I DISTURBI DELL'UMORE

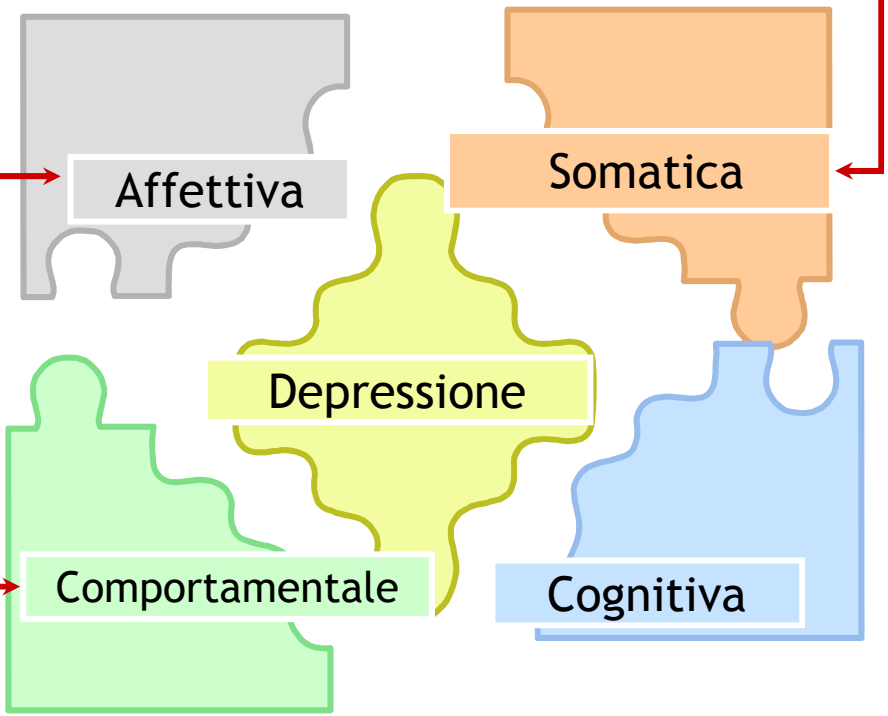
I disturbi dell'umore

- Rappresentano la più comune patologia psichiatrica della età adulta
- Consistono in gravi sbalzi dell'umore
- Comportano un rischio di suicidio del 19%
- Due categorie principali:
  - disturbo unipolare (depressione)
  - disturbo bipolare (forma maniaco-depressiva)

Disturbi depressivi

- Insorgenza lenta
- Durata di settimane o mesi
- Incidenza: 17% della popolazione USA (rapporto maschi/femmine=1/2)
- *Prevista come la seconda malattia più onerosa al mondo a partire dal 2020*

Disturbi Depressivi: caratteristiche



Restrizioni dell'espressione emotiva, pensiero, linguaggio, piacere, motivazione e attenzione

Disturbi del sonno

Disturbi dell'appetito

Affaticabilità e diminuzione dell'energia

Perdita di interesse in numerose attività,

Sintomi neurovegetativi

Dolori inspiegabili

Espressione triste, pianto

Rallentamento dei movimenti e della parola

Movimenti agitati ed irrequieti

Triade di Beck (1967):

1. visione negativa di sé e relativa attribuzione di causalità
2. interpretazione negativa delle esperienze
3. visione negativa del futuro, estensione dello stato presente

Disturbi bipolari

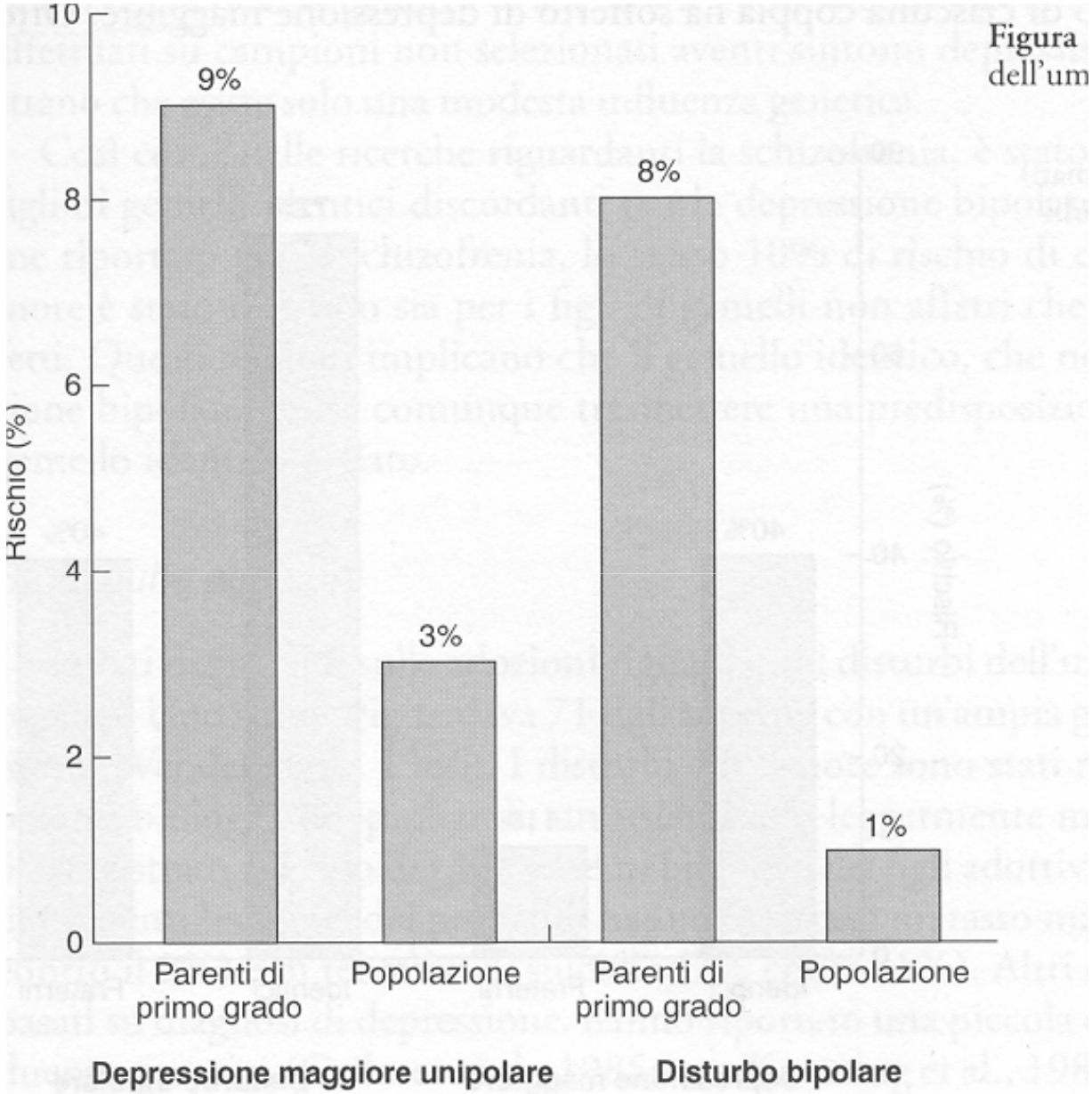
- Alternanza tra fasi maniacali e depressive

- Caratteristicche dello stato maniacale:
  - euforia
  - autostima esagerata
  - riduzione del bisogno di sonno
  - loquacità
  - tendenza alla competizione
  - Iperattività

- Esordio e fine improvvisi (età media di esordio: 21 anni)

- Incidenza: 1% della popolazione (rapporto M/F= 1/1)

Figura
dell'um



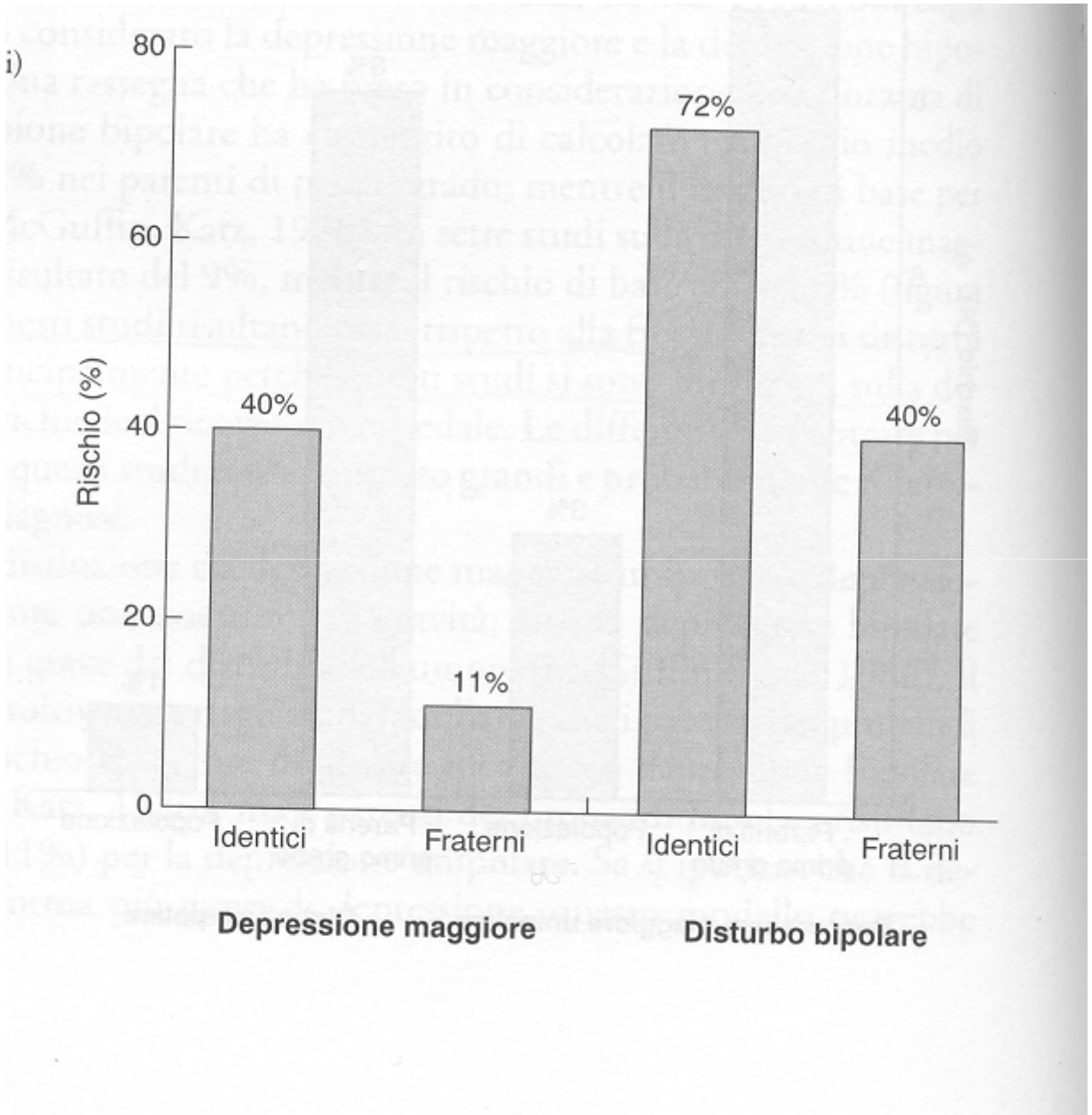

80
60
40
20
0
Rischio (%)
40%
11%
72%
40%
Identici
Fraterni
Identici
Fraterni
Depressione maggiore
Disturbo bipolare

Table 1 Genetic epidemiology of mood disorders

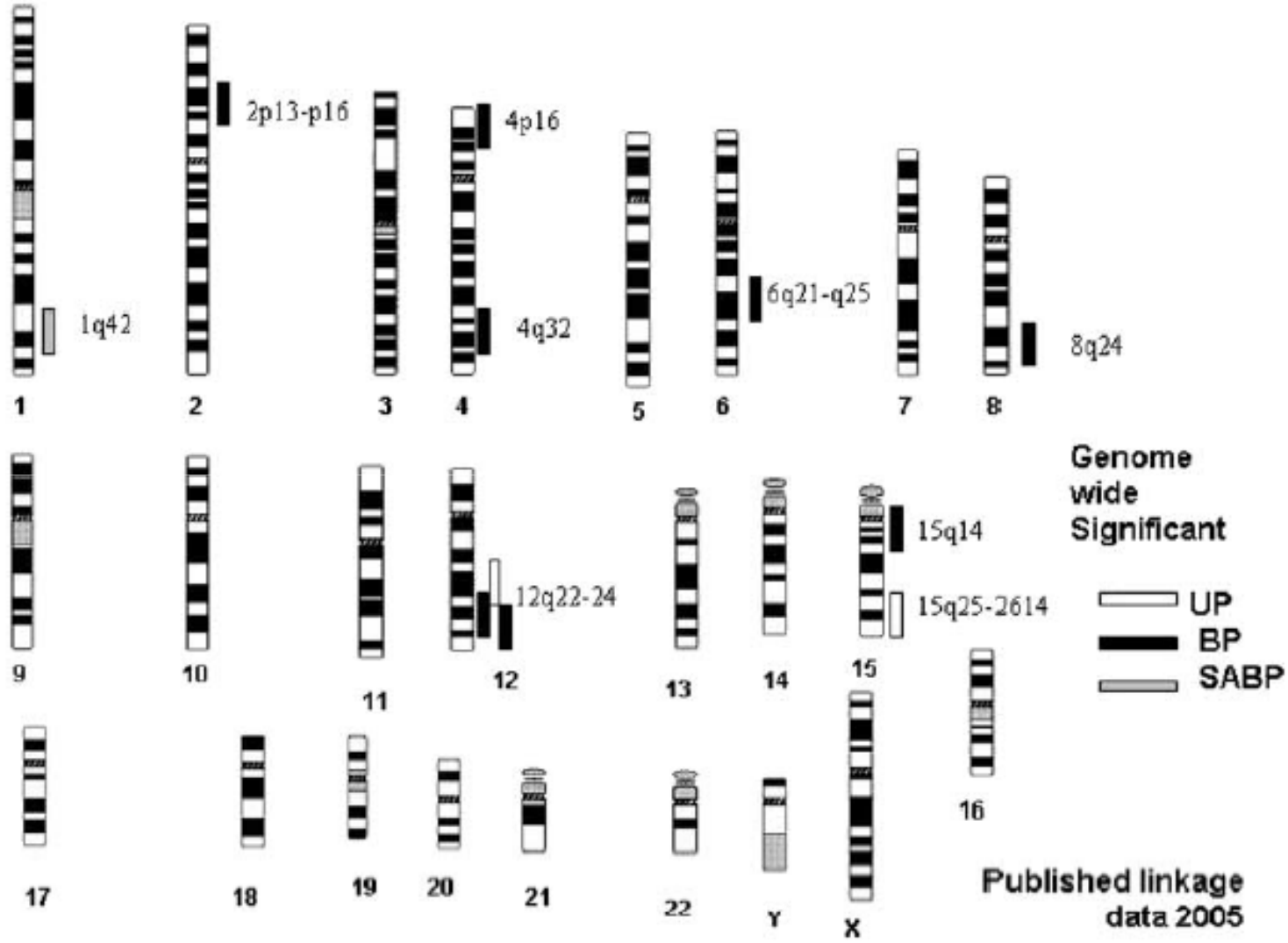
	Bipolar disorder	*Unipolar depression*
Recurrence risk in sibling of a proband (λ_S)	5–10	2.5–3.5
Proband-wise MZ twin concordance (%)	45–70	40–50
Heritability estimate (%)	80–90	33–42

Rapporto tra rischio di disturbi unipolari e bipolari

- Parenti di pazienti unipolari non hanno un aumentato rischio di disturbi bipolari
- Parenti di pazienti bipolari hanno un aumentato rischio di disturbi unipolari (11%)

La genetica dei disturbi dell'umore

- Esiste una influenza genetica sui disturbi dell'umore
- Tale influenza è meno chiara nella depressione unipolare, più evidente nelle forme più gravi
- I figli di gemelli monozigoti *discordanti* hanno lo stesso rischio di sviluppare disturbi dell'umore, dimostrando che *anche il gemello sano trasmette la predisposizione*


1q42
2p13-p16
4p16
4q32
6q21-q25
8q24
12q22-24
15q14
15q25-2614
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Y
X
Genome wide Significant
UP
BP
SABP
Published linkage data 2005

Il gene BDNF
(Brain derived neurotrophic factor)

- Membro della famiglia delle neurotrofine
- Gioca un ruolo importante nel promuovere e modificare la crescita neuronale ed è coinvolto nella plasticità neuronale
- Candidato come associato ai disturbi bipolari a cicli frequenti (4 o più episodi per anno) piuttosto che ai disturbi dell'umore in generale

Il gene hSERT (5HTT)

- Codifica per un trasportatore della serotonina che permette la sua cattura nelle sinapsi cerebrali
- Queste sinapsi sono il sito di azione di alcuni antidepressivi (Prozac)
- Polimorfismi del gene hSERT sono stati associati ai disturbi dell'umore

to guanine; A to G) (Wendland et al., 2006). The L_G variant and the S allele appear to be very similar in terms of transcriptional activity; therefore, only the L_A variant is high expressing with regard to transcriptional activity (Hu et al., 2005).

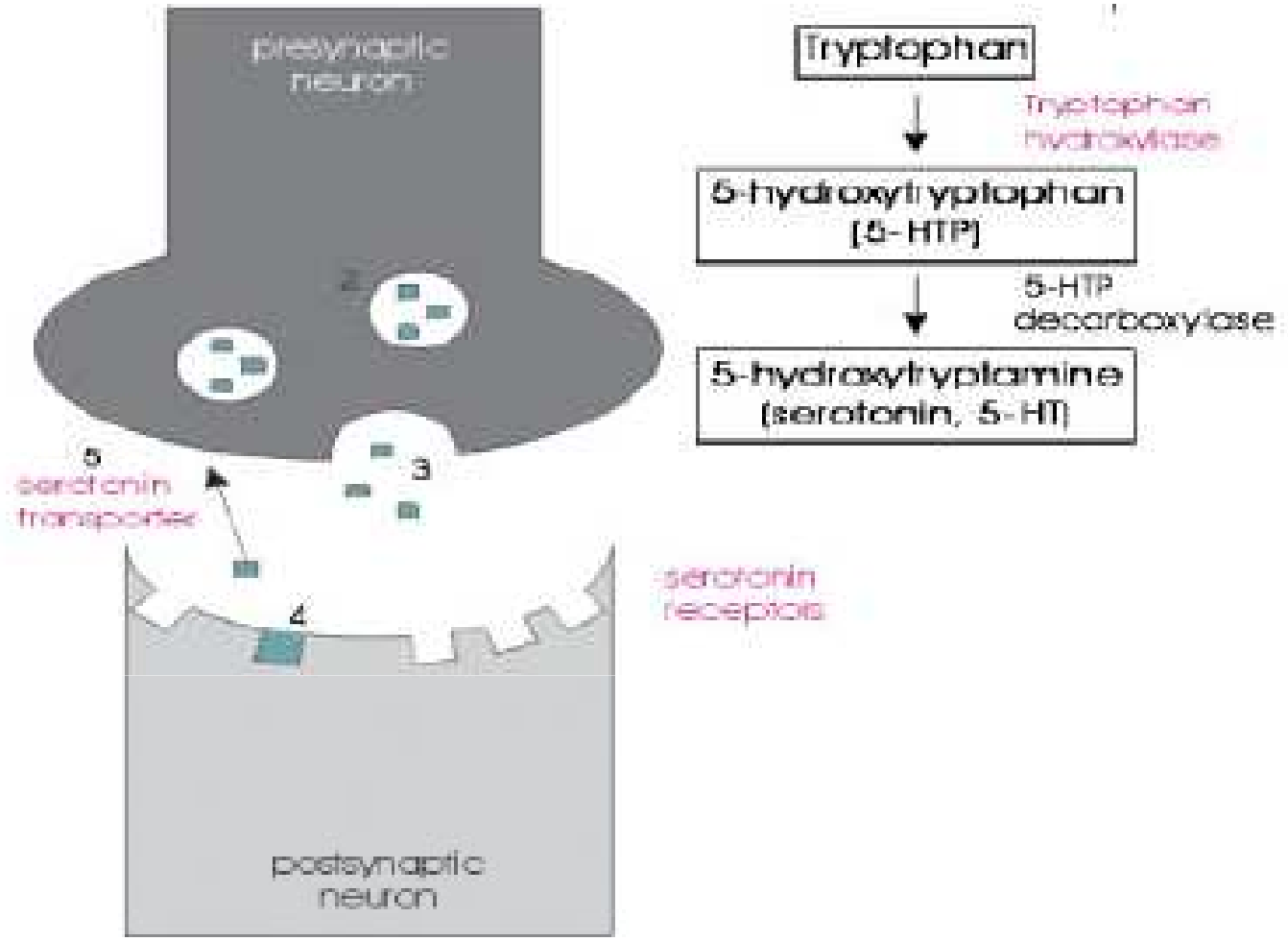


FIGURE 1. Genes involved in the serotonin pathway. 1.The synthesis of serotonin from tryptophan; 2. Storage of serotonin in vesicles; 3. Release of serotonin into synaptic cleft; 4. Activation of postsynaptic receptors; and 5. Inactivation mechanism of neurotransmission: reuptake of serotonin in presynaptic neuron. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

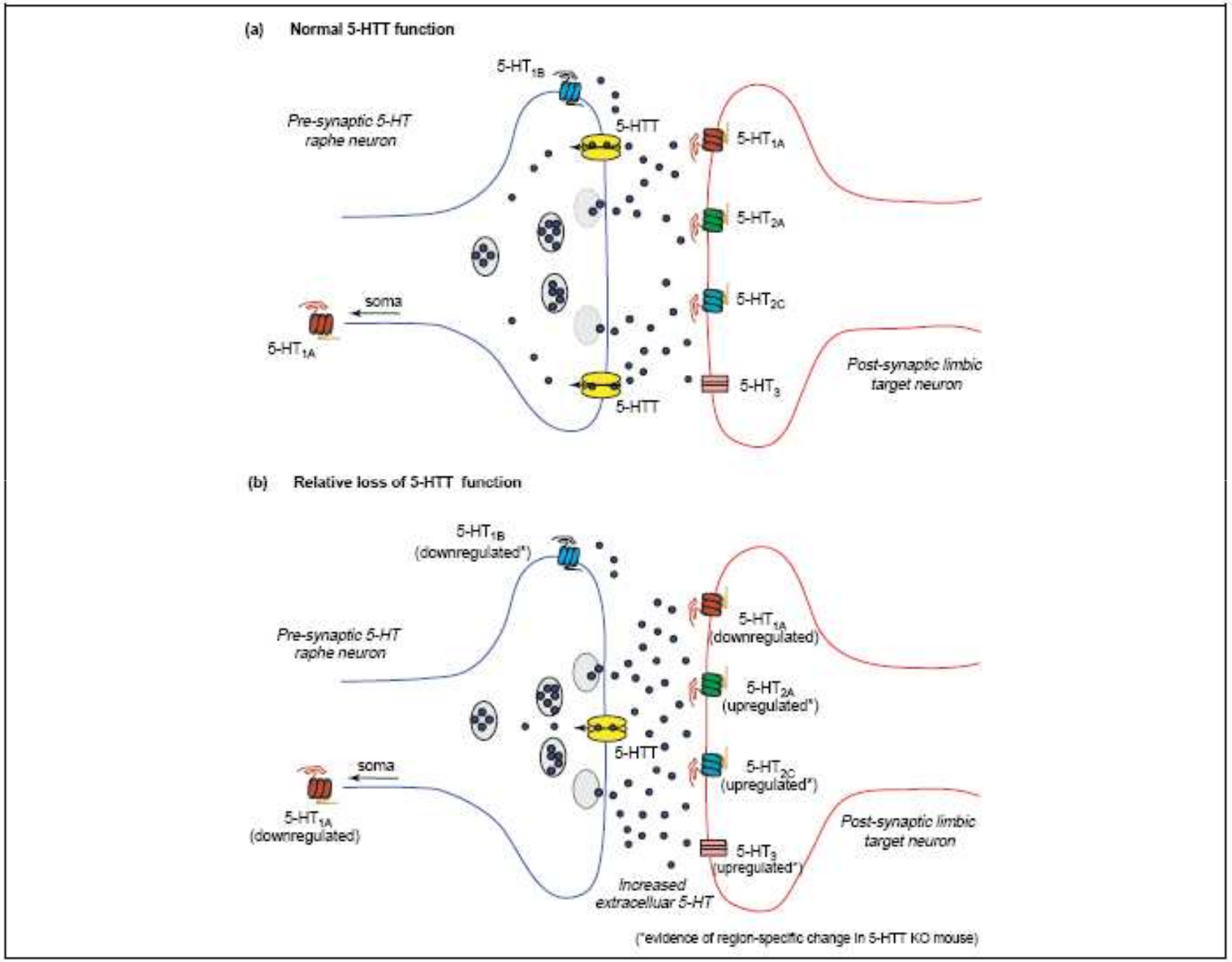

(a) Normal 5-HTT function
5-HT1B
Pre-synaptic 5-HT raphe neuron
5-HTT
5-HT1A
5-HT2A
5-HT2C
soma
5-HT1A
Post-synaptic limbic target neuron
5-HT3
5-HTT
(b) Relative loss of 5-HTT function
5-HT1B (downregulated*)
Pre-synaptic 5-HT raphe neuron
5-HT1A (downregulated)
5-HT2A (upregulated*)
5-HTT
soma
5-HT2C (upregulated*)
5-HT1A (downregulated)
Post-synaptic limbic target neuron
5-HT3 (upregulated*)
Increased extracelluar 5-HT
(*evidence of region-specific change in 5-HTT KO mouse)

Table 1. Relative loss of 5-HTT gene function is associated with increased vulnerability to environmental stress across species

Environmental stressor	Endpoint measure
Low-expressing form of the human 5-HTT gene	
Multiple traumatic life events	Increased incidence of depression [31–33]
Childhood abuse or neglect	Increased incidence of depression [31,32]
Tryptophan depletion	Increased relapse to depression [38]
Unemployment and low socio-economic status	Increased 'mental distress' and decreased 5-HT responsivity [36,37]
Low-expressing form of the Rhesus macaque 5-HTT gene	
Early life maternal separation	Exaggerated behavioral and neuroendocrine response to stress [43,44]
Mutant mice lacking a functional 5-HTT	
Exposure to rat predator	Exaggerated catecholamine responses [46]
Intraperitoneal injection of saline	Exaggerated neuroendocrine response [45]
Exposure to cat odor	Increased anxiety-like response [47]

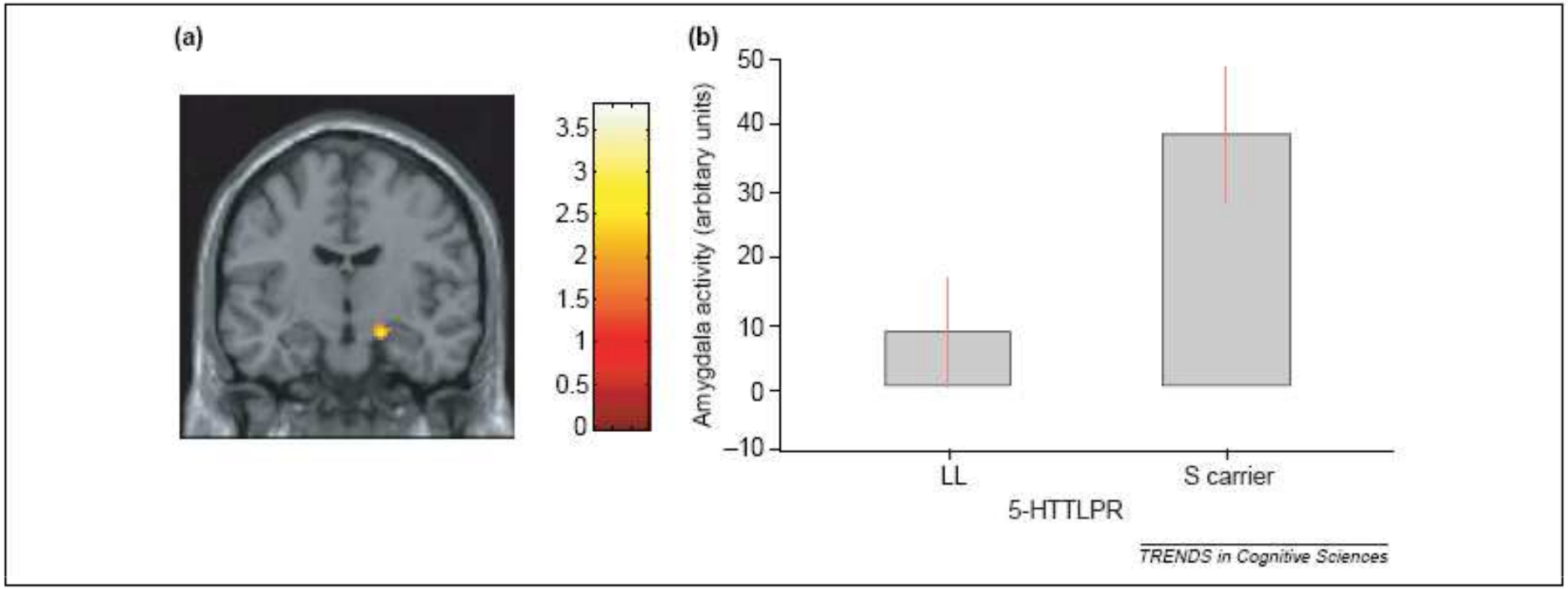


Figure 2. The low-expressing (S allele) 5-HTT gene variant is associated with greater amygdala reactivity in response to emotionally provocative stimuli. **(a)** Illustration of the greater mean right amygdala activity in S allele carriers than in L allele homozygotes (S carriers > LL). Reproduced with permission from [18]. **(b)** Activity of this same right amygdala region in single-subjects from both genotype groups (S carriers versus LL). Note, sample size in most studies has limited the analyses of genotype effects to S carriers (SS and LS) versus L homozygotes (LL). However, both the initial in vitro studies of the 5-HTTLPR [9,11], and a subsequent in vivo study [18] indicate that the S allele has a dominant effect on gene expression and amygdala activity and, thus, support this more general classification scheme.

Table 2. Imaging genetics studies of 5-HTTLPR effects on amygdala reactivity to emotionally provocative stimuli

Sample demographics (reference)	Challenge stimuli	5-HTTLPR effect on amygdala reactivity
American volunteers (N = 28) [50]	Angry and fearful faces	S carriers > LL
American volunteers (N = 93) [18]	Angry and fearful faces	S carriers > LL
German volunteers (N = 29) [53]	Aversive, pleasant, and neutral pictures	S carriers > LL
Italian volunteers (N = 28) [58]	Angry and fearful faces	S carriers > LL
American volunteers (N = 41) [55]	Negative, positive, and neutral words	S carriers > LL
American volunteers (N = 55) [60]	Angry and fearful faces	S carriers > LL
German patients with panic disorder (N = 20) [57]	Angry, fearful, happy and neutral faces	S carriers > LL
Dutch patients with social phobia (N = 17) [58]	Public speaking task during O15 PET	S carriers > LL

Krepelin, 1913…

Table 1. Relationship between temperament and manic depressive illness.

Temperament	Description	Depression (%)	Mania (%)	Combined (%)
Depressive	Gloomy, pessimistic and incapable of fun; quiet, passive and indecisive; broody and given to worry; lack of self-confidence; conscientious; self critical and self reproaching; preoccupied with failure and negative events	64.2	8.3	27.5
Hyperthymic	Irritable, cheerful, exuberant, naïve, overconfident, bombastic, loquacious, extroverted, warm, meddlesome, uninhibited, haughty, stubborn, insubordinate	35.6	23.3	41.1
Irritable	Moody, irritable, hot-tempered, paranoid, brooding, hypercritical and complaining, obtrusive, dysphorically restless and impulsive	45.5	24.4	30.1
Cyclothymic	Introverted self-absorption alternating with people seeking; decreased verbal output alternating with talkativeness; unexplained tearfulness alternating with jocularity; pessimism alternating with optimism; low self-esteem alternating with grandiosity; mental confusion alternating with creative thinking	35.5	11.7	53.0

Data from Kraepelin (1913) cited in Angst (7), p. 181. Temperament description from Akiskal and Mallya (102), pp. 71–72. Reprinted with permission

Gli endofenotipi della depressione

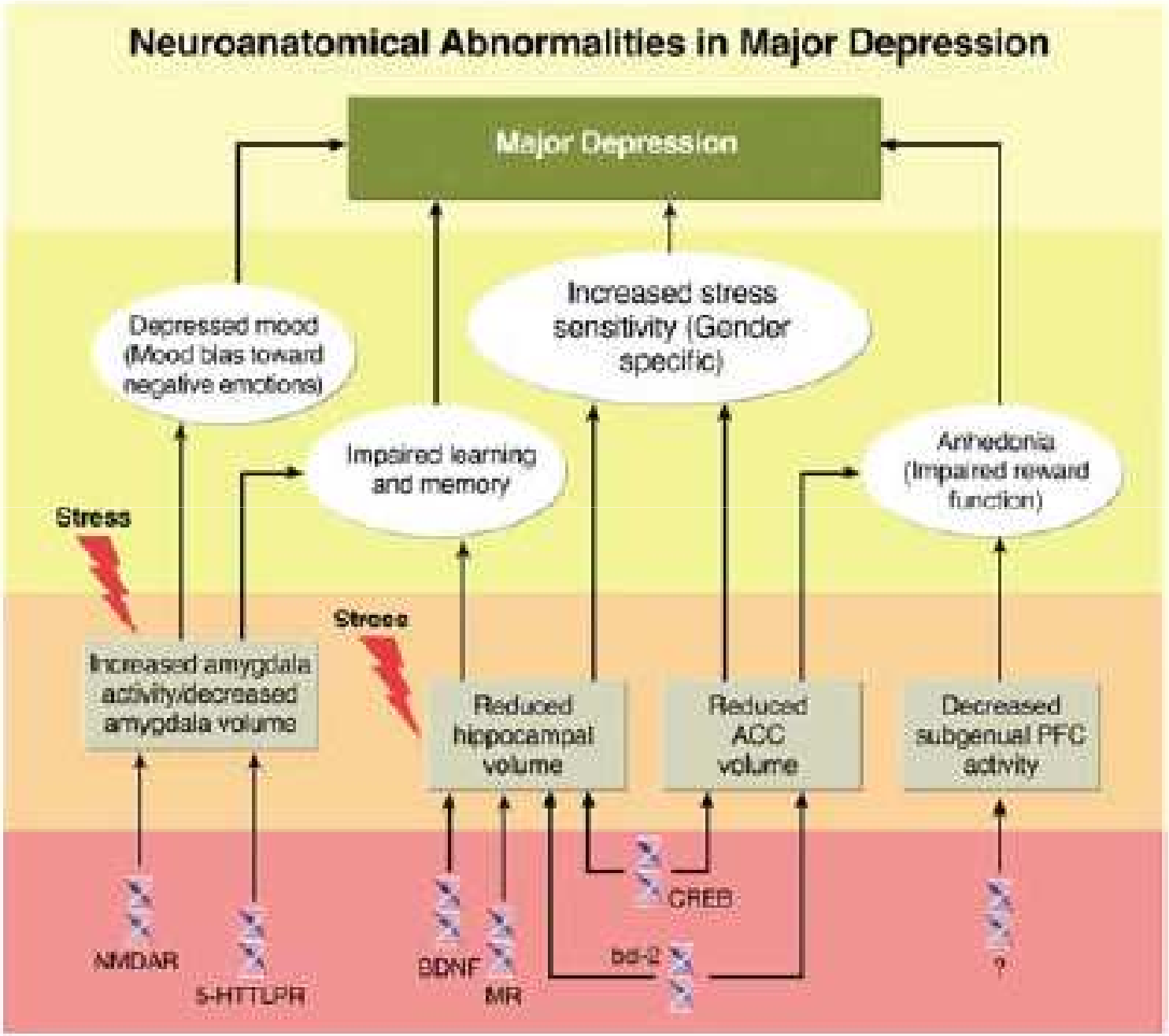
- Endofenotipo:
  - Fenotipo “interno”, direttamente provocato dalla variante genica (genotipo) e contribuente allo sviluppo della patologia (fenotipo)

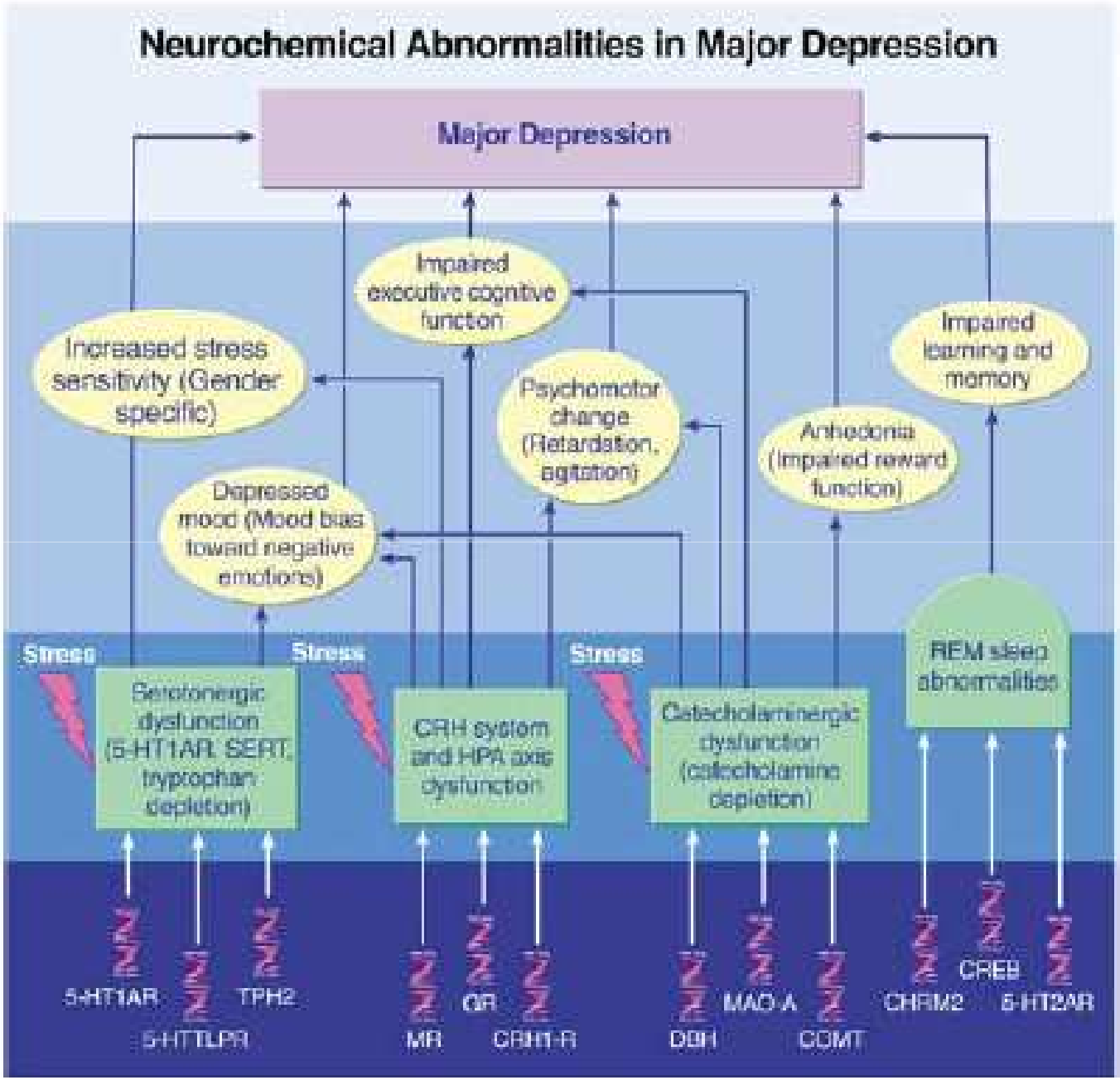
Caratteristiche degli endofenotipi

- Associazione con la malattia in un numero rilevante di casi
- Indipendenza dallo stato della malattia
  - L'endofenotipo deve essere presente tanto nelle fasi di benessere che in quelle di malattia
- Ereditabilità
- All'interno di una famiglia, endofenotipo e malattia devono essere trasmessi assieme
- Gli endofenotipi presenti nei malati devono essere presenti nei parenti sani con una incidenza maggiore che nella popolazione generale

La “dissezione” della depressione maggiore: i componenti chiave

- Umore depresso
- Anedonia
- Alterazioni dell’apprendimento e della memoria
- Segni neurovegetativi
- Ritmo circadiano dei sintomi
- Alterata capacità reattiva

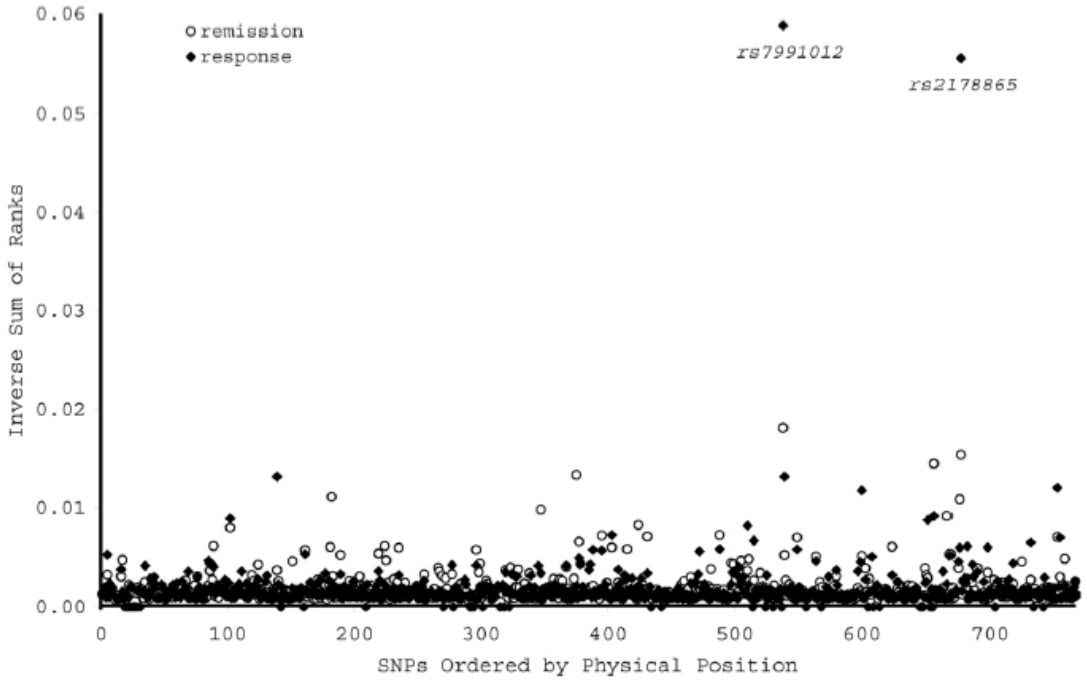

Neuroanatomical Abnormalities in Major Depression
Major Depression
Depressed mood (Mood bias toward negative emotions)
Impaired learning and memory
Increased stress sensitivity (Gender specific)
Anhedonia (Impaired reward function)
Stress
Stress
Increased amygdala activity/decreased amygdala volume
Reduced hippocampal volume
Reduced ACC volume
Decreased subgenual PFC activity
NMDAR
5-HTTLPR
BDNF
MR
CREB
bd-2
?


Neurochemical Abnormalities in Major Depression
Major Depression
Impaired executive cognitive function
Increased stress sensitivity (Gender specific)
Psychomotor change (Retardation, agitation)
Impaired learning and memory
Anhedonia (Impaired reward function)
Depressed mood (Mood bias toward negative emotions)
Stress
Stress
Stress
Serotonergic dysfunction (5-HT1AR, SERT, tryptophan depletion)
CRH system and HPA axis dysfunction
Catecholaminergic dysfunction (catecholamine depletion)
REM sleep abnormalities
5-HT1AR
5-HTTLPR
TPH2
MR
GR
CRHR-R
DBH
MAO-A
COMT
CHRM2
CREB
5-HT2AR

Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment

Francis J. McMahon,[1,*] Silvia Buervenich,[1,*] Dennis Charney,[3] Robert Lipsky,[4] A. John Rush,[5] Alexander F. Wilson,[6] Alexa J. M. Sorant,[6] George J. Papanicolaou,[6] Gonzalo Laje,[1] Maurizio Fava,[7] Madhukar H. Trivedi,[5] Stephen R. Wisniewski,[8] and Husseini Manji[2]

[1]Genetic Basis of Mood and Anxiety Disorders and [2]Laboratory of Molecular Pathophysiology, Mood and Anxiety Program, National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Bethesda; [3]Departments of Psychiatry, Neuroscience, and Pharmacology & Biological Chemistry, Mount Sinai School of Medicine, New York; [4]Section of Molecular Genetics, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS, Rockville, MD; [5]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas; [6]Genometrics Section, Inherited Disease Research Branch, National Human Genome Research Institute, NIH, DHHS, Baltimore; [7]Massachusetts General Hospital, Boston; and [8]Department of Epidemiology, University of Pittsburgh, Pittsburgh



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Depression and the role of genes involved in dopamine metabolism and signalling

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ABSTRACT

Major depressive disorder (MDD) is a common psychiatric disorder and leading cause of disability worldwide. It is associated with increased mortality, especially from suicide. Heritability of MDD is estimated around 40%, suggesting that genotyping is a promising field for research into the development of MDD. According to the dopamine theory of affective disorders, a deficiency in dopaminergic neurotransmission may play a role in the major symptoms of MDD. Specific polymorphisms in genes that affect dopamine transmission could increase susceptibility to MDD. To determine the extent to which these genes influence vulnerability to MDD, we discuss genes for crucial steps in dopamine neurotransmission: synthesis, signalling and inactivation. The val158met polymorphism of the COMT gene exemplifies the lack of consensus in the literature: although it is one of the most reported polymorphisms that relates to MDD vulnerability, its role is not corroborated by meta-analysis. Gene–gene interactions and gene–environment interactions provide more explanatory potential than single gene associations. Two notable exceptions are the DRD4 and DAT gene: both have variable tandem repeat polymorphisms which may have a "single gene" influence on susceptibility to MDD.

FEATURE REVIEW

The GABAergic deficit hypothesis of major depressive disorder

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Increasing evidence points to an association between major depressive disorders (MDDs) and diverse types of GABAergic deficits. In this review, we summarize clinical and preclinical evidence supporting a central and causal role of GABAergic deficits in the etiology of depressive disorders. Studies of depressed patients indicate that MDDs are accompanied by reduced brain concentration of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and by alterations in the subunit composition of the principal receptors ($GABA_A$ receptors) mediating GABAergic inhibition. In addition, there is abundant evidence that suggests that GABA has a prominent role in the brain control of stress, the most important vulnerability factor in mood disorders. Furthermore, preclinical evidence suggests that currently used antidepressant drugs (ADs) designed to alter monoaminergic transmission and nonpharmacological therapies may ultimately act to counteract GABAergic deficits. In particular, GABAergic transmission has an important role in the control of hippocampal neurogenesis and neural maturation, which are now established as cellular substrates of most if not all antidepressant therapies. Finally, comparatively modest deficits in GABAergic transmission in $GABA_A$ receptor-deficient mice are sufficient to cause behavioral, cognitive, neuroanatomical and neuroendocrine phenotypes, as well as AD response characteristics expected of an animal model of MDD. The GABAergic hypothesis of MDD suggests that alterations in GABAergic transmission represent fundamentally important aspects of the etiological sequelae of MDDs that are reversed by monoaminergic AD action.

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Resilience under conditions of extreme stress: a multilevel perspective

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In our laboratory, we conducted a multigenic study examining the interaction between polymorphisms of 5-HTT and MAOA genes in a large sample of maltreated children in relation to depressive symptomatology (67). Adolescents from low socioeconomic backgrounds with a history of child maltreatment or no such history were administered a semi-structured diagnostic interview for mental disorders; moreover, these adolescents provided buccal cells for genetic analysis. Heightened depressive symptoms were found among extensively maltreated youth with low MAOA activity. Among comparably maltreated youths with high MAOA activity, self-coping strategies related to lower depressive symptoms. The finding that self-coping strategies and high MAOA activity were related to lower depressive symptoms calls to mind results from a number of our studies on resilience in maltreated children. Specifically, self-reliance and self-determination were found to be predictors of resilient functioning in maltreated children (32). It is conceivable that the maltreated children with positive self-system characteristics who functioned resiliently also may have possessed polymorphic variants of genes (such as high MAOA activity) that served a protective function against maladaptation.

This GxE interaction was further moderated by MAOA activity level. Specifically, we found that sexually abused adolescents with one or two copies of the 5-HTT short allele had significantly reduced levels of internalizing symptoms if they also had the high activity version of the MAOA gene (67).

Ancora Geni + Ambiente…

- L’assetto genetico di un individuo appare in qualche modo creare una personalità più suscettibile a reagire in modo esagerato agli stress esterni
- La genetica assume quindi un ruolo *predisponente*, l’ambiente un ruolo *scatenante*