faulty circuits

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Mental disorders such as depression display no conspicuous brain damage, they were long thought to stem from purely psychological processes.

Understanding the biology of mental disorders will clarify the sources of malfunction in a circuit, provide objective methods of diagnosis and lead to targeted treatments.

Neural imaging is revealing that abnormal activity along a circuit of brain structures involved in mental processing underlies many mental disorders, making the physical dysfunction causing the mental symptoms visible for the first time.
How do you feel the new antidepressant combo is working?

I’ll tell ya Doc, I’ve got a splitting headache. My tongue feels like dry leather. I can’t hold anything down. I’m anxious, restless, and even lost my sex drive!

So then it’s WORKING.

Medication Management
Mental disorders

Depression, OCD

No conspicuous lesions

Classical neurological illness

Stroke, PD

Visible damage

— a physical cause is still not obvious
Neuroimaging has opened up the black box of the brain
Coordination between areas

Mental disorders studied as abnormalities in connections between distant areas

Electrical circuit malfunction

Understanding underlying causes → treatment

neuroimaging
Major depressive disorder

- 16% of all Americans
- Most prevalent illness in developed world

Leading cause of

- Medical disability among people between the ages 15 and 44

Mental Symptoms

- Profound sense of despair
- Helplessness & hopelessness

Physical symptoms

- Loss of appetite
- Sleep disturbances and Fatigue
- Disturbs immune and hormonal systems
Depression sufferers have low energy and mood

• reaction times and memory formation are inhibited
• anxiety and sleep disturbances, suggest certain brain areas are overactive
Also known as subgenual cingulate cortex (Cg25)
depression circuit
- An imbalance
- Fear
- Anxiety
- Fear
- Anxiety
- Stress response
- Memory processing
- Processes sensory perceptions

Area 25

amygdala

Hippocampus

hypothalamus

Insula
1. Body Belong
2. Sleep
3. LSD
4. Oxytocin
5. Mind Blast (TBI)
6. BCI-
7. Memory
8. Sexual Dimorphic
CHAPTER 3.5

Serotonin in Mood and Emotion

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Abstract: The topographical organization of serotonergic innervation of the forebrain, as well as the paracrine nature of serotonergic neurotransmission in limbic structures, support the contention that serotonin plays a neuromodulatory role in the brain. The lack of synaptic specializations at serotonergic terminals and varicosities in many brain regions suggests that serotonergic innervation may be particularly pliable. As conscious feeling or the cognitive aspect of emotion involves learning and memory, the serotonergic system may be particularly well suited for modulating mood. Pharmacological manipulations of serotonergic neurotransmission alter emotional processing, attentional bias, emotional memory, dysfunctional attitudes and decision-making. In healthy human subjects, increases in serotonergic neurotransmission result in enhanced attention and recognition of positive emotional material. Contrary to expectation, acute increases in serotonergic neurotransmission also increase attentional bias towards negative or fearful stimuli. In general, decreased serotonergic neurotransmission results in impaired attention and recognition of positive emotional material, and increases the attentional bias towards negative stimuli in healthy subjects. A polymorphism in the serotonin transporter gene also alters emotional processing. Understanding not only the neurobiology of emotional responses, but also serotonergic modulation of emotional states, will be important as we attempt to elucidate the etiology of emotional disorders. Future research with agents specific to various serotonin receptors may identify important therapeutic targets for the treatment of cognitive and affective disorders.

Keywords: limbic system, serotonin receptors, tryptophan depletion, selective serotonin reuptake inhibitors, serotonin transporter, MDMA, fenfluramine.
Serotonin relays signals from one region to another

Serotonin is manufactured in the brain

90% of the supply is found in the digestive tract and in blood platelets

Tryptophan is a serotonin precursor

Tryptophan hydroxylase is the needed enzyme.
Figure 1 The amygdala serves as a hub, connecting the hypothalamus and brainstem, responsible for unconscious visceral responses associated with emotion, with cortical areas and hippocampus responsible for conscious feeling or cognitive aspects of emotion. BNST, bed nucleus of the stria terminalis; DMV, dorsal nucleus of the vagus; NA, nucleus ambiguus; RPC, nucleus reticularis pontis oralis; RVL, rostral ventral nucleus of the medulla. This figure was published in Eichenbaum, H.B. ‘Learning and memory: brain systems’, pp. 1299–1328, Fundamental Neuroscience, 2nd edition, edited by L.R. Squire et al. Copyright Elsevier (2003).
Serotonin transporter gene polymorphism and emotional processing

The serotonin transporter is responsible for terminating the action of serotonin in the extracellular space through the energy dependent reuptake of serotonin into the presynaptic terminal. Thus, the serotonin transporter plays a key role in regulating serotonergic neurotransmission. The serotonin transporter gene (5-HTTLPR) has two frequent alleles, designated long (l) and short (s). The s-allele results in decreased serotonin transporter function and expression in vitro (Heils et al., 1995, 1996; Lesch et al., 1996). A functional, single nucleotide variant has been recently detected within the l-allele, designated l4 and l5. l4 is associated with increased expression of the serotonin transporter in vitro, whereas l5 is similar to s in being associated with low expression (Nakamura et al., 2000; Hu et al., 2006). Imaging studies using the new and highly selective ligand [11C]DASB have extended these in vitro studies, reporting that these alleles are indeed associated with differences in serotonin transporter expression in vivo (Praschak-Rieder et al., 2007; Reimold et al., 2007).

Emotional appraisal, or how emotions are interpreted and reflected upon, is one of the most important aspects of emotional regulation. A recent study has compared emotional appraisal profiles of negative (fear and sadness) and positive (joy) emotions as a function of serotonin transporter gene alleles. Healthy volunteers that carry the s-allele of the serotonin transporter gene score higher than non-carriers for unpleasantness and goal-hindrance, and scored lower for coping ability in the case of fear and sadness (Szily et al., 2008) (Table 2). These findings suggest that the s-allele, which conveys decreased function and expression of the serotonin transporter, is associated with a vulnerable cognitive style related to the appraisal of negative emotions (Szily et al., 2008). Indeed, the s-allele has been shown to be associated with major depressive disorder in those who have experienced traumatic or stressful life events (see, for example, Caspi et al., 2003; Kendler et al., 2005; Jacobs et al., 2006) (Table 2).

The effect of acute tryptophan depletion on the processing of emotional facial expressions has also been shown to vary as a function of genotype at the 5-HTTLPR. Tryptophan depletion significantly impairs the recognition of fearful facial expressions in carriers of the s-allele (Marsh et al., 2006). This impairment is specific to fear expressions. However, in healthy volunteers homozygous for the l-allele, acute tryptophan depletion did not alter the recognition of fearful faces (Marsh et al., 2006). The findings of this study suggest that individuals homozygous for the l-allele are less sensitive to the effects of tryptophan depletion on emotional processing (Table 2).
Low expression and/or function of the serotonin transporter associated with the s-allele might be expected to result in increased serotonin in the extracellular space, and enhanced emotional processing of positively valenced material as a result of increased serotonergic neurotransmission. However, genetic determinants of serotonin transporter function most likely result in physiological and neuroadaptive changes during development, and may not necessarily result in increases in serotonergic neurotransmission in the long term. For example, serotonin transporter knockout mice exhibit a variety of neurologi-

cal and physiological abnormalities, and exhibit enhanced fear, and anxiety-like and depression-like behaviors (for review, see Murphy and Lesch, 2008).

Carriers of the s-allele of the serotonin transporter exhibit increased activation of the amygdala in response to fearful stimuli compared with individuals homozygous for the l-allele (Hariri et al., 2002) (Table 2). These results indicate genotype-related differences in excitability of the amygdala to emotional stimuli, which may contribute to the increased fear and anxiety typically associated with the s-allele (Murphy and Lesch, 2008). Morphometric analyses indicate genotype-related differences in anatomy as well. Healthy individuals who are carriers of the s-allele have reduced gray matter volume in limbic regions believed to be critical for the processing of negative emotion, specifically perigenual cingulate and amygdala (Pezawas et al., 2005). Neuroimaging techniques show tight functional coupling of these brain regions during perceptual processing of fearful stimuli. The functional connectivity between these brain regions is critical for emotion regulation and for the extinction of negative affect and fear (see, for example, Pezawas et al., 2005; Phelps and LeDoux, 2005; Quirk and Mueller, 2008). Most interestingly, s-allele carriers showed a relative uncoupling of this circuit, which inversely predicted almost 30 percent of variation in temperamental anxiety (Pezawas et al., 2005). These functional and neuroanatomical studies provide evidence of a systems-level mechanism underlying normal emotional reactivity and genetic susceptibility for depression.
<table>
<thead>
<tr>
<th></th>
<th>$s$-allele carriers ($s/s$, $s/l$)</th>
<th>$l$-allele homozygotes ($l/l$)</th>
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<tr>
<td>$\uparrow$</td>
<td>Emotional appraisal score for negative emotions</td>
<td>Recognition of emotional facial expressions with tryptophan depletion</td>
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Cg25 – Subgenual cingulate cortex

- Increased activation during acute sadness in healthy volunteers.
- (PET)

Cg25 activity decreased after...

- Depressed patients treated with fluoxetine.
- Fluoxetine- SSRI - Prozac, Sarafem
Cg25

- Rich with serotonin transporters
- Participants with “short” variation of the 5HTP transporter gene –
- Leads to higher depression risk.

depression

- Abnormal activity in Cg25 disrupts the hypothalamus, amygdala, insula, hippocampus and prefrontal cortex.
Serotonin transporters

Molecules that manage the amount of neurotransmitter available to neurons

Short and long variations of transporter gene

Short variation → less transporter protein → reduced volume of Cg25
1. Manufacturing XMTR in soma
2. Trafficking to terminal
   Specific receptors POST
synapse

XMTZ

receptor
Putative effects of 5-HTT gene variation on human 5-HT neurotransmission based on findings from 5-HTT knockout mice. (a) Following release of 5-HT, 5-HTT actively returns 5-HT to the presynaptic neuron and thereby determines the duration and intensity of 5-HT communication with its receptors on postsynaptic targets located in limbic regions mediating emotion. (b) A low-expressing ('S allele') form of the human 5-HTT gene has been associated with relatively lesser 5-HTT mRNA transcription and 5-HTT binding, and reduced platelet 5-HT reuptake [9–11], as well as reduced 5-HT1A receptor binding in brain [61]. In mice genetically engineered without a functioning 5-HTT, loss of 5-HTT gene function increases extracellular levels of 5-HT and leads to brain region-specific reductions in 5-HT1A and 5-HT1B receptor binding and increases in 5-HT2A, 5-HT2C and 5-HT3 receptor mRNA levels and/or ligand binding [15–17,24,60]. Although the net effect of these complex changes is not fully understood, they might contribute to alterations in emotional processing associated with a relative loss of 5-HTT function in S allele carriers.
<table>
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<tr>
<th>Brain Region</th>
<th>Functions</th>
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<tr>
<td>Hypothalamus and brainstem</td>
<td>• influence changes in appetite, sleep and energy</td>
</tr>
<tr>
<td>Amygdala and insula</td>
<td>• affect anxiety and mood</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>• critical to memory processing and attention</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>• mediate insight and self-esteem</td>
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</tbody>
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Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Ahmad R. Hariri,1 Venkata S. Mattay,1 Alessandro Tessitore,1 Bhaskar Kolachana,1 Francesco Fera,1 David Goldman,2 Michael F. Egan,1 Daniel R. Weinberger1*

A functional polymorphism in the promoter region of the human serotonin transporter gene (SLC6A4) has been associated with several dimensions of neuroticism and psychopathology, especially anxiety traits, but the predictive value of this genotype against these complex behaviors has been inconsistent. Serotonin [5-hydroxytryptamine, (5-HT)] function influences normal fear as well as pathological anxiety, behaviors critically dependent on the amygdala in animal models and in clinical studies. We now report that individuals with one or two copies of the short allele of the serotonin transporter (5-HTT) promoter polymorphism, which has been associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors, exhibit greater amygdala neuronal activity, as assessed by BOLD functional magnetic resonance imaging, in response to fearful stimuli compared with individuals homozygous for the long allele. These results demonstrate genetically driven variation in the response of brain regions underlying human emotional behavior and suggest that differential excitability of the amygdala to emotional stimuli may contribute to the increased fear and anxiety typically associated with the short SLC6A4 allele.
Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter

Andreas Heinz¹,⁶, Dieter F Braus²,⁶, Michael N Smolka³,⁶, Jana Wrase¹, Imke Puls¹, Derik Hermann³, Sabine Klein³, Sabine M Grüsser⁴, Herta Flor³, Gunter Schumann³, Karl Mann³ & Christian Büchel⁵

Major depression is conditionally linked to a polymorphism of the human serotonin transporter gene (SLC6A4). During the presentation of aversive, but not pleasant, pictures, healthy carriers of the SLC6A4 short (s) allele showed stronger activation of the amygdala on functional magnetic resonance imaging. s carriers also showed greater coupling between the amygdala and the ventromedial prefrontal cortex, which may contribute to the abnormally high activity in the amygdala and medial prefrontal cortex seen in major depression.
Obsessive-compulsive disorder

- OCD
- Once considered as neurosis – psychic conflict

Characteristics:

- Intrusive, repetitive thoughts -- obsessions
- Impaired by the need to perform stereotyped, repetitive rituals – compulsions

Examples

- Contaminated – wash hands repetitively
- Failed responsibility – keep checking stove

Patients know

- Their thoughts are senseless
- Cannot control the obsession or compulsion – “mental tics”
Dopaminergic Network Differences in Human Impulsivity

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Buckholtz J. et al. July 30, 2010 Science
Impulsivity variation among individuals

Ability to deliberate on consequences of an action.

Impulsivity linked to dopamine

Learning and reward.
PET scans of 32 healthy and psychiatrically normal test subjects. 
Two rounds of impulsivity task
  1\textsuperscript{st} round: subjects take a placebo
  2\textsuperscript{nd} round: subjects given amphetamine (stimulate DA)

Results:
Subjects with higher impulsivity scores had lowest D2/D3 autoreceptor activity in the midbrain.
Under the influence of amphetamine – the impulsive subjects released more DA than the less impulsive counterparts.
Special type of biomarker.

Divide behavioral symptoms into phenotypes.

Needs to have a clear genetic connection.

Term borrowed from insect biology.

What is endophenotype?
Neurocognitive endophenotypes of obsessive-compulsive disorder

Lara Menzies, Sophie Achard, Samuel R. Chamberlain, Naomi Fineberg, Chi-Hua Chen, Natalia del Campo, Barbara J. Sahakian, Trevor W. Robbins and Ed Bullmore

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Impairment in brain regions controlling flexible behavior.

- **Risk**
  - 2-3% population
  - Genetic

- **Question**
  - OCD + Close relatives
  - Distinctive brain structure

Vulnerability factor.
• OCD patients
• Close relatives
• Age matched controls

• Computer test
• Press appropriate button when an arrow appeared on a screen

• When a bell rang, subjects had to attempt to stop their responses.
Brain maps illustrating regions where grey matter density was most strongly correlated with latency of motor inhibitory response

Red/yellow regions indicate areas with impaired response inhibition.

OCD patients and close relatives showed decreases of grey matter in brain regions important in suppressing responses and habits – the orbitofrontal and right inferior frontal regions.
Orbitofrontal Dysfunction in Patients with Obsessive-Compulsive Disorder and Their Unaffected Relatives

Samuel R. Chamberlain,1,2,3* Lara Menzies,1,2,3 Adam Hampshire,4 John Suckling,1,2 Naomi A. Fineberg,1,3 Natalia del Campo,1,2 Mike Aitken,2,5 Kevin Craig,1,2,3 Adrian M. Owen,4 Edward T. Bullmore,1,2,6 Trevor W. Robbins,2,5 Barbara J. Sahakian1,2

Obsessive-compulsive disorder (OCD) is characterized by repetitive thoughts and behaviors associated with underlying dysregulation of frontostriatal circuitry. Central to neurobiological models of OCD is the orbitofrontal cortex, a neural region that facilitates behavioral flexibility after negative feedback (reversal learning). We identified abnormally reduced activation of several cortical regions, including the lateral orbitofrontal cortex, during reversal learning in OCD patients and their clinically unaffected close relatives, supporting the existence of an underlying previously undiscovered endophenotype for this disorder.
Patients with OCD and their unaffected relatives showed underactivation during reversal learning bilaterally in the lateral orbitofrontal cortex (OFC), lateral prefrontal cortex (PFC), and parietal cortices.

The images are of representative brain slices showing regions activated during reversal learning across all subjects (yellow areas; false discovery rate–corrected, P < 0.05) and regions in which there was a significant effect of group (blue areas; corrected to less than one false-positive cluster across the whole map).

In reversal learning, the individual first learns to make a discrimination, such as choosing a black object in a black–white discrimination problem, and then is supposed to learn to reverse his choice—i.e., to choose the white object. Such reversals tend to be difficult for most learners since there are negative transfer effects; e.g., the individual tends to persist...
Orbitofrontal cortex
- Involved in complex tasks
- e.g. decision making

Ventral caudate nucleus
- Located within the basal ganglia
- Basal ganglia: centers for initiating and coordinating various aspects of movement (including involuntary tics)

Thalamus
- Relays and integrates sensory information
INSTRUCTIONS:
RINSE
REPEAT
REPEAT
REPEAT

OCD SHAMPOO
"Ambien makes my husband eat in his sleep. Ritalin gives my son hallucinations. What do you have for depression?"
Employees with O.C.D. must wash hands repeatedly.
Now, I want the tomatoes cut diagonally on 3/4 of the lettuce bed, and horizontally on 1/4. The cucumbers must be dispersed evenly over the surface with one olive placed between each third spacing. Each drop of dressing must be positioned over a radish or tomato, never on a cucumber.

Now as for the dimensions of the bowl, it is of utmost importance that no vegetable is too close to the rim, so I'll need at least a four centimeter space at the top. Fresh pepper can be added "ad libitum" but for precisely three seconds and only over the olives. Say, are you writing this all down?—Now regarding the...
"OK, Captain Anxiety. I took some Polaroids before we left. Exhibit A: the stove with all burners clearly in the "off" position. Exhibit B: the back door with its deadbolt latched. Exhibit C: my curling iron unplugged."