural circuits. Perhaps this preference reflects the dissatisfaction with the current obsession with categorical diagnosis denuded of dissatisfaction with the current obsession with categorical diagnosis denuded of physiological foundations.

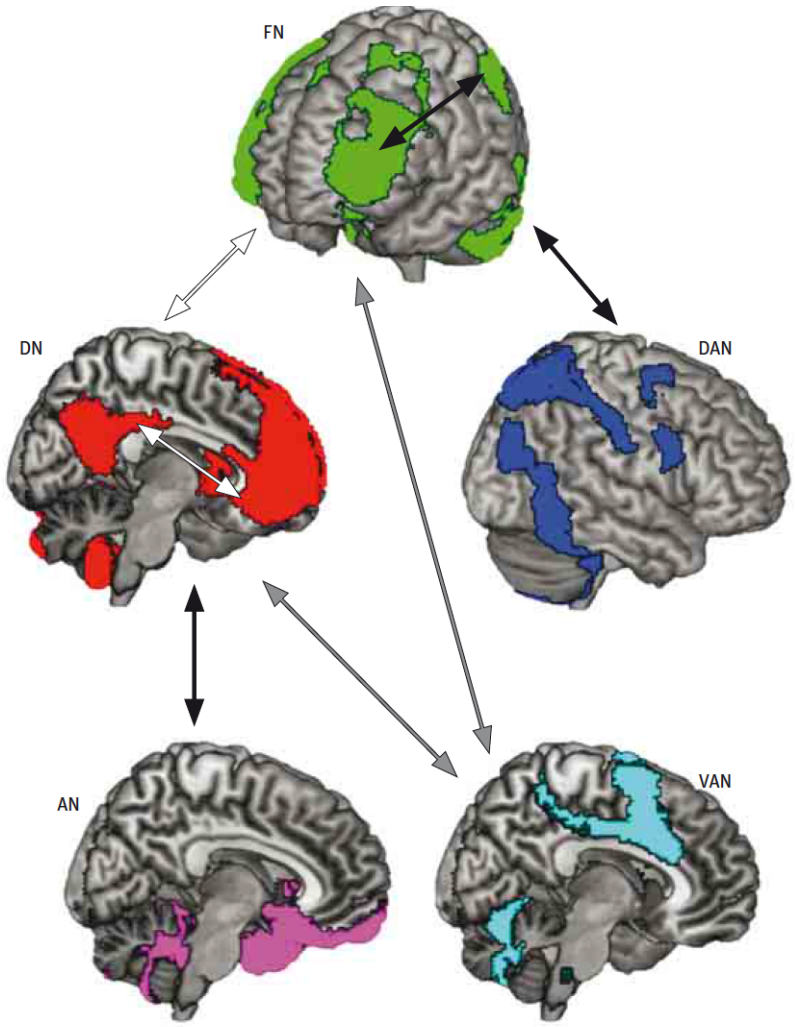
Fig. 28



[a] Panel A is a schematic diagram highlighting key nodes in emotion-processing and emotion-regulation neural circuitry in healthy individuals; arrows represent key regulatory connections between prefrontal cortical regions and the amygdala. In panel B, key functional abnormalities in individuals with bipolar disorder are highlighted in red (in regions and connections between regions); these include abnormally increased amygdala activity during emotion processing, emotion regulation, and performance of nonemotional tasks; abnormally decreased activity in the ventrolateral prefrontal cortex and orbitofrontal cortex during emotion regulation; and decreased functional connectivity between these prefrontal cortical regions and the amygdala during emotion regulation. In parallel, there are widespread abnormal decreases in gray matter volume and cortical thickness in prefrontal cortical regions, decreased gray matter volume in the amygdala and hippocampus, and abnormally decreased fractional anisotropy in white matter tracts connecting the ventral prefrontal cortex and anterior temporal regions. These changes are indicated by smaller sizes of ovals representing these regions. ACC=anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; mdPFC=mediodorsal prefrontal cortex; OFC=orbitofrontal cortex; vlPFC=ventrolateral prefrontal cortex.

Fig. 27
Neural Circuitry in Bipolar Disorder
from Phillips and Swartz, 2014

Fig. 28



Reduced connectivity among regions of the frontoparietal network (FN) may underlie general deficits in cognitive control, whereas increased connectivity between the FN and default network (DN) and reduced connectivity between the FN and dorsal attention network (DAN) may reflect biases toward ruminative thoughts at the cost of attending to the external world. Meanwhile, reduced connectivity between the affective network (AN) and medial prefrontal cortex regions that mediate top-down regulation may reflect impaired ability to upregulate or downregulate emotions or arousal, whereas abnormal connectivity between the ventral attention network (VAN) and posterior regions may reflect altered or biased salience monitoring. Black arrows indicate hypoconnectivity in MDD; white arrows, hyperconnectivity in MDD; and gray arrows, generally abnormal (both hypoconnectivity and hyperconnectivity in MDD).

Fig. 28

Fig. 28

Fig. 29

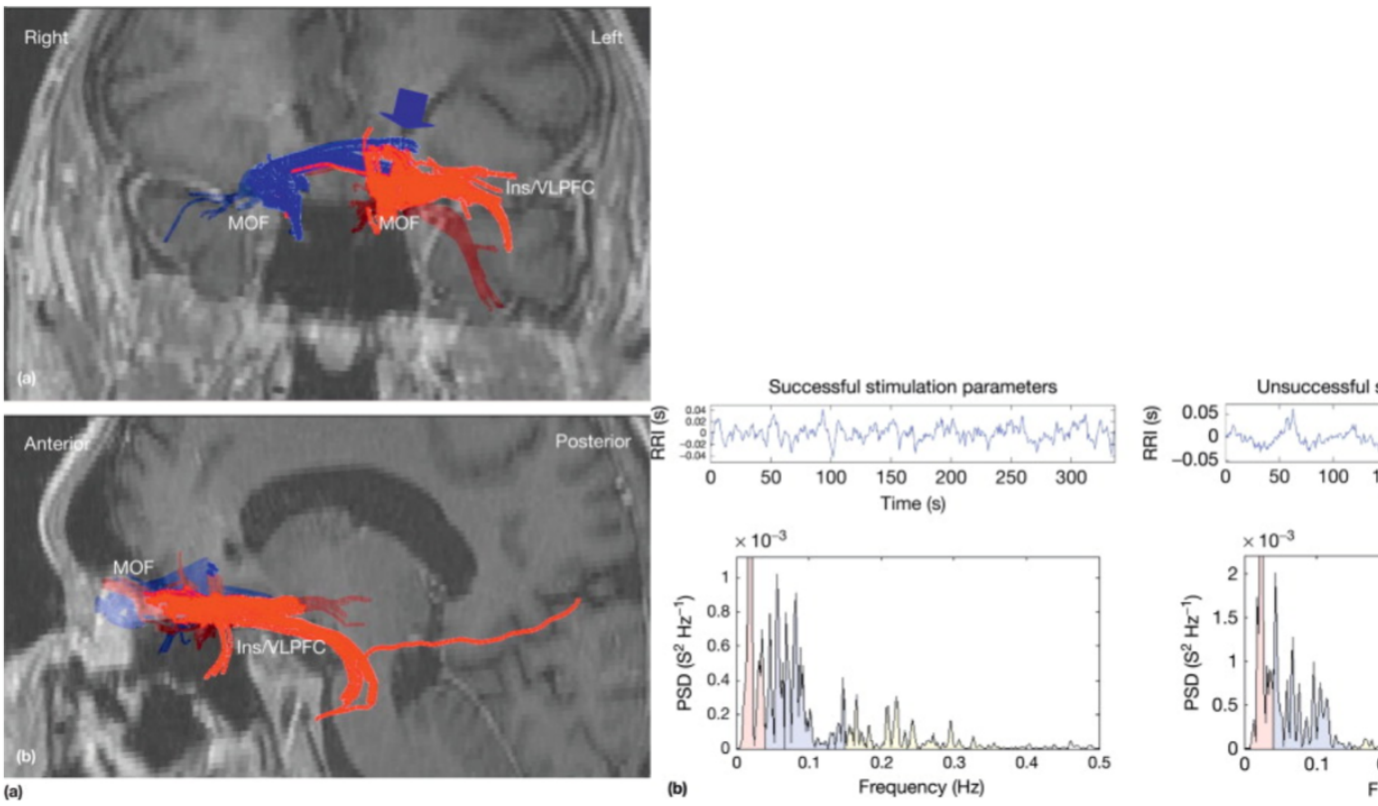


Fig.

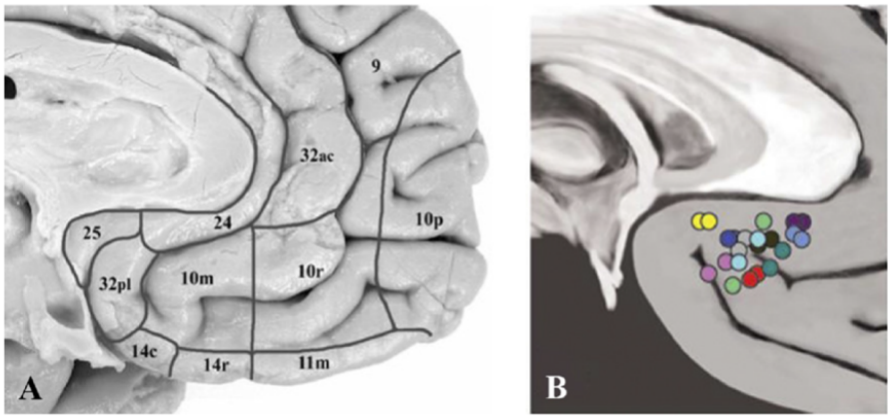
Diffusion Imaging of white matter tracts in the vicinity of DBS electrodes in a patient with successful deep brain stimulation of area 25 (panel (a)) and autonomic activity profiles brought about by DBS parameters associated with goo left plots) and poor (right plots) response (b). The modification of circuits involving the prefrontal, allocortical, and subcortical/autonomic structures seems to be for full antidepressant effect (please see the text for details and Figure 2) Reproduced from Guinjoan, S. M., Mayberg, H. S., Costanzo, E. Y.,, R. D., Tenca, E., Antico, J., et al. (2010). Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. **The Journal of Neuropsychiatry and Clinical Neuroscience 22(3), 265–277**

From:

Brain Mapping: An Encyclopedic Reference http://dx.doi.org/10.1016/B978-0-12-397025-1.00119-6

Fig. 28

Subcallosal Brain Stimulation in Depression



Anatomic regions potentially influenced by brain stimulation of the subcallosal region by brain stimulation of the subcallosal region. (A) Architectonic of the medial surface of the human brain according to Ongur and colleagues (reprinted from [Ongur et al, 2003] with permission from John Wiley and Sons). (B) Location of deep brain stimulation electrodes in p patients who responded to surgery in the series. Note that contacts used for chronic stimulation (colored circles) were clustered in the subcallosal region, not only in cingulate areas 25, 24, and 32pl but also 10m (reprinted from the Journal of Neurosurgery [Hamani et al, 2009], with permission from the AANS)

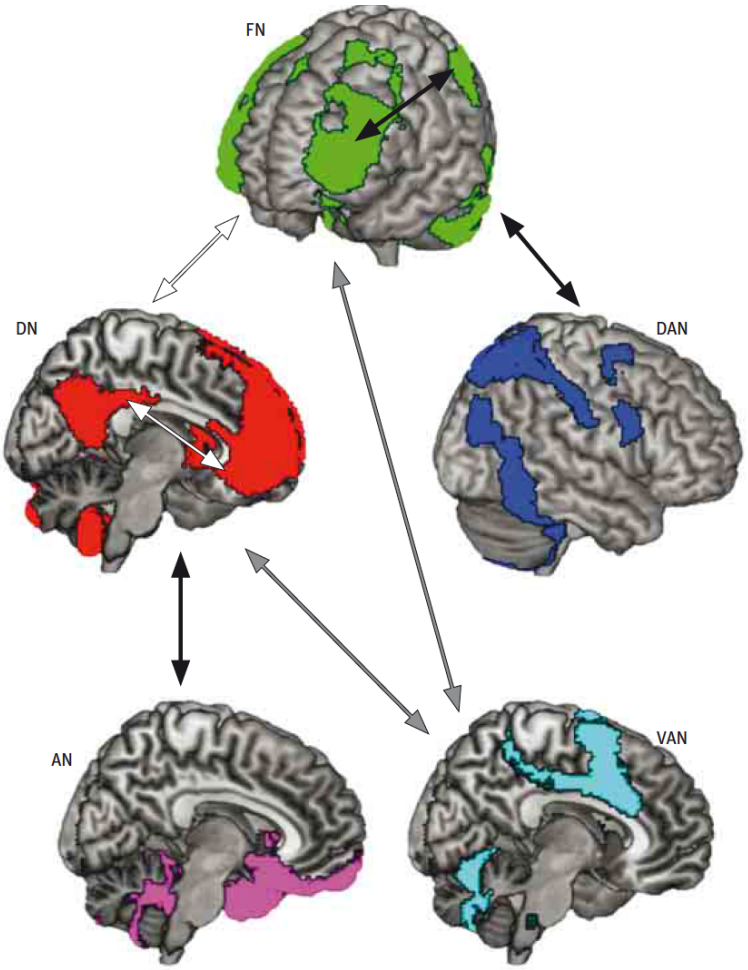
From Hamani et al, 2011

Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, Lozano AM (2009): Deep brain stimulation of the subcallosal cingulate gyrus for depression: Anatomical location of active contacts in clinical responders and a suggested guideline for targeting. J Neurosurg 111: 1209–1215.

Ongur D, Ferry AT, Price JL (2003): Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 460:425–449.

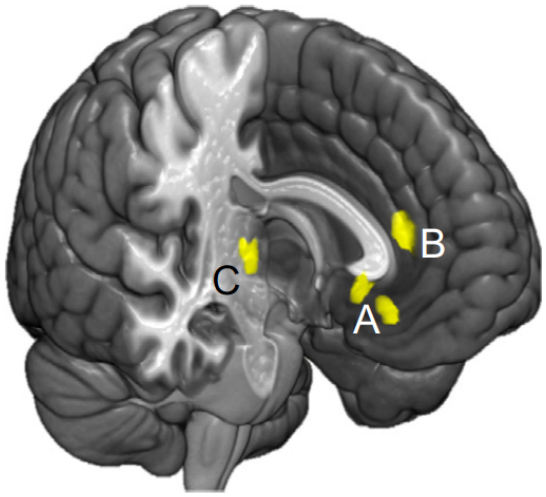
Fig. 30

Fig. 28



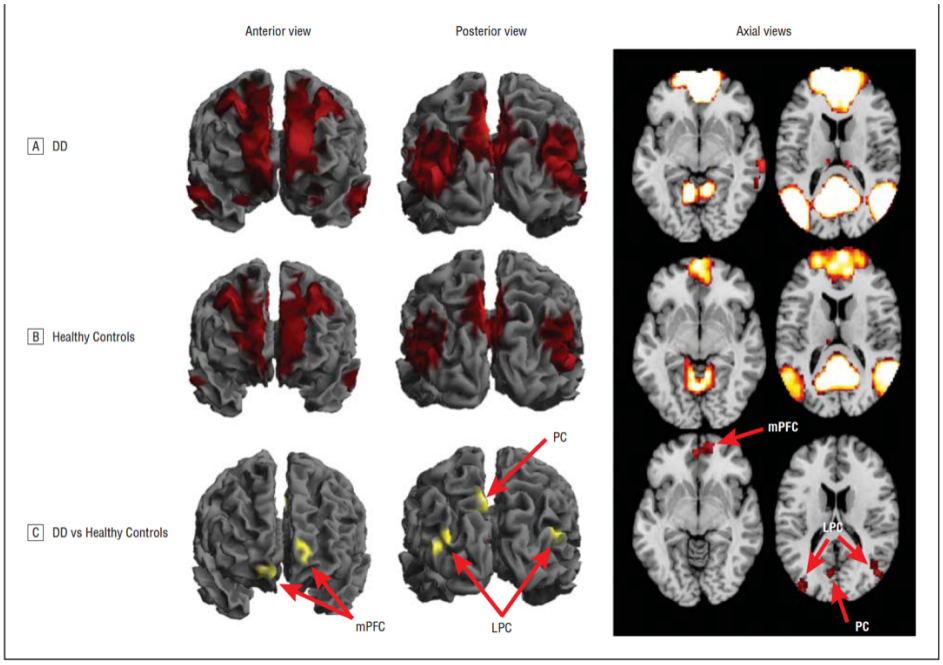
Reduced connectivity among regions of the frontoparietal network (FN) may underlie general deficits in cognitive control, whereas increased connectivity between the FN and default network (DN) and reduced connectivity between the FN and dorsal attention network (DAN) may reflect biases toward ruminative thoughts at the cost of attending to the external world. Meanwhile, reduced connectivity between the affective network (AN) and medial prefrontal cortex regions that mediate top-down regulation may reflect impaired ability to upregulate or downregulate emotions or arousal, whereas abnormal connectivity between the ventral attention network (VAN) and posterior regions may reflect altered or biased salience monitoring. Black arrows indicate hypoconnectivity in MDD; white arrows, hyperconnectivity in MDD; and gray arrows, generally abnormal (both hypoconnectivity and hyperconnectivity in MDD).

Fig. 31 *Large Scale Network Dysfunction in Major Depressive Disorder from* ***Kaiser et al (2015)***



Region	Voxels	X	Y	Z	Figure
Subgenual prefrontal cortex (bimodal cluster)	1281	0	26	-10	A
Left dorsal anterior cingulate	976	-6	37	12	B
Right medial dorsal thalamus	891	9	-18	5	C
Right posterior lateral parietal cortex	734	42	-67	29	

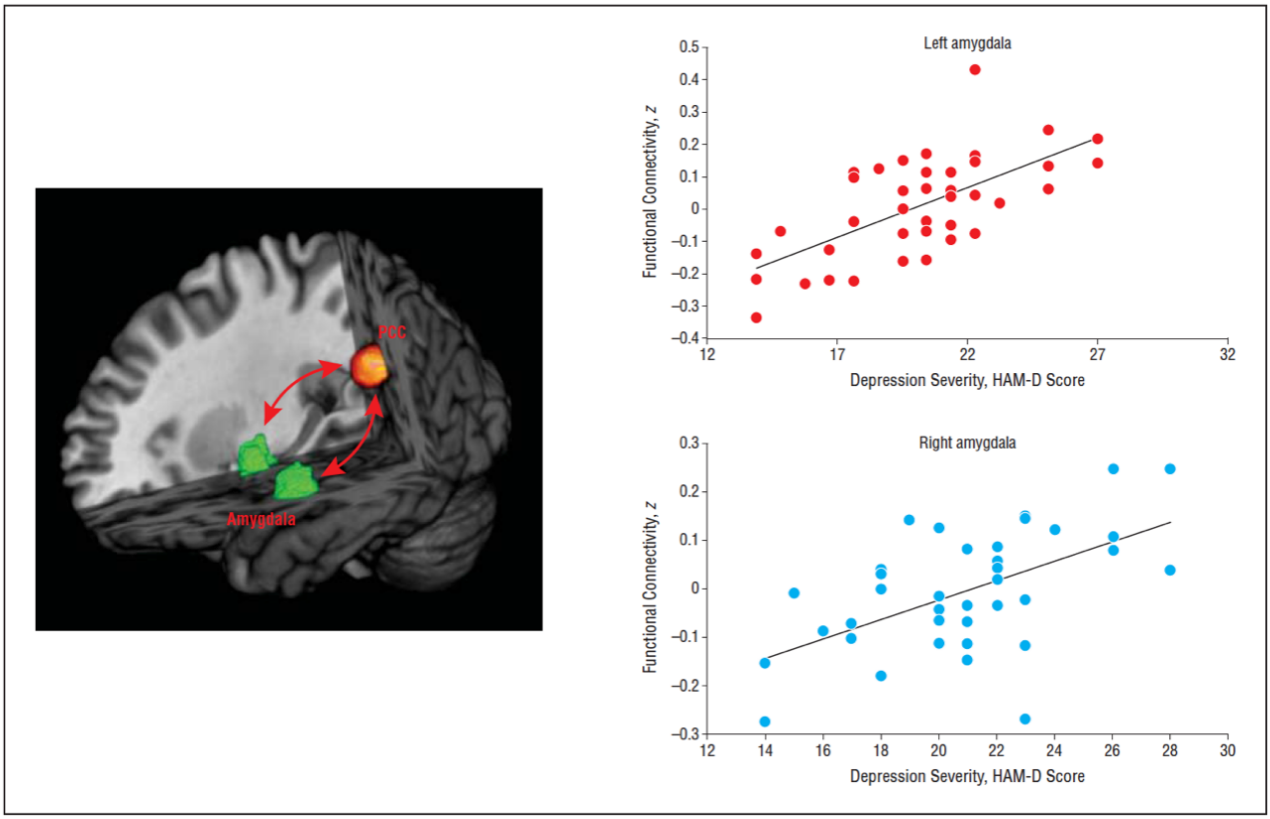
Fig. 32 Regions showing reliably increased connectivity with the-mode network in major depressive disorder.
Hamilton et al, 2015



Whole-brain resting-state functional-connectivity maps with seed region in the posterior cingulate cortex. Qualitatively, the connectivity maps the commonly observed connectivity pattern of the default mode network in both the participants with dysthymic disorder (DD; N = 41) (A) and in the healthy control participants (N = 25) (B). C, Comparison of the 2 groups demonstrated that the participants with DD had stronger connections from the posterior with DD had stronger connections from the posterior cortex to the mesial prefrontal cortex (mPFC) bilaterally, lateral parietal lobes (LPC) bilaterally, and precuneus (PC).

From: **Posner et al, 2013**

Fig. 33

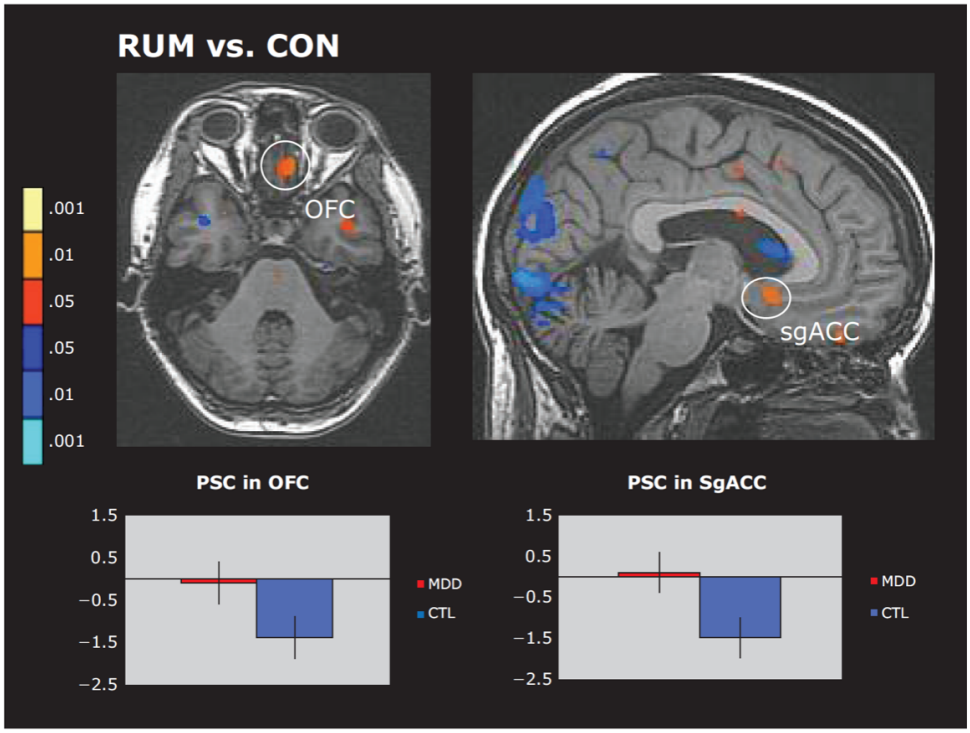


Connection strength between the posterior cingulate cortex (PCC) and left amygdala (peak voxel Montreal Neurological Institute coordinates: x = 18, = 4, z = 22) predicted depressive symptoms on the Hamilton Depression Rating Scale (HAM-D) (r = 0.65; P .001; cluster size, 503 voxels) in patients with (N = 41). The connection strength between the PCC and the right amygdala was also a predictor of HAM-D scores (r = 0.58; P .001; peak voxel Neurological Institute coordinates: x = 36, y = 0, z = 26; cluster size, 43 voxels), but this finding did not reach both arms of our statistical threshold.

From: **Posner et al, 2013.**

Fig. 34

Fig. 35



Activations to rumination (RUM) versus concrete (CoN) distraction contrast. Yellow activations, Mdd . Ctl; blue activations, Ctl , Mdd. left 5 left. orbitofrontal cortex (4, 30, 226). subgenual anterior cingulate (**BA 25;** 24, 15, 27), p , .02, corrected. Mdd, depressed group; Ctl, control group.

Cooney et al, 2010

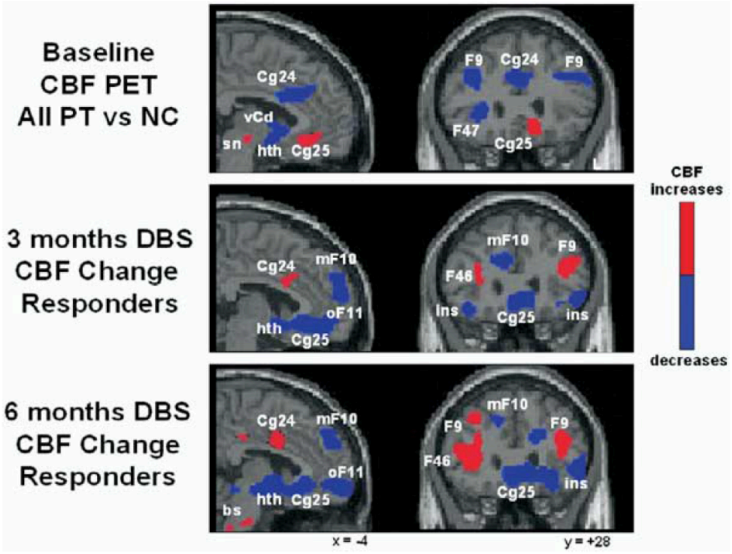
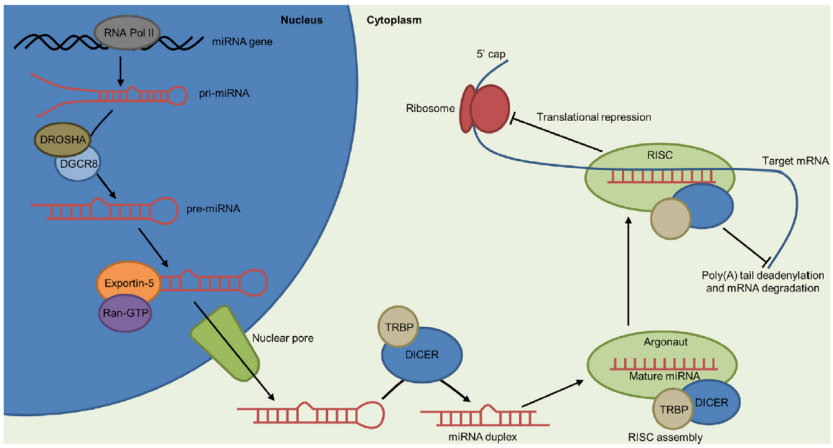


Figure 2. PET Scans

Regional cerebral blood flow changes (CBF PET) in TRD patients at baseline (row 1) and after 3 months (row 2) and 6 months (row 3) of successful treatment with continuous DBS. Sagittal (left) and coronal (right) views. Baseline CBF abnormalities are seen relative to age- and gender-matched healthy control subjects (NC): increases in subgenual cingulate (Cg25) and decrease in dorsolateral prefrontal (F9), ventrolateral prefrontal (F47) and anterior cingulate (Cg24) cortices (row 1, patients 1–5). Three months of DBS relative to baseline (row 2, patients 1, 3, and 5): decreases in Cg25, hypothalamus (Hth), anterior insula (ins), medial frontal (mF10) and orbital frontal (oF11); increases in prefrontal (F9/46) and dorsal cingulate (cg24). This same pattern is maintained at 6 months, although additional increases are seen in the brainstem (bs) (row 3). Slice location is in millimeters relative to anterior commissure. Numbers are Brodmann designations. L, left. Significant CBF increases in red; decreases in blue ($p < 0.001$).

Mayberg et al, Neuron, Vol. 45, 651–660, March 3, 2005

In this study, we have demonstrated that high-frequency DBS of the Cg25WM can produce striking behavioral changes in patients with TRD. Acute behavioral effects were time locked to stimulation intraoperatively and during short-term testing sessions. Furthermore, sustained clinical improvements decreased with blinded discontinuation of chronic DBS and were recaptured with reinstitution of stimulation, providing evidence as to the specificity of DBS-mediated changes. PET scan data further indicate that Cg25WM DBS has profound effects on the cerebral networks involved in depression and suggest that reversal of baseline abnormalities correlates with antidepressant benefits. While the number of subjects is small, four of six patients (66%) achieved sustained clinical response or remission at the end of 6 months without changes in concurrent medications. This response rate is striking



MicroRNA (miRNA) structure, biogenesis, and function. RNA polymerase II transcribes the primary miRNA transcript, which is processed in the by Drosha and the microprocessor complex into the 70 -nt precursor miRNA hairpin. This hairpin is exported to the cytoplasm by Exportin -5 and-GTP, where Dicer cuts off the loop end of the hairpin, leaving an 22-nt long, imperfectly base-paired RNA duplex. One of these strands is the mature miRNA, which is loaded into the RNA-induced silencing complex, which then mediates the silencing of messenger RNA molecules, which are targeted based complementarity to the loaded miRNA. The RNA-induced silencing complex silences gene expression by inhibiting translation through interference 50 capbinding protein interactions or degrading the target messenger RNA by compromising its stability through poly(A) tail deadenylation, 50 cap loss, and degradation. DGCR8, DiGeorge syndrome critical region 8; mRNA, messenger RNA; pre-miRNA, precursor microRNA; pri- miRNA, primary transcript; RISC, RNA-induced silencing complex.
Geaghan and Cairns, 2015.

Summary

In this paper we attempt to challenge a set of long standing ideas that appears to support a natural mind/body dualism. Consciousness, Phenomenal First Person Experience (Qualia), Free Will, and the idea of the Soul have all been used to stake out an ontological domain that is seen as non-compatible with a unified physicalist view of the universe. The result is a separation of mind and body which has an immediate impact on how we view psychiatric illness and on the way psychiatric residents perceive their identity as physicians. We have reviewed recent findings from neuroscience to deconstruct the notions of mind/body and self, consciousness and the soul. The "explanatory gap" separating the brain from first person experience is rapidly closing. Current studies are showing that the brain is constantly modified on time scales from seconds to decades by epigenetic modification of genes and modification of brain circuitry and brain

The major components of the metabolic syndrome are generally agreed to include central obesity, hyper- tension, dyslipidemia, and glucose intolerance or insulin resistance. The metabolic syndrome confers a 5–6-fold increase in the risk of developing type 2 diabetes mellitus and a 3–6-fold increase in the risk of death from coronary heart disease.

A review of prospective, longitudinal studies of the early cardiovascular and metabolic adverse effects (such as weight gain, hyperglycemia, hypertension and dyslipidemia) of antipsychotic drug treatment in patients treated for a first-episode psychotic disorder revealed that cardiovascular risk increased significantly after the patients' initial exposure to the antipsychotic drug.

De Hert, M. et al. Nat. Rev. Endocrinol. 8, 114–126 (2012)

Patients with schizophrenia are twice as likely dying from cardiovascular disease as the general population, and tend to have an average of 9–12 years of life loss

Casey DE. Metabolic issues and cardiovascular diseases in patients with psychiatric disorders. Am J Med 2005; 118: 15s–22s.

Lambert TJ, Velakoulis D, Pantelis C. Medical comorbidity in schizophrenia. Med J Aust 2003; 178: S67–S70

Is Metabolic Syndrome On the Radar?

Improving Real-Time Detection of Metabolic Syndrome and Physician Response by Computerized Scan of the Electronic Medical Record

Kingwai Lui, DO[a]; Gagandeep Randhawa, MD[a]; Vicken Totten, MD, MS[b]; Adam E. Smith, PhD[c]; and Joachim Raese, MD[a,*]

Prim Care Companion CNS Disord
2016;18(1):doi:10.4088/PCC.15m01849

Table 1. Patients Meeting Criteria for Metabolic Syndrome Postintervention (n = 454)[a]

Variable	Patients
Age, mean (median [SD]), range, y	40.7 (39.0 [13.1]), 18–87
Gender	
Male	254 (55.9)
Female	200 (44.1)
Axis I diagnosis at admission	
Psychotic disorder	216 (47.6)
Bipolar disorder	80 (17.6)
Depression	122 (26.9)
Other[b]	36 (7.9)
No. of metabolic syndrome criteria met[c]	
3	249 (54.8)
4	165 (36.3)
5	40 (8.8)
SGA prescribed at admission (n = 209)	
Clozapine	7 (3.3)
Olanzapine	75 (35.9)
Quetiapine	52 (24.9)
Risperidone	75 (35.9)
SGA prescribed at discharge (n = 199)	
Clozapine	8 (4.0)
Olanzapine	68 (34.2)
Quetiapine	48 (24.2)
Risperidone	75 (37.7)

[a]Data are presented as n (%) unless otherwise specified.
[b]Other (mood disorder not otherwise specified, adjustment disorder).
[c]Metabolic syndrome criteria: (1) hypertension: systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg, (2) body mass index > 25 kg/m^2, (3) fasting glucose > 110 mg/dL, (4) fasting high-density lipoproteins < 40 mg/dL in males (< 50 mg/dL in females), and (5) fasting triglycerides > 150 mg/dL.
Abbreviation: SGA = second-generation antipsychotic.

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Prim Care Companion CNS Disord 2016;18(1):doi:10.4088/PCC.15m01849

Table 2. Interventions for Metabolic Syndrome[a]

Variable	Phase 2[b] (n = 232)	Phase 3[c] (n = 222)
Axis III diagnosis	0 (0)	65 (29.3)
Change in antipsychotic use[d]		
Removal	8 (3.4)	6 (2.7)
Addition	7 (3.0)	6 (2.7)
Medication prescribed treatment for components of metabolic syndrome		
Hypertension	79/217 (36.4)	74/154 (48.1)
Hyperlipidemia	43/77 (55.8)	23/102 (22.5)
Hyperglycemia	44/63 (69.8)	36/55 (65.5)
Metformin use		
At admission	13/63 (20.6)	24/55 (43.6)
At discharge	25/63 (39.7)	21/55 (38.2)
Completeness of metabolic syndrome treatment		
Not treated	122 (52.6)	133 (60.0)
Partially treated	52 (22.4)	37 (16.7)
Completely treated	58 (25.0)	52 (23.4)

[a]Data are presented as n (%).
[b]Phase 2: without e-mail notification of physicians of the diagnosis of metabolic syndrome.
[c]Phase 3: with e-mail notification of physicians of the diagnosis of metabolic syndrome.
[d]Second-generation antipsychotic of interest (clozapine, risperidone, olanzapine, quetiapine).

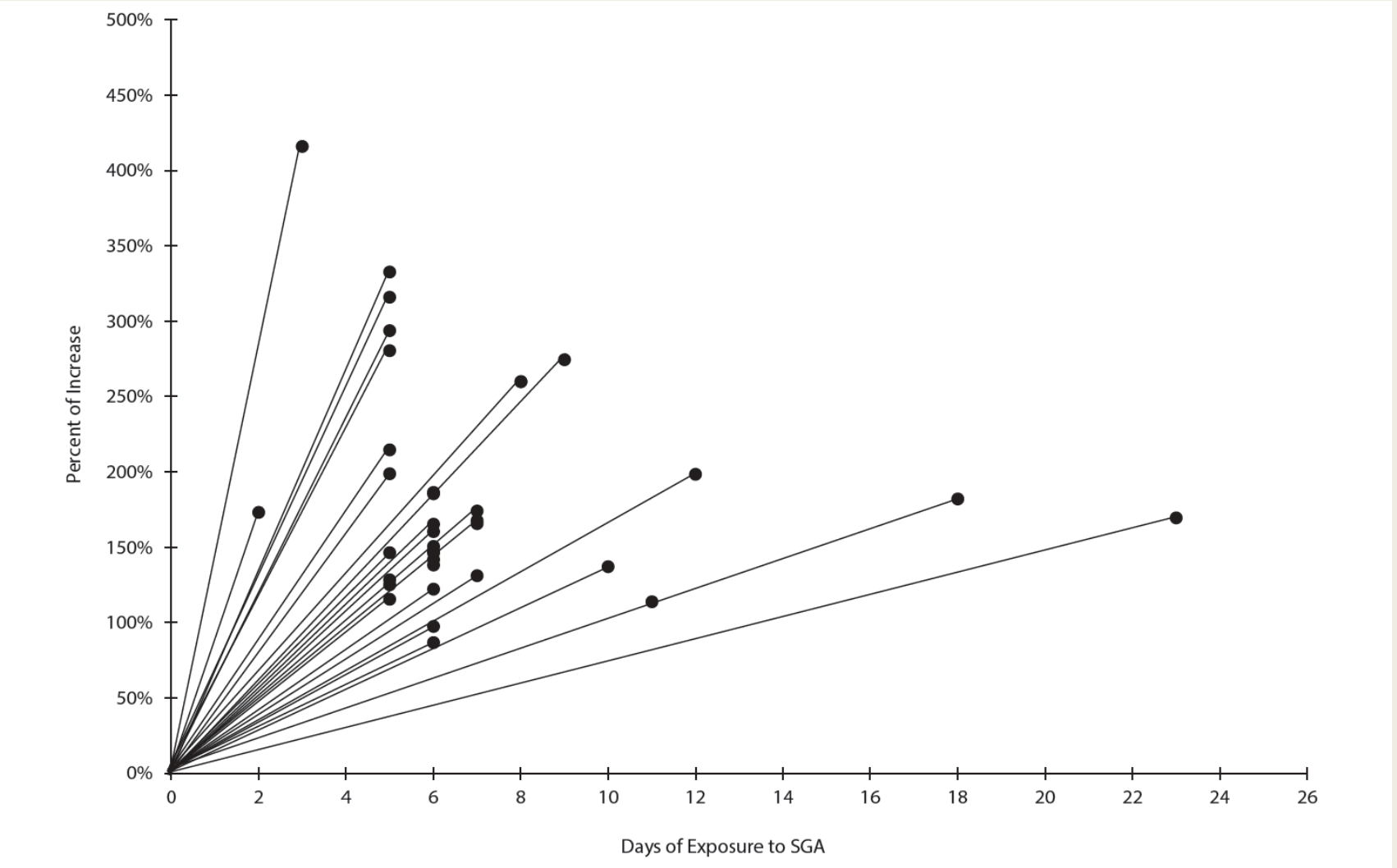
Prim Care Companion CNS Disord 2016;18(1):doi:10.4088/PCC.15m01849

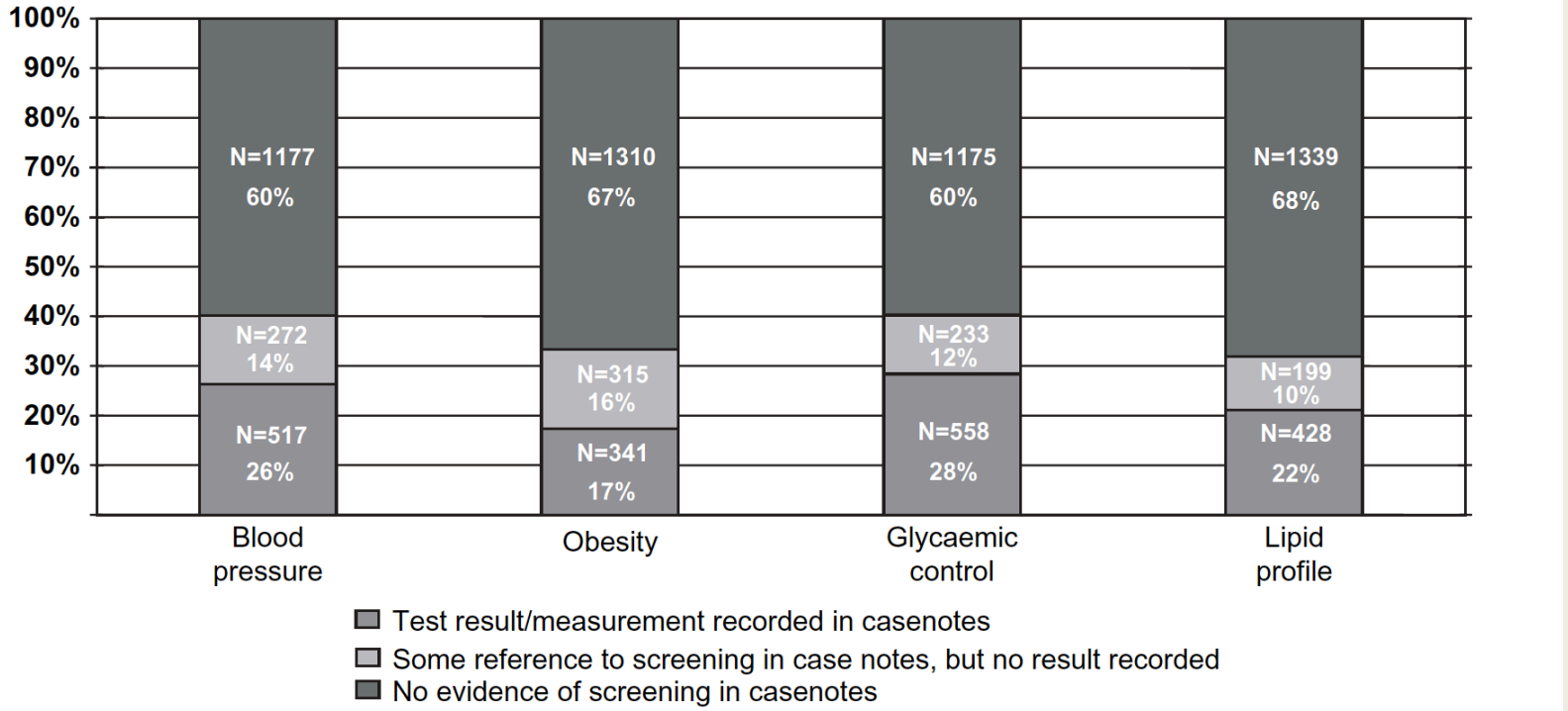
Table 3. Rapid Increase in Triglycerides With Use of Second-Generation Antipsychotics (SGAs)[a]

Age (y)	Gender	Duration of SGA Treatment (d)	Triglyceride Level Before (mg/dL)	Triglyceride Level After (mg/dL)	SGA	Intervention
48	Male	6	173	286	Olanzapine	None
46	Male	6	105	145	Olanzapine	None
58	Male	5	142	417	Quetiapine	None
44	Female	6	153	187	Clozapine	None
36	Male	3	101	420	Olanzapine	None
34	Female	6	63	101	Risperidone	None
46	Male	9	21	349	Olanzapine	None
51	Male	2	52	90	Olanzapine	None
48	Male	7	131	228	Olanzapine	None
31	Male	10	116	159	Olanzapine	None
20	Male	5	89	296	Olanzapine	None
53	Female	18	249	453	Quetiapine	None
18	Female	6	122	180	Olanzapine	None
59	Male	5	145	186	Quetiapine	None
50	Male	5	148	185	Olanzapine	None
24	Male	5	61	171	Risperidone	None
28	Female	7	132	173	Risperidone	None
18	Male	5	62	133	Olanzapine	None
37	Male	9	428	266	Quetiapine	Atorvastatin 20 mg
34	Male	4	161	135	Risperidone	Fenofibrate 160 mg
44	Female	2	468	268	Quetiapine	Atorvastatin 40 mg
38	Male	39	152	173	Risperidone	None
28	Female	28	132	173	Risperidone	None
50	Female	17	195	225	Quetiapine	None
50	Female	10	195	201	Quetiapine	None
38	Male	8	226	259	Olanzapine	None
18	Male	12	126	250	Haloperidol,	None
18	Male	12	87	226	Risperidone	None
30	Male	7	194	168	Olanzapine	None
25	Male	1	85	144	Haldol	None
39	Female	2	132	193	Olanzapine	None
37	Male	5	154	255	Olanzapine	None
21	Female	16	82	152	Olanzapine	None
21	Male	13	63	199	Quetiapine	None
21	Male	9	153	224	Quetiapine	None
59	Male	35	125	343	Quetiapine	Simvastatin 10 mg
47	Female	15	206	292	Risperidone	Atorvastatin 20 mg
33	Male	8	108	181	Quetiapine	None

[a]Thirty-eight patients with metabolic syndrome received repeat lipid panels during continuation of SGA treatment with length of treatment from 3 to 39 days. A subset of 30 patients showed a greater than 20% increase in triglyceride level. Atorvastatin, fenofibrate, and simvastatin may have a protective effect on SGA-induced hypertriglyceridemia.

Figure 1. Triglyceride Level Increase Associated With Continued Use of a Second-Generation Antipsychotic (SGA) (olanzapine, risperidone, quetiapine, or clozapine)





We conducted an audit of the clinical records of 1966 eligible patients under the care of 48 multidisciplinary, assertive outreach clinical teams in 21 mental health services across the United Kingdom.

Percentage of patients screened for each of the 4 aspects of the metabolic syndrome in the total national sample (n =1966).

Barnes et al (2007) Schizophrenia Bulletin 33:1397–1403

In the Clinical Antipsychotic of Intervention Effectiveness study,[7,37] where fasting or random plasma glucose was measured in 689 people with schizophrenia, 13% were found to have diabetes.

7. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res. 2005;80:45–53.

37. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES 111. Schizophr Res. 2005;80:19–32.

Original Investigation | META-ANALYSIS

Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics
A Systematic Review and Meta-analysis

Britta Galling, MD; Alexandra Roldán, MD; René E. Nielsen, MD, PhD; Jimmi Nielsen, MD, PhD; Tobias Gerhard, PhD; Maren Carbon, MD; Brendon Stubbs, PhD; Davy Vancampfort, PhD; Marc De Hert, MD, PhD; Mark Olfson, MD, MPH; Kai G. Kahl, MD; Andres Martin, MD; Jeff J. Guo, MD; Hsien-Yuan Lane, MD, PhD; Fung-Chang Sung, PhD, MPH; Chun-Hui Liao, MD; Celso Arango, MD; Christoph U. Correll, MD

CONCLUSIONS AND RELEVANCE Although T2DM seems rare in antipsychotic-exposed youth, cumulative risk and exposure-adjusted incidences and IRRs were significantly higher than in healthy controls and psychiatric controls. Olanzapine treatment and antipsychotic exposure time were the main modifiable risk factors for T2DM development in antipsychotic-exposed youth. Antipsychotics should be used judiciously and for the shortest necessary duration, and their efficacy and safety should be monitored proactively.

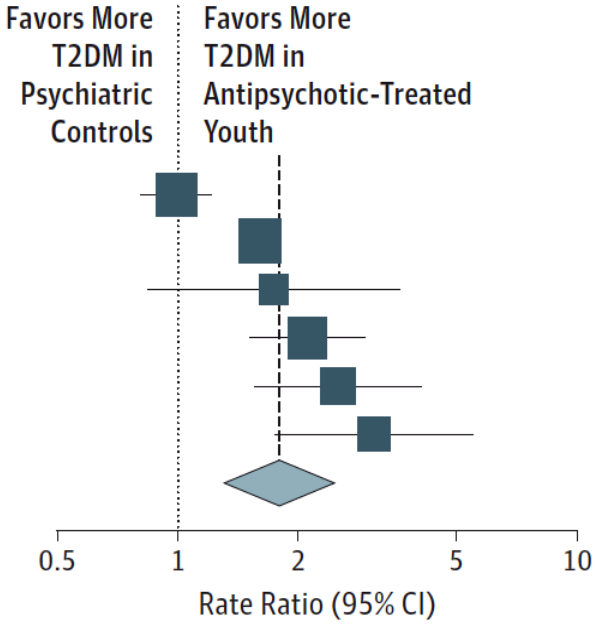
Galling et al, JAMA Psychiatry.
doi:10.1001/jamapsychiatry.2015.2923
Published online January 20, 2016

Antipsychotic-exposed youth had a cumulative T2DM risk of 5.72 (95% CI, 3.45-9.48; P < .001) per 1000 patients. The incidence rate was 3.09 (95% CI, 2.35-3.82; P < .001) cases per 1000 patient-years. Compared with healthy controls, cumulative T2DM risk (odds ratio [OR], 2.58; 95% CI, 1.56-4.24; P < .0001) and incidence rate ratio (IRR) (IRR, 3.02; 95% CI, 1.71-5.35; P < .0001) were significantly greater in antipsychotic-exposed youth. Similarly, compared with psychiatric controls, antipsychotic-exposed youth had significantly higher cumulative T2DM risk (OR, 2.09; 95% CI, 1.50-5 2.90; P < .0001) and IRR (IRR, 1.79; 95% CI, 1.31-2.44; P < .0001).

Galling, B., Roldán, A., Nielsen, R., Nielsen, J., Gerhard, T., Carbon, M., Stubbs, B., et al. (2016). Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *73*(3), 247. jama. doi:10.1001/jamapsychiatry.2015.2923

Figure 1. Forest Plot of Incidence Rate Ratio for T2DM per Patient-Years in Antipsychotic-Exposed Youth vs Psychiatric Controls

Source	Statistics for Each Study			No. With Diabetes/Total No.		Relative Weight
	Rate Ratio (95% CI)	*Z*-Value	*P* Value	Antipsychotic-Exposed Youth	Psychiatric Controls	
McIntyre and Jerrell,[48] 2008	0.987 (0.810-1.202)	-0.130	.90	125/36473	469/135072	21.04
Rubin et al,[54] 2015	1.600 (1.440-1.778)	8.753	<.001	401/171185	2563/1750722	22.40
Andrade et al,[34] 2011	1.742 (0.845-3.588)	1.505	.13	12/3710	19/10231	10.26
Nielsen et al,[51] 2014	2.117 (1.523-2.943)	4.463	<.001	52/32647	111/147539	18.28
Enger et al,[47] 2013	2.519 (1.562-4.064)	3.786	<.001	71/12309	22/9608	14.90
Bobo et al,[35] 2013	3.105 (1.769-5.447)	3.949	<.001	92/38022	14/17963	13.13
Total	1.791 (1.312-2.445)	3.672	<.001			

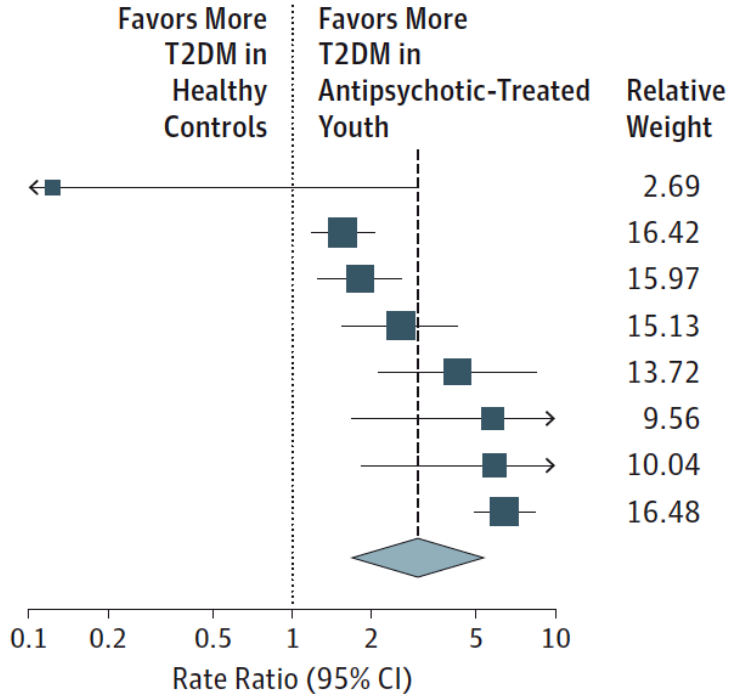


T2DM indicates type 2 diabetes mellitus.

Galling et al, JAMA Psychiatry.
doi:10.1001/jamapsychiatry.2015.2923
Published online January 20, 2016

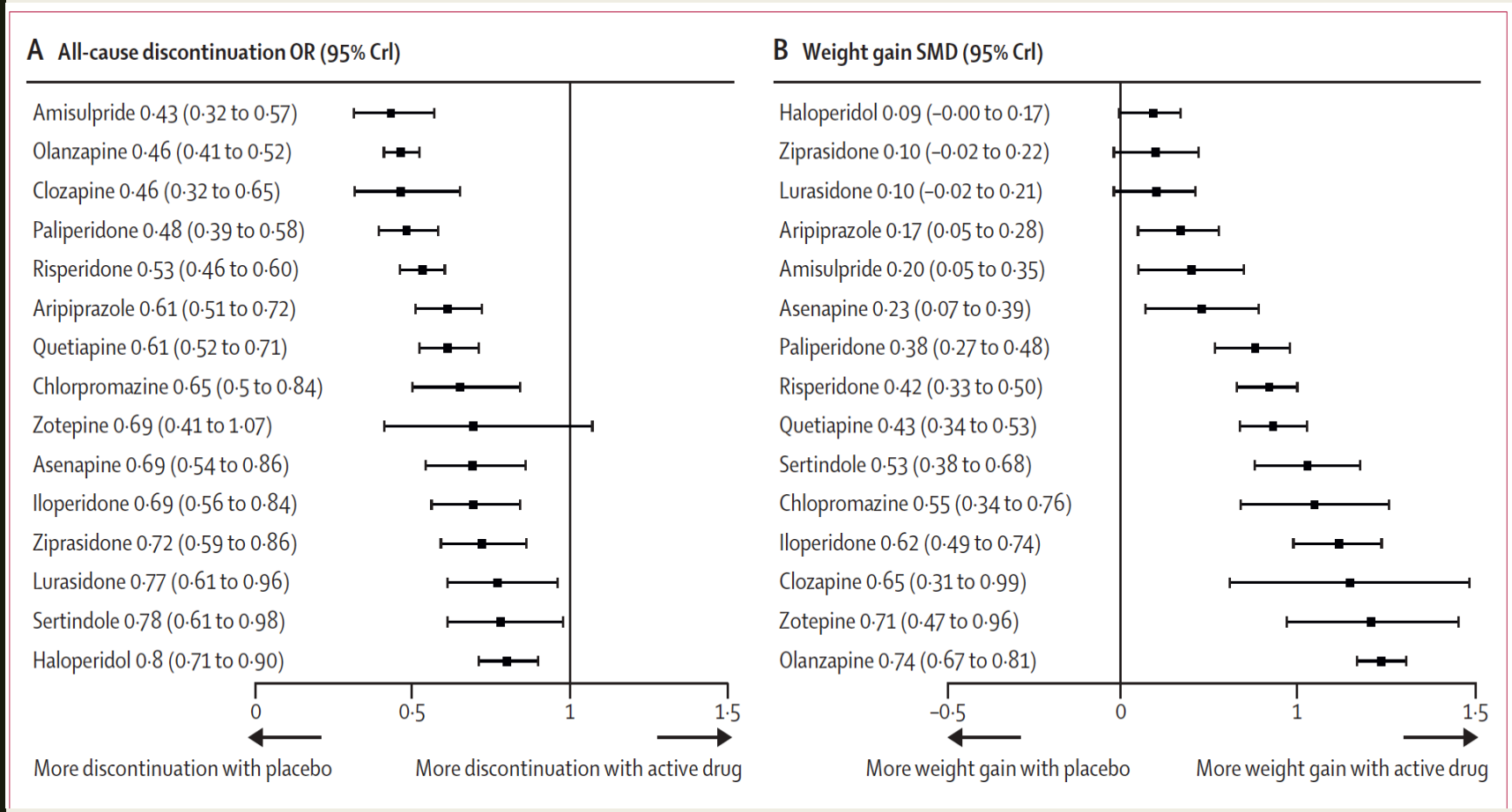
Figure 2. Forest Plot of Incidence Rate Ratio for T2DM per Patient-Years in Antipsychotic-Exposed Youth vs Healthy Controls

Source	Statistics for Each Study: Rate Ratio (95% CI)	Z-Value	P Value	No. With Diabetes/Total No.: Antipsychotic-Exposed Youth	Healthy Controls
Arango et al,[46] 2014	0.123 (0.005-3.030)	-1.281	.200	1/136	0/6
McIntyre and Jerrell,[48] 2008	1.560 (1.185-2.055)	3.165	.002	125/36 473	85/38 700
Morrato et al,[50] 2010	1.812 (1.260-2.605)	3.207	.001	48/2648	74/7397
Sohn et al,[55] 2015	2.574 (1.568-4.228)	3.736	<.001	27/8161	37/28 792
Andrade et al,[34] 2011	4.249 (2.144-8.421)	4.145	<.001	12/3710	26/34 156
Liao et al,[52] 2011 (SGA)	5.774 (1.690-19.725)	2.797	.005	4/1755	7/17 734
Liao et al,[52] 2011 (FGA)	5.889 (1.847-18.775)	2.997	.003	4/2835	10/41 735
Enger et al,[47] 2013	6.412 (4.934-8.331)	13.904	<.001	71/12 309	265/294 564
Total	3.019 (1.703-5.351)	3.783	<.001		



FGA indicates first-generation antipsychotic; SGA, second-generation antipsychotic; and T2DM, type 2 diabetes mellitus.

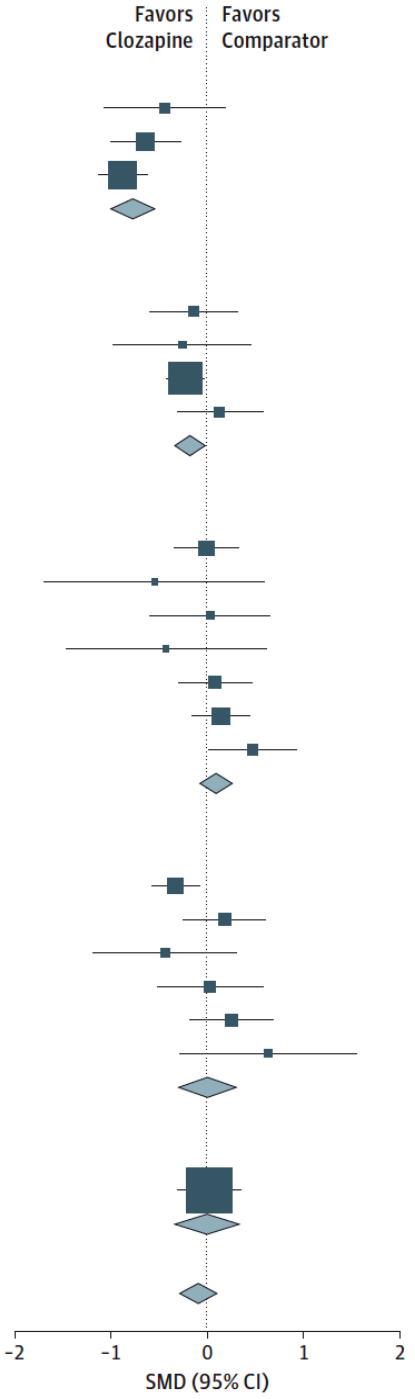
Galling et al, JAMA Psychiatry.
doi:10.1001/jamapsychiatry.2015.2923
Published online January 20, 2016



Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis.
***The Lancet*, *379*(9831), 2063–2071.**

Depot preparations reduced relapse (RR 0·31, 95% CI 0·21–0·41) more than did oral drugs (0·46, 0·37–0·57; p=0·03); depot Haloperidol (RR 0·14, 95% CI 0·04–0·55) and fluphenazine (0·23, 0·14–0·39) had the greatest effects.

Clozapine Comparator	No. of Patients	SMD (95% CI)
Chlorpromazine		
Hong et al,[57] 1997	40	-0.44 (-1.07 to 0.19)
Honigfeld et al,[53] 1984	125	-0.64 (-1.00 to -0.28)
Kane et al,[5,6] 1988	265	-0.88 (-1.13 to -0.63)
Total	430	-0.75 (-0.97 to -0.53)
$\tau^2=0.01$; $\chi_2=2.27$; $P=.32$; $I^2=12\%$		
Haloperidol		
Buchanan et al,[7] 1998	75	-0.14 (-0.59 to 0.31)
Kane et al,[58] 2001	34	-0.26 (-0.98 to 0.46)
Rosenheck et al,[8] 1997	423	-0.23 (-0.42 to -0.04)
Volavka et al,[59] 2002	77	0.13 (-0.31 to 0.57)
Total	609	-0.17 (-0.33 to -0.01)
$\tau^2=0.00$; $\chi_2=2.19$; $P=.53$; $I^2=0\%$		
Olanzapine		
Bitter et al,[60] 2004	140	-0.01 (-0.34 to 0.32)
Conley et al,[61] 2003	13	-0.55 (-1.69 to 0.59)
Meltzer et al,[62] 2008	40	0.03 (-0.59 to 0.65)
Moresco et al,[63] 2004	15	-0.43 (-1.48 to 0.62)
Naber et al,[64] 2005	108	0.08 (-0.30 to 0.46)
Tollefson et al,[65] 2001	176	0.14 (-0.16 to 0.44)
Volavka et al,[59] 2002	79	0.47 (0.02 to 0.92)
Total	571	0.10 (-0.07 to 0.27)
$\tau^2=0.00$; $\chi_2=5.36$; $P=.50$; $I^2=0\%$		
Risperidone		
Azorin et al,[56] 2001	256	-0.33 (-0.58 to -0.08)
Bondolfi et al,[66] 1998	86	0.18 (-0.25 to 0.61)
Breier et al,[67] 1999	29	-0.44 (-1.18 to 0.30)
McGurk et al,[68] 2005	52	0.03 (-0.52 to 0.58)
Volavka et al,[59] 2002	81	0.25 (-0.18 to 0.68)
Wahlbeck et al,[69] 2000	19	0.63 (-0.29 to 1.55)
Total	523	0.00 (-0.29 to 0.29)
$\tau^2=0.07$; $\chi_2=10.92$; $P=.05$; $I^2=54\%$		
Ziprasidone		
Sacchetti et al,[70] 2009	144	0.02 (-0.31 to 0.35)
Total	144	0.02 (-0.31 to 0.35)
$\tau^2=0.09$; $\chi_2=67.75$; $P<.001$; $I^2=70\%$		
Combined	2277	-0.11 (-0.28 to 0.06)



The size of squares reflects the weight attributed to each study for every separate pairwise meta-analysis (per drug) and not vs all drugs combined. The diamonds illustrate the summary effect sizes (per separate drug and vs all drugs combined). The middle of each diamond sits on the value for the summary effect size, and the width of the diamond depicts the width of the overall CI. The last comparison (combined) presents the summary effect size for the pairwise meta-analysis of clozapine vs all other antipsychotics. Error bars indicate 95% CI; SMD, standardized mean difference.

At present, insufficient blinded evidence exists on which antipsychotic is more efficacious for patients with treatment resistant schizophrenia.

Clozapine's superiority over the FGAs has been demonstrated repeatedly, which establishes clozapine as the standard treatment in this specific population, but evidence from blinded RCTs for the comparison of clozapine with other SGAs is lacking. Our analysis suggests that more trials comparing clozapine with other SGAs in patients with more severe illness and using high clozapine doses are warranted. Moreover, the evidence on antipsychotics other than clozapine, haloperidol, olanzapine, and risperidone is scarce, and their results can change if further studies become published.

Samara et al,
JAMA Psychiatry Published online February 3, 2016

Original Investigation

Cardiometabolic Risk in Patients With First-Episode Schizophrenia Spectrum Disorders

Baseline Results From the RAISE-ETP Study

Christoph U. Correll, MD; Delbert G. Robinson, MD; Nina R. Schooler, PhD; Mary F. Brunette, MD; Kim T. Mueser, PhD; Robert A. Rosenheck, MD; Patricia Marcy, BSN; Jean Addington, PhD; Sue E. Estroff, PhD; James Robinson, MEd; David L. Penn, PhD; Susan Azrin, PhD; Amy Goldstein, PhD; Joanne Severe, MS; Robert Heinssen, PhD; John M. Kane, MD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.1314

The finding that higher levels of triglycerides, insulin, and insulin resistance were associated with olanzapine treatment is consistent with a large body of evidence regarding the cardiometabolic risk of olanzapine.(20,21,24,50-53) That the cardiometabolic effect was observable this early is alarming and supports the Schizophrenia Patient Outcomes Research Team's recommendation that clozapine and olanzapine should not be given as first-line treatment in FES.(54) The finding that a higher triglycerides to HDL-C ratio a marker of insulin resistance, was associated with quetiapine treatment is concerning.

Together with other data suggesting a marked and early adverse lipid signal with quetiapine despite similar weight gain as risperidone,(19-21,23,50) its first-line use in first-episode psychosis may need to be reevaluated.

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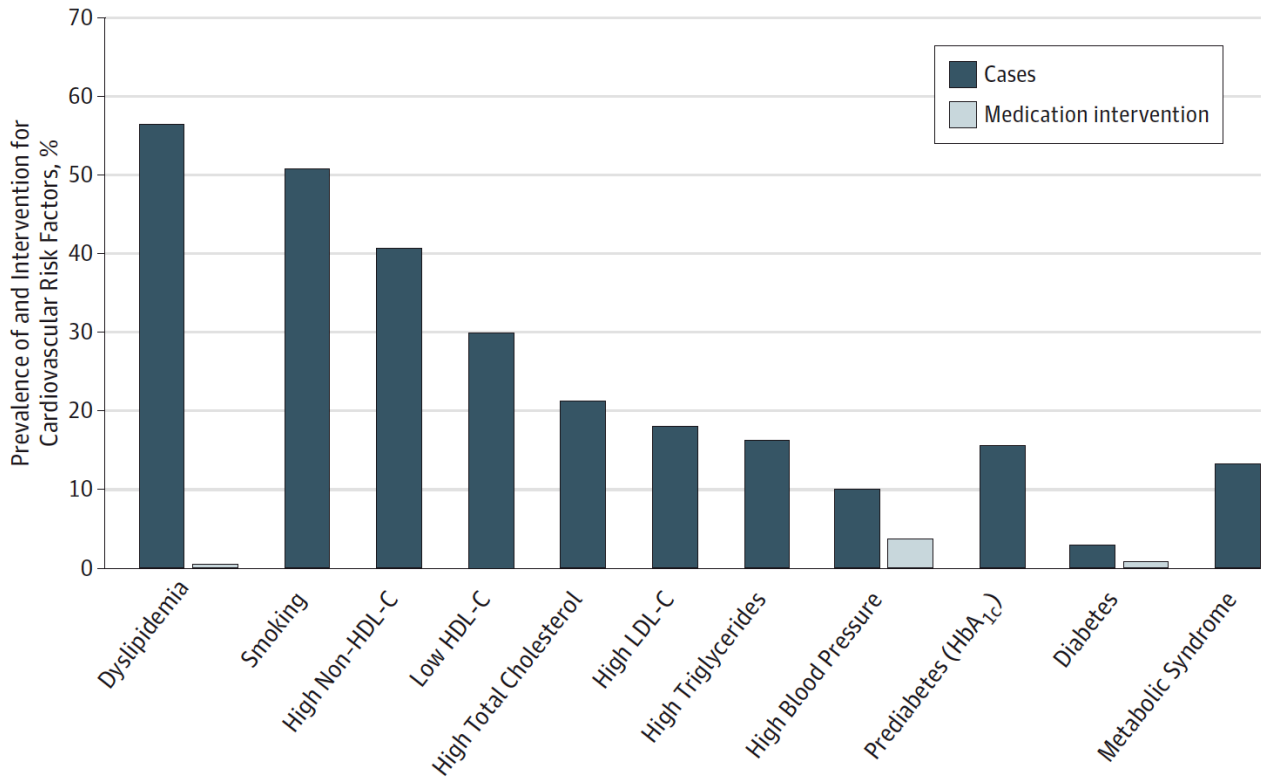
JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.1314

Figure 2. Prevalence of Smoking, Lipid Abnormalities, Hypertension, Diabetes, and Metabolic Syndrome and Respective Medication Treatment for the Conditions



Dyslipidemia indicates an elevated low-density lipoprotein cholesterol (LDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated non–high-density lipoprotein cholesterol (HDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated triglycerides level (≥150 mg/dL; to convert to millimoles per liter, multiply by 0.0113), or a low HDL-C level (<40 mg/dL in males and <50 mg/dL in females; to convert to millimoles per liter, multiply by 0.0259). HbA_{1c} indicates hemoglobin A_{1c}.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.1314

Conclusions

Early in psychotic illness and after a mean of **only 6.7 weeks** of antipsychotic exposure, lipid abnormalities and insulin resistance markers were Elevated and significantly related to lifetime and individual antipsychotic exposure.

These results reinforce the importance of assessing all patients for cardiometabolic risk prior to and throughout treatment, choosing low-risk antipsychotics, and managing cardiometabolic adverse effects that emerge in the care of patients with FES. Further research is needed to assess the trajectory of cardiometabolic risk, underlying mechanisms, and mediating variables, including preferred treatment choices for FES and/or cardiometabolic risk factors.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.1314

ONLINE FIRST

Association Between Common Variants Near the Melanocortin 4 Receptor Gene and Severe Antipsychotic Drug–Induced Weight Gain

Anil K. Malhotra, MD; Christoph U. Correll, MD; Nabilah I. Chowdhury, BSc; Daniel J. Müller, MD; Peter K. Gregersen, MD; Annette T. Lee, PhD; Arun K. Tiwari, PhD; John M. Kane, MD; W. Wolfgang Fleischhacker, MD; Rene S. Kahn, MD; Roel A. Ophoff, PhD; Jeffrey A. Lieberman, MD; Herbert Y. Meltzer, MD; Todd Lencz, PhD; James L. Kennedy, MD

Arch Gen Psychiatry. 2012;69(9):904-912.

Results: Our genome-wide association study yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of $P < 10^{-5}$. This locus, near the melanocortin 4 receptor (*MC4R*) gene, overlaps a region previously identified by large-scale genome-wide association studies of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect ($P = 5.59 \times 10^{-12}$). Moreover, we observed consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels.

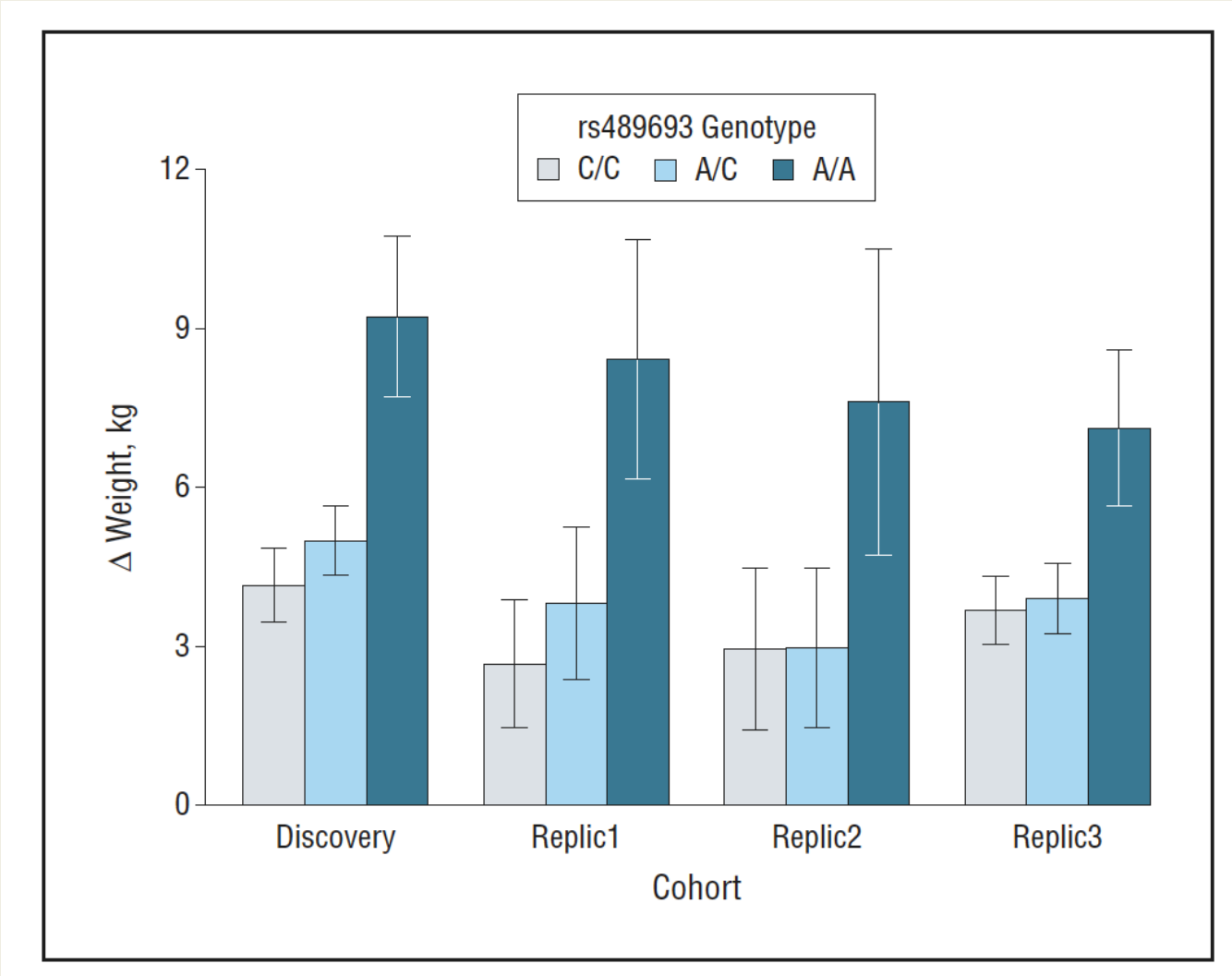
This locus near the melanocortin 4 receptor (MC4R) gene, Overlaps a region identified by large-scale genome-wide association studies of obesity in the general population.

Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, Balding D, Scott J, Kooner JS. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. **Nat Genet.** 2008;40(6):716-718.

Loos et al (2008). Common variants near MC4R are associated with fat mass, weight and risk of obesity. **Nat Genet.** 2008;40(6):768-775

In the present study the critical environmental factor predisposing individuals to weight gain was antipsychotic drug administration over a short period of time. The experimental control of this one factor provided us with sufficient environmental homogeneity to detect genome-wide significant results in a study of slightly more than 100, rather than thousands, of subjects.

Arch Gen Psychiatry. 2012;69(9):904-912



Single-nucleotide polymorphism rs489693 genotype and antipsychotic drug–induced weight gain in 4 cohorts of subjects. Replic1 indicates the first replication cohort; Replic2, the second replication cohort; Recplic3, the third replication cohort.

Arch Gen Psychiatry. 2012;69(9):904-912

A priori identification of those subjects at increased risk of severe weight gain could lead to alternative treatments (i.e., other than SGAs), particularly in patients without an Axis I psychotic disorder. Of note, recent data from the 2007 National Ambulatory Medical Care survey (30) indicate that antipsychotic drugs (most commonly quetiapine and risperidone) were prescribed in 21.3% of patient visits for anxiety disorders, with the largest increase in new patient visits, despite the fact that there is little evidence for these drugs' efficacy in anxiety. Therefore, it might be plausible to consider pharmacotherapeutic strategies that would not include antipsychotic drugs for those nonpsychotic individuals who carry the high-risk genotype for weight gain, as well as increased behavioral and psychosocial interventions focused on dietary and exercise habits.

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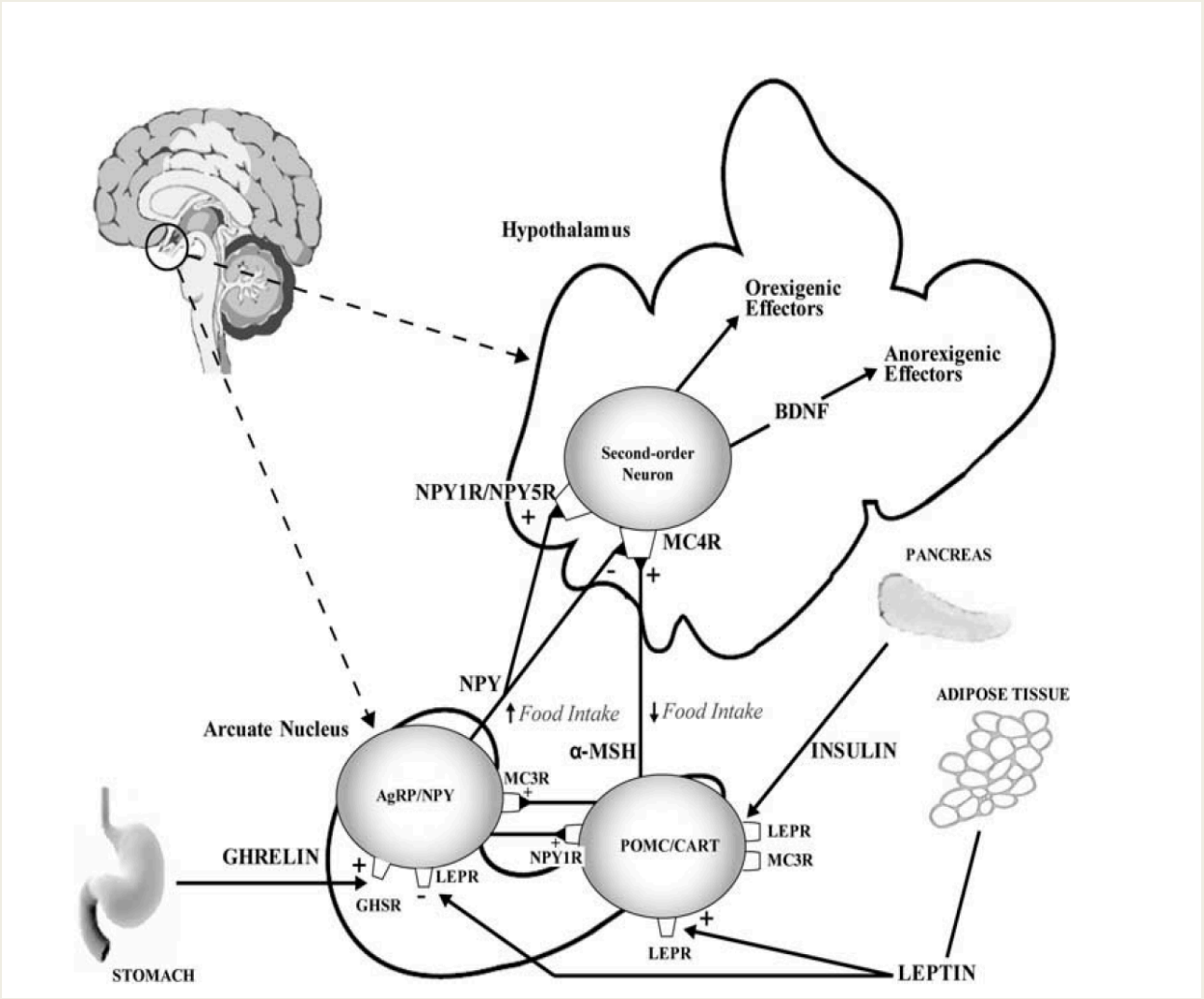
Arch Gen Psychiatry. 2012;69(9):904-912



Schematic representation of the leptin–melanocortin system.

Higher amounts of adipose tissue lead to increased level of leptin in fat tissue. Leptin stimulates POMC neurons in the arcuate nucleus of the hypothalamus. POMC is posttranslationally cleaved to produce a-MSH. The a-MSH binds to MC4R. Stimulation of MC4R results in an upregulation of downstream effectors such as BDNF, leading to anorexigenic results such as decreased food intake and increased energy expenditure. Simultaneously, leptin inhibits another population of neurons in the arcuate nucleus that produce orexigenic hormones (AgRP and NPY). The AgRP acts as an MC4R antagonist, stimulating downstream orexigenic effectors.

a-MSH, a-melanocytes-stimulating hormone; AgRP, AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; CART, cocaine and amphetamine-regulated transcript; GHSR, growth hormone secretagogue receptor; LEPR, leptin receptor; MC3R, melanocortin receptor 3 ;MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; NPY1R, neuropeptide Y1 receptor; NPY5R, neuropeptide Y5 receptor; POMC, proopiomelanocortin.

Lett et al (2012) Molecular Psychiatry 17:242–266

connectivity. The challenge is to demonstrate how the profound plasticity of the human brain allows for a unitary, non-dualistic formulation of psychiatry.

There are implications of these findings for the training of young psychiatrists

1. Mind/Body Dualism continues to be pervasive in teachers and residents and leads to stigmatization of mental illness.
2. Mind/Body Dualism is buttressed by the exemption of first person phenomenological consciousness, free will, the self and its soul from scientific analysis and by assigning them a unique ontological status and locating them outside a unified physicalist reality.
3. An increasing number of converging studies demonstrate that consciousness and first-person experience can be studied by physical science and mapped to specific brain circuits.
4. A unified physicalist description of psychiatric diagnosis and treatment is now in reach. This will map brain changes in time scales ranging from minutes to decades produced by epigenetic changes of gene expression (social forces) and changes in brain connectivity by both psychopharmacology and psychotherapy.
5. Residents training in psychiatry can self identify as brain specialists gaining increasingly refined insight into the potential of the plasticity of the human brain interacting with the world an will learn to apply these insights for the benefit of their patients.

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