

**PHARMACOTHERAPEUTIC RECEPTOR SPECIFICITIES AND
SELECTIVITY CLASSES, AND PLACEBO EFFECTS: A PERSPECTIVE**

LUIGI ROSSINI¹⁺ and PAOLA ROSSINI^{*+}

Section of Pharmacology, Department of Neuroscience; Clinical Pharmacology and Toxicology Service and ⁺Section of Human Pharmacotoxicology, I.M.O. Interuniversity Centre, Polytechnic University of Ancona, Via Tronto 10A, Ancona 60.129, Italy (Tel +39-(0)71-2181028; Fax +39-(0)71-2206037);

**Psychiatry, Ospedale S. Giacomo, ASL 22, Novi Ligure, Italy*

¹ Corresponding author: Luigi Rossini (l.rossini@univpm.it).

SUMMARY

The authors review some experimental and clinical contributions - prevalently of analytical pharmacotoxicology - on concurrent dynamic and kinetic modulations which have not yet been systematically evaluated specifically or selectively, and propose a critical view of cognitive, predictive and motivation-associated placebo effects that could provide a more correct and integrated description of class effects, and potential drug substitutions.

“... Who can say why they stopped here? But in every abandoned place there remains a void, an expectation”. Cesare Pavese, Gli Dei (Dialoghi con Leucò, 1947)

“...: I organise an impossible situation, and I need the reader to accept my proposal. If he does, I can assure you that everything becomes implacably logical”. José Saramago, As Intermittencias da Morte, 2005.

Keywords: *Placebo effects, Integrated receptor modulations, Therapeutic class effects and substitutions.*

1. Introduction

In the previous note of this series [1, p. 26] we mentioned that the current classifications of medicinal pharmaceutical and therapeutic products, which on present reductionist criteria are based and focused on receptor molecular and functional specificity and/or selectivity [2], are too unstable and even unreliable. For instance, current *Mini-Review: Expert Opinions* [3, 4] substantially avoid the problem, recommending apodictically to accept the traditional conservative view. In fact, the variability could reflect as yet unquantified covariates associated with favourable and/or adverse placebo effects (PEs) involving increased or decreased specific and even selective effectiveness, rather than therapeutic risks which are traditionally randomised but destined to arise in more homogeneous subgroups or even variants of haplotypes and occasional single polymorphisms [Cf.: 5]. Other examples are pleiotropic effects, which give rise to potentially more interesting differential results [6], and hormetic effects [7], which are amplified by scaling ups [8]. The Italian *Rivista d'informazione regolativa* has equally generically dealt with the issue of PEs by use of ambiguous images of merely virtual spaces [9]. By contrast, in *Lettere dalla Facoltà* [10] kinetic dynamics, signally those of dopaminergic and glutamatergic nature related to drugs abuse and manias, have already begun to be addressed based especially on recent findings in Parkinson's disease and painful and depressive syndromes, in which the significance of PEs is no longer considered negligible.

We will herein update and extend our overview published in *Lettere dalla Facoltà* by developing its original contributions on receptor classifications [11-17], which have preceded those similarly standardised according to the guidelines proposed by IUPHAR since 1994, which in 2006 have reached their 57th edition [18]. At the time it was widely believed that overlap of the asymptotic ends – that is the somewhat unresolved α - vs β - distribution errors - of the phenotypic functional profile distributions described down to the deconstructed subcellular level (today definitely attributed to integration networks of the same confirmedly complex genomic dynamics) deserved investigation of the knowledge gaps existing in relation to PEs, which are not adequately recognised among the causes of biological pathophysiological variations in current experimentation and clinical practice, especially human. Indeed, any active interventions following the more updated principles shared by pharmacological-therapeutic allopathic medicine should be based on the essential prerequisite of the analytical and systematic rationalisation of the multiplicity of factors involved, in parallel with their observational explorative and epidemiological evidence [Cf.: 19], and study and identify iteratively their complexity by exploiting the increasingly sophisticated and potentially conclusive available methods of investigation.

2. Placebo effects (PEs) and alternative / complementary medicine

Non-conventional medicine is increasingly being appreciated [20, 21]; for some this reflects the crisis of traditional medicine [22] in relation to well-known conflicts of interest [23, 24] and the very ethical and scientific value of experimental and clinical trials, which have often been debated [see 1, 5, 25-48]. At the same time, the prestige of WHO interventions [49, 50] has appeared diminished after the first report on acupuncture, in 2003, has failed to evolve into a consensus report on homeopathy [51]. After the discussion and extension [52] of decade-old contributions [53-55], the debate is currently centred on homeopathy, which is widely held to be substantially based on PEs; nonetheless, these have so far been analysed merely as generic, indistinct effects and not suitably investigated using the phase method, like interventions such as psychotherapy [56-85]. It is countered that “if everything has to be double-blinded, randomised, and evidence-based, where

does that leave new ideas?" [86-91], but surely, the statistic method, which in the present case has not however been applied as it has originally and convincingly been proposed recently [92], reflects well-known conventional and widely discussed cases [93-108], provided that adherence to medication is known [109]. Unfortunately, it has again been necessary to recall the still not uncommon case of inappropriate reverse experiments, if one is to adhere to the view of the "evidence of the validity of the null hypothesis rather than simply failing to find evidence against it", which requires equivalence tests [110].

Here, we should humbly like to point out that, given the pace of human, maybe "too human" progress of mythology [111] and more generally of science (not merely medicine) [69, 88, 112-113], "rather than doing further placebo-controlled trials of Homoeopathy, future research efforts should focus on the nature of context effects and on the place of Homeopathy in health-care systems" [Cf.: 52]. This approach can be extended if the current biology of PEs is investigated as we shall try to outline below.

3. Placebo effects (PEs) and the potential findings of therapeutic features associated with drug use and misuse (including addiction)

The characteristics of PEs, signally those described by Skinner [114] and Wise [115] (see also [116]), are not dissimilar from those associated with drug abuse and addiction and to those related to the instinctive drives characteristic of the hedonistic rewards of food intake (among which alcohol consumption is on the rise [117]), sexual arousal, leisure activities and intensive agonistic practice. Their diverse significance in terms of individual v. species fitness would be interesting to explore.

After recognition of the distinction between receptor specificity and iso-receptor selectivity [2], PEs are now accepted to contribute consistently, and far from negligibly, to their unique functional properties. As research into therapeutic drugs advances, patients should be informed that addiction may be one of the PEs of a prescribed drug. The need not only to maximise the probability of benefit and its potential, but also to reduce the risk of adverse effects [118, 119] also applies to cases where PEs are prevalently based on environmental cues and are evoked even in the absence of concurrent diagnostic pharmacological, therapeutic and rehabilitation interventions. Cravings associated with drug abuse and addiction, triggered by these cues and apt to induce relapse, are of crucial topical social and legal interest.

4. Results of non-invasive basic, experimental and clinical pharmaco-toxicological studies

Pharmacological science distinguishes between "heroic" substances, those traditionally considered as the most active, and less effective substances with a clinically appreciable, and at least psychological, effects [i.e.: 120]. Pathophysiological chemistry associated with kinetic studies of PEs using techniques as uninvasive as possible (as repeatedly advocated [1, 121, 122]) have contributed to identifying unique drug properties with distinctive dynamics. One well-known example is positron emission tomography (PET), which has made it possible to depict the kinetic succession of functional events in patients with Parkinson's disease (PD), including paradoxical (including verbal) kinesia [123-124]. Their application to painful and depressive syndromes, which are associated with several diseases, is expected to provide significant insights [i.e.: 125-129. Ref. 130-132 will be recalled below]. Interestingly, in the introduction to brain imaging studies on PEs, also with depressed patients [133], the studies are presented as part of a growing research body exploring mind states – including empathy, imitation, and "theory of mind" - which have in

common the creation of interior representations of what another individual is experiencing, a type of representation shown by the discovery of “mirror neurons” [Cf.: 134-139], that embrace the limits of past and future boundaries [140].

In particular, the increased release of dopamine (DA) in the dorsal striatum (caudate and putamen) connected with placebo administration has been seen to correspond with the expectation of a potential clinical benefit or to precede the reward of the healing process consequent to administration of levodopa (and apomorphine and/or their analogues). Whereas the placebo effect was observed in all PD patients – with improvements in motor function in around 50% – DA levels in the ventral striatum (nucleus accumbens) were similar in all subjects, whether or not they had received the drug and whether or not they had derived a motor benefit [123, 141-142]. Such findings led the authors to conclude that DA release is simultaneous with, and sustains, the anticipation of a clinical benefit rather than its actual perceptual meaning. In partial agreement with them, other researchers [143- 145] noted placebo-induced DA transporter down-regulation and an indirect n. accumbens DA increment, in line with the notion that the placebo contributes substantially to triggering reward mechanisms.

It is appropriate to note here that the transport currents of low-concentration DA (peaking at 50 nM), which coincide with increases in Cl⁻ conductance, correspond with the phases of tonic activity of dopaminergic neurons (~ 4 Hz), whereas 2-6 spike phasic activity (~15 Hz) connected with K⁺ channel opening and Ca²⁺ channel closure takes place at higher DA concentrations (~1 μM). Phasic activity involves the inhibitory, depressive mediation of D₂ autoreceptors, together with sensory afferent pathways of reward stimuli which underlie conditioned learning processes [146-150]. Tonic v. phasic subsecond DA release activities, which specifically promote cocaine seeking and more general habit formation [151-153; see also 154-158 for contributions on selective Ach signalling, and 157-164 for those by glutamate iso-reception and -transport] are only some examples of behaviours that could usefully be explored with frequency-domain methodologies (see next paragraph), which have not yet been applied to PEs characterisation.

In the majority of PD clinical trials, placebo effects induced significant improvement in up to 59% of cases compared with patients treated with the more active principles of current therapies [167-169]. As expected, such improvements included pathognomonic symptoms, which responded in different ways– e.g. bradykinesia and stiffness tended to be more susceptible than tremor [169]. Incidentally, in the presymptomatic clinical phase of PD (when 80% of nigrostriatal dopaminergic neurons are already lost) compensatory, either DA-related and non-dopaminergic mechanisms, whose possible association with PEs is still unknown, have been observed both within and outside the striatum [170; other related topics in: 171-184]. In this context, the pharmacologist’s integrated approach is stimulated by findings that supersede myriad previous contributions obtained with inadequate methods.

As regards dopaminergic transmission and modulation, the more than 300 references included in [121], addressing the prevalent reward functions of n. accumbens, on which the vast majority of abuse substances act by increasing DA release, describe both behavioural and motor functional equivalents, particularly craving and drug-seeking behaviours, that compensate for intrinsic mediator deficit syndrome. In fact, DA release is triggered not by an event coinciding with accumbens release, but by its anticipation – as described, among others, by Schultz [185] and Garris *et al.* [186]. In addition, anticipatory and/or expectant DA release in PD patients is detected not only in the ventral striatum (accumbens), but also in its dorsal portion [123].

Thus, it would be useful to investigate systematically whether similar, overlapping, or even identical PE mechanisms also obtain in drug use and misuse, including addiction. If they do, it

should be explored whether such mechanisms may be strengthened and harnessed in detoxification and maintenance programmes aimed at preventing the onset of diversions (e.g.: development of methadone dependence), at fostering recovery and active behavioural rehabilitation, and at promoting unequivocal change and the disappearance/suppression of the tendency to relapse. Utilisation of acamprosate [187] to prevent relapse by reducing craving and, more recently, of topiramate [188, 189], should not be confined to alcohol dependence. Since discontinuation and/or reduction of the placebo, an addictive substance, produces withdrawal syndromes, it may become a model for clinical trials and explorative-epidemiological surveys aimed at gaining insights into the characteristic phases of such syndromes. The quantification of anticipation effects is expected to contribute substantially to defining the specificities associated with the various classes of substances, including prescribed drugs and drugs of abuse, like the new entries (i.e.: “designer drugs”).

5. Additional experimental contributions

Integrated *in vivo* investigations have allowed rapid DA release kinetics to be described in n. accumbens and in ventral tegmental area dopaminergic neuron projections of rats exposed to self-administered cocaine cycles, both in control and in treated subjects. Fast-scan cyclical voltammetry with 0.1 sec cyclical repetitions [190, 146-147] showed initial (anticipatory) responses associated with the environmental context upon presentation of the reinforcing agent in the form of bursts of phasic activity in the range of 200 msec; this DA surge mounted gradually, peaking upon actual intake and persisting at high tonic levels for minutes during and after administration [148-157].

Thus, both in the phase of conditioned seeking behaviour (expectation) and in the phase of perceived reward (intake), the DA neurochemical modulation message appears to work as a signal or diagnostic marker of both triggering and intake. The reward neurons in VTA are uniformly inhibited by an aversive stimulus, while the 3% to 49% of neurons that are excited are not dopaminergic [191]. In all studies of these mechanisms, the time course of the phenomenon has evidenced the presence of essential, intrinsic, functional cyclical fluctuations that stand out clearly against the background noise; these fluctuations, which are shared by several neuro-pathophysiological and psychiatric processes [153], are measured as currents related to DA transport [143-152]; their analysis with non-invasive time and frequency domain methods has already and repeatedly been advocated [1, 192-194]. See [195], as [130-132], and more References below, for a further explanation of PEs that focuses more on adaptive coding of the reward value of DA neurons and even considers addiction as a new computational process, and the relations to the tonic-phasic DA hypothesis extended to specific/selective neuropsychiatric phenotypes. It is interesting to note that, for addictive substances, the multiple conditioning and conditioned effects associated with the general context of the *milieu interieur* (according to the seminal definition of the founder of Experimental Medicine), as well as the effects of environmental cues, can be described kinetically and analytically, albeit this has not as yet been done exhaustively.

It should nonetheless be stressed that a) we seem to be imperfectly efficient in recognising a context, at least one consisting of environmental cues: indeed, in a very common and repetitive sensory field our actual ability, compared with the abstract, theoretical one, has been found to diminish with increasing task complexity. Measurable cognitive limitations of learning and adaptation mechanisms have also been identified [196-197], as if the features of the single substances and related events were somehow connected in a way that we are not allowed to assess fully due to their increasing holistic complexity. Here, again, our hopes are pinned to the analytical potential of non-invasive techniques. Another important question is b) the current revolution regarding the processes that can be generalised, which have been extended to include DA mediation and risk validations, the latter having moved from the toxicological to the legal domain. Such

questions pertain to the hormetic pharmacometric revolution, where dose-response relationships range from detectable stimulatory effects at lower doses to an opposite, inhibitory effect at higher doses [7, 198-199]; the mechanisms associated with such opposite drug-related effects can also be recognised at the levels of GABA A and B receptor sites, opiate/noradrenergic and BDNF mediated, even highly integrated, time-dependent effects [200-213]. Indeed, with the exception of nicotine dependence [214; i.e.: 154-157], the contexts studied to date have not yet benefited from in-depth analyses of the PEs associated with drug addiction syndromes arising from different doses. Finally, it is worth noting that c) glutamatergic (excitatory) mediation has repeatedly been mentioned [121; 159-166] as the single site of the higher integrated cerebral kinetics and dynamics of several parameters, whose fluctuating phases have been studied using more or less invasive experimental and clinical models of drug addiction syndromes. However, multiple brain sites are now held to be involved at different time points; these effects are strongly characterised by Hebbian synaptic adaptations, and may be sustained by extrasynaptic, direct and retrograde mechanisms as well as by neurochemical volume transmission [154-158, 215-220]. With reference to the studies mentioned above, it should be stressed that triggering of inverse tolerance, i.e. of sensitisation processes due to repeated exposure to/intake of gnomonic substances of abuse requires, at least in some cases and transiently, an initial adaptation expressed by elevated levels of ventral tegmental area and n. accumbens AMPA glutamatergic receptor R1 subunits. The involvement of these sites has nevertheless been considered as a primary or secondary indistinct, causative effect [164-166, 221].

Dopaminergic receptor fields thus modulate specifically and even selectively (e.g. the GABA and AMPA subgroups) the information—both memory drives and motivation—from these converging pathways, whereas the tonic DA increment in n. accumbens (in the core but not in the shell [222-226]) represents the sign of the integration process contributing to generate the object-achieving behaviour. Such hypotheses are considered by some researchers to be paradoxical and increasingly, hopelessly baffling, given that the literature is to all effects swamped with discoveries of receptor proteins involved in multiple and even opposite behaviours as a function of dosage range, time of action, and of interactions in micro-compartmented, strictly undefined distribution volumes, cell-based receptor fields, etc [i.e.: 227-228]. It bears repeating that this also stems from the failure to adopt appropriate, non-contingent, optimised study techniques that should be consistent with the nature of the phenomena investigated.

6. Additional clarifying elements

The PEs associated with administration may thus represent a (subconscious) assessment of the probability of therapeutic benefit and success, or of the risk of toxicological damage. This assessment is based on knowledge acquired intellectually (cultural-social criteria), or else derived from the subject's own experience of activities that have instinctive, unconditioned, inherent, primitive, spontaneous, but according to Skinner [114] operational priming roots.

The appeal, allure and arousal experienced during gambling have recently been studied in the midbrain of a conscious monkey subjected to cycles of Pavlovian conditioning (where different stimuli had a different probability of being followed by a reward) with recording of the firing of individual dopaminergic mesostriatal neurons [229-231]. The highest probability of the subject's taking the risk, which may be subsumed under the definition of previous, expected or predicted PEs v. reward PEs connected with exposure, was associated with the more uncertain rewards, while the probability was lower for less uncertain rewards. These effects are more than faintly reminiscent of those connected with drug addiction agents. Such patterns were interpreted by the authors as serving to increase allocation of attention in the phases of uncertainty, since this may promote

learning of better predictors and actions in more complex natural environments than the laboratory setting of a casino. According to these researchers, the greater DA release triggered and sustained by situations of greater uncertainty could act as a reinforcement to learning, a pathological form of which is represented by the extinction-resistant sensitisation typical of current substances of abuse that is observed both in their presence and, after priming, in their absence [232]. Hence the cycle of spiralling dysregulation of brain reward systems observed in consumers-turned-addicts, which ultimately induces craving, a permanent, compulsive, allostatic maladaptive behaviour [233].

It remains to be elucidated how and why DA neurons consistently exhibit two types of responses: brief, phasic activation, which increases with rising probability of reward, and slower, tonically more sustained responses, which increase with rising uncertainty. These phenomena may nonetheless be encoded independently in single neurons and can be studied, for instance, with frequency domain techniques [192-194], as we have often advocated, since they must be integrated in the most extensive of neuronal networks and in the functions of the receptor fields of more recent evolution (e.g. dorsal striatum and paleo- and neocortical projections [234]). In fact, 50 years from the enunciation of the uncertainty principle by Werner Heisenberg (1901-1976), an analysis of the causal deterministic relationship (rather than the casual relationship) in macroscopic pharmacotoxicology (rather than molecular-atomic and quantum pharmacotoxicology), is overdue in biology, physics, history, and even philosophy, not only in science (epistemology)[228]. This should be done by identifying frequency domain boundaries according to the seminal, and to date unsurpassed, experiments and modelling by the author himself, by weighting the individual covariates (possibly also including those of PEs), even when the effects are related to own, differentiated up and down kinetics, and until their “disappearance” ([225- 235]; see also the more recent additional references: i.e.: [236-240]).

Thus, decisions today appear to be the fruit of integration and to be influenced by emotional and cognitive factors, where the uncertainty of reward—thanks to the heightened attention accompanying the phases of sustained dopaminergic firing of the mid-striatum—could promote learning of better predictors and consequent actions in line with the theories advanced by Shannon [241] and discussed by Rescorla and Wagner [242], and Pearce and Hall [243]. In particular, and significantly, Shannon’s construct is consistent with the addictive effects of behavioural aspects; in these, the cognitive control governed by psychophysical rules formally similar to the law of Weber and Fechner underpinning human perception, indicates connected principles of neuronal networks shared by cognitive and perceptive control. This can be inferred from the measurement, consistent with the “brain cascade”, of contextual and sensory episodic signals from the rostral to the caudal regions of human prefrontal cortex and of premotor regions [244]. Berridge and Robinson, in discussing their parsing reward hypothesis [245] (see [246]), make reference to the model of organisation of the cerebral information flow analysed with functional MR imaging (fMRI) by Koechlin *et al.* [244]. The two teams, however, ignore each other. The studies of the roles of phasic or sustained dopaminergic signals and of distinctive reinforcement functions of learning processes and actions [195, 247] must be taken into account if animal models of escalated drug intake [232] and, ultimately, the human genome, are to provide insights into the syntenic presence of quantitative trait loci (QTLs) of predisposing factors [248], to detect vulnerability. These advances should allow to explain those behaviours that from the extended amygdala itself [249] become holistic, involving multiple functional receptors, and no longer merely the dopaminergic receptors of the cerebral complex [250]. *In conclusion*, we learned from Wittgenstein that “we are on a journey towards language, needful of care” (i.e. [194]), while the language of proteins [227] is only just beginning to be understood and we admit to the existence in animal models of a common dopaminergic pathway involving, via DARPP-32 and specific phosphatase and kinase, dynamic effects of agonists, also of enteraminergic nature (D-amphetamine and LSD), and of glutamatergic antagonists (phencyclidine) [251]. We will not address here single contributions that have appeared

after the seminal research mentioned above. Nonetheless, it is firmly established that the iso-receptor interactions of dopaminergic classes and beyond are endowed with a metabolism-dependent complexity that can no longer be neglected, and that the same dynamic and kinetic neuronal and glial interactions at the various sites (see: [252-278]) extend well beyond the dependence and manias studied to date [10]. This is well known to the advocates of integrated pharmacotoxicology, which is finally being included among the main purposes of several works besides the present one.

The complementary review by Jacobs and co-workers [279] was published while a draft of this overview was being written. The authors study animal models subjected to the yoked control-operant paradigm, discussing topics similar to ours without however defining them as PEs. The external v. internal active-anticipated and expected v. possibility-associated cue effects they describe during pretreatment and thereafter are in line with our views of addiction processes; they also express similar views of PEs, reach conclusions that imply the hormetic phenomena mentioned above, and they, too, advocate further targeted studies.

7. Updating of technological and statistical analyses

We refer the reader to the literature on other available experimental and clinical study techniques [280-305], and to their statistical modelling [295-318; see also 92, 113, 195, 204], which has the potential to highlight functional associations with PEs at the various integrated receptor levels. These are among the main challenges currently facing physiology and pharmacotoxicology. For laboratory contributions to time v. frequency reviews, see [1, 192-194]; for recent advances see [319-346].

8. Conclusive remarks

Besides being involved in the final functional steps of the motor output, the mesencephalic dopaminergic system has been hypothesised to be directly implicated in the structuring of reward and motivation habits according to the early concept of dopaminergic dysfunction anhedonia, whereby concurrent DA release is viewed as the hedonic signal equivalent to reward perception. This hypothesis, now superseded, was later modified by Berridge and Robinson [347] into that of “incentive salience”, or increment of goal identification, and envisages extracellular DA involvement in reward anticipation or seeking behaviours. The system is now being studied using algorithms that attempt to describe which desired objects, or expressions of expected values, arise in successive temporal difference (TD) learning acts. TD learning models sustain kinetic prediction error analyses, which are subject to boosting or extinctions as a function of continuously evolving “liking” experiences, defined by McClure and co-workers as “consummatory reward behaviours” [348]. In the light of recent neuro-patho-physiological findings, dopaminergic mediation thus appears to serve less as an internal focal representative of the stimulus of the transactional object of attraction – simplified as “like” – than as the operative equivalent of acquired motivations – “want”. The initial anhedonia hypothesis, which viewed DA as being associated with primary, unconditioned/instinctive reward perception, has eventually been rejected based on experiments, where reduction in dopaminergic function did not alter the primary hedonic responses of increased DA neuron activity associated with the events preceding reward consumption. The alternative hypothesis proposes its occurring in anticipation of reward-seeking when such events appear initially to overlap, and the model integrates the DA function of “incentive salience” into the dominant prediction error of “future reward”.

Here we do not address the analysis of molecular subcellular mechanisms, as do [251], nor the involvement of cAMP-response element-binding proteins (CREB), which are genic transcription factors involved in the regulation of neuropeptide Y gene expression [349] identified in the phase of anxiety of alcohol dependence, where brain-derived neurotrophic factor (BDNF) and its receptor trkB activate CREB via C γ -phospholipase. This is a crucial step in long-term potentiation (LTP) [276, 350-353], which has been discussed in previous reviews [121, 132, 192-194]. Long-term memories are encoded on bases that are in turn prevalently structural and prevalently chemical, and are subject to swift processes of radical reorganisation [354-355] of Hebbian synaptic adaptation, which may be pharmacologically modulated [152-156, 200-205, 356], and require non-invasive investigation of conscious models, like the PET studies mentioned above and “event-imaging” fMRI [i.e.: 130-133; etc, § 7 above]. In fact, the non-invasive fMRI techniques show that the rostral anterior cingulate cortex implements a conflict-monitoring function, with the engagement of the step leading to the consequential recruitment of the cognitive control exerted in the presupplementary motor area [357] and in the lateral prefrontal cortex [358]. These same affective brain areas respond to both experienced and imagined pain and the neurons activated by empathy are also activated by the anticipation of pain, two phenomena that are closely connected with the placebo response [357-361]. Cognitive control may thus be crucial for down-regulating the pain and placebo circuitry, and it may be possible to predict a patient’s integrated response to medication by looking at the “expectation component” in their brain scans. The “observing self” of the conscious brain [362] or, in the absence of a conscious stimulus percept [363-364], the neural correlates of the preparatory set [365] and the state- and item-related successful memory encoding [366] attached to the modulation of our subjective perception of time [367], appear to represent both conscious and unconscious affective experience, by virtue of the power and accuracy of fMRI in documenting changes in brain activity also through indirect monitoring [368].

Without jumping on the bandwagon of systems biology, tracing the life circuitry of how biological networks work and behave, from cells to whole organisms – “the beginning of real biomedicine” [369-370] – requires essential non-invasive pharmacotoxicological techniques [371-372]. Again, models are often inaccurate, although some may be useful if subjected to analytical and explorative research [19].

Clearly, we daily have the opportunity for better experimental animal and human studies [373], which must be integrated with appropriate computational bioinformatic modelling [374] if we are to train better physicians and researchers for personalised medicine [375].

In this context PEs remain a crucial issue. They are found in all processes, not only those related to general addictive assumptions/administrations and specific/selective dynamic and kinetic molecular modulations, but also in a very large number of known pathophysiological issues, where research is beginning to focus on common network basic factors up to the very wide “instant, but evolving” self and external global integrating contexts. We refer the interested reader to the most recent work on this topic, where the descending parabola of medicine since the 1970s is analysed and held to require a reduction of expectations; in this framework, multifactorial PE analysis is believed to be able to contribute to the “latest benefits to mankind” [376] by adding to the most recent works in the field of cognitive science [377], as also demonstrated by perusal of the latest general contributions, listed here as usual in inverted order [378-444].

The repetition of the disasters of drug discontinuation and the most glaring inadequacies of private v. public pharmacovigilance practices/programmes [5, 445; see also: [446-449] call for a reconsideration of basic pharmacotoxicological research and development. The current distinction between receptor specificities and iso-receptor selectivities can obviously have a counterpart in interrelated haplotypes and even single nucleotide polymorphisms, where geno-phenotypic

correspondences may be less successful in outlining functional profile variabilities in sub-populations and ultimately individual patterns of reactivity, v. the elusive nature of intrinsic activities or efficacies, if not better efficiencies [1; i.e.: 450-452]. Neither pharmaceutical chemistry nor medicinal chemistry receptor classifications include all relevant features of drug effects or take into due account current and/or potential acquisitions regarding PE dynamics and kinetics in continuously evolving preclinical and clinical experimental studies. DA release and turnover are mostly seen as contributing to the more general reward effects and therapeutic expectations, but only in some models. However, their kinetic integration in specific/selective time and space with other signalling cascades has not yet been described, and it is still unclear whether and how these are quantitatively associated with PEs. Some clinical PEs have recently been challenged [95-98]. Nevertheless the reinforcing PEs, particularly in drug and other reward contexts and conditions, have been ignored, not only in declared nature v. nurture reinforcing cues of drug-related addictions. A more comprehensive re-classification of drug analogues and iso-receptor classes and families could therefore ameliorate drug use results, particularly if one establishes where and when positive and negative PEs are analytically disproved to be of solely scarce help [i.e.: 453].

In the light of the considerations made above, we hope we have made a convincing case for the usefulness of non-invasive kinetic TD learning studies [i.e.: 92, 195, 204, 247, 348, 357, 360, 378, 391, 414, 422] in providing a substantial contribution towards a better identification of the Placebo Effects related to the topics addressed in the course of the overview.

Acknowledgements

The authors would like to thank Professor Silvia Modena for her contribution towards revising the English, and Dr Ivano Paglione for his help with the References.

9. References

1. Rossini L. Drugs and the future. *Pharmacologyonline* 2005; 1: 12-44.
2. Walker RJ. Editorial: The IUPHAR Guidelines regarding the classification of new receptor subtypes. *Gen Pharmac* 1996; 27: 1.
3. Kereiakes DJ, Willerson JT. Therapeutic substitution: guilty until proven innocent. *Circulation* 2003; 108: 2611-2615.
4. Antman EM, Ferguson JJ. Should evidence-based proof of efficacy as defined for a specific therapeutic agent be extrapolated to encompass a therapeutic class of agents? *Circulation* 2003; 108: 2604-2610.
5. Rossini L. Corso monografico sperimentazione dei farmaci e farmacovigilanza 2006; submitted to *Lettere dalla Facoltà*: 1-15.
6. Chatterjee PK. Pleiotropic renal actions of erythropoietin. *The Lancet* 2005; 365: 1890-1892.
7. Calabrese E, Baldwin LA. The dose response revolution. *Ann Rev Pharmacol Toxicol* 2003; 43: 175-197.
8. Kim JY, Gilks C. Scaling up treatment – why we can't wait. *N Eng J Med* 2005; 353: 2392-2396.
9. Bertelè V, Garattini S. Escher, l'ambiguità degli spazi e l'effetto placebo. *BiF* 2005; 2: 84-88.

10. Rossini L, Rossini P. Evoluzione di alcune conoscenze base in tema di tossicoassunzioni e tossicomanie, Quinquennio 1998-2003. Ia Parte: Dipendenze, specificita' e selettivita' degli effetti *placebo* e trasmissione-modulazione dopaminergica. Lettere dalla Facoltà 2005; 8: 19-26.
11. Bradu D, Di Sarra B, Concettoni C, Moretti V, Pagelli R, Re L, Rossini L, Tonnini C. Characterization of the rabbit aorta endothelium- dependent cholinergic receptor by agonist equipotent molar doses. *J Pharmacol Methods* 1989; 22: 219-231.
12. Cingolani ML, Re L, Rossini L. The usefulness, in pharmacological classification, of complementary pattern- recognition techniques and structure modelling as afforded by the iterative collation of multiple trial data in data banks. *Pharmacol Res Commun* 1985; 17: 1-22.
13. Bradu D, Cingolani ML, Ferrante L, Re L, Rescigno A, Rossini L. A contribution to the advancement of the computational procedures as applied to the classification of drugs and receptor congeners. In: *Highlights in receptor chemistry*, Melchiorre C, Giannella M Eds, Amsterdam: Elsevier Science Publishers 1984, 251-294.
14. Rossini L, Bastianelli P, Bradu D, Cingolani ML, Ferrante L, Gamba G, Re L. Ordering and grouping drug analogues and receptor effects. In: *The impact of computer technology on drug information*, Manell P, Johannson SG Eds, Amsterdam: North-Holland, IFIP-IMIA 1982: 181-183.
15. Rossini L. Reclassifying cholinergic receptors. *Trends Pharmacol Sci* 1981; 2: I-IV.
16. Rossini L, Bastianelli P, Cingolani ML, Gamba G, Giannella M, Gualtieri F, Leone L, Martorana F, Melchiorre C, Moretti V, Periti PF, Pigni M, Pigni P, Re L, Roda G, Tuccella S. Pattern recognition in profiling pharmacological receptors. In: *Portonovo Conferences, II* De Martinis C, Rossini L Eds, Padova: Piccin Int Ed 1978, 257-290.
17. Rossini L, Martorana F, Periti P. Clustering cholinergic receptors by muscarine and muscarone analogues. In: *Rationality of drug development*, Bergamini N, Bachini V Eds, Amsterdam: Excerpta medica – American Elsevier 1976: 223-228.
18. Bathgate RA, Ivell R, Sanborn BM, Sherwood D, Summers RJ. International union of pharmacology LVII: recommendations for the nomenclature of receptors for relaxin family peptides. *Pharmacol Rev* 2006; 58: 7-31.
19. Black J. Pharmacology: analysis and exploration. *Br Med J* 1986; 293: 252-255.
20. Anonymous. Agopuntura. *The Medical Letter It Ed* 2006; 35: 50-51.
21. Gerlin A. Not so complementary. *Time* 2006; 26: 34-35.
22. Licata G. L'omeopatia come espressione di crisi della sanità. *Ann Ital Med Int* 1999; 14: 209-213.
23. Blumenthal D. Doctors and drug companies. *N Eng J Med* 2004; 351: 1885-1890.
24. Studdert DM, Mello MM, Brennan TA. Financial conflicts of interest in physicians' relationships with the pharmaceutical industry – self-regulation in the shadow of federal prosecution. *N Eng J Med* 2004; 351: 1891-1900.
25. Editorial. Clinical trials in children, for children. *The Lancet* 2006; 367: 1953.
26. Nylenna M, Simonsen S. Scientific misconduct: a new approach to prevention. *The Lancet* 2006; 367: 1882-1884.
27. Avorn J, Shrank W. Highlights and a hidden hazard – the FDA's new labeling regulations. *N Eng J Med* 2006; 354: 2409-2411.
28. Hoffmann DE, Rothenberg KH. When should judges admit or compel genetic tests? *Science* 2005; 310: 241-242.
29. Couzin J. Plan B: a collision of science and politics. *Science* 2005; 310: 38-39.
30. Littlejohns P, Kelly M. The changing face of NICE: the same but different. *The Lancet* 2005; 366: 791-794.

31. Young C, Horton R. Putting clinical trials into context. *The Lancet* 2005; 366: 107-108.
32. Grimes DA, Hubacher D, Nanda K, Shultz KF, Moher D, Altman DG. The good clinical practice guideline: a bronze standard for clinical research. *The Lancet* 2005; 366: 172-174.
33. Devi S. Research scandal forces Israel to tighten up supervision. *The Lancet* 2005; 365: 1915.
34. Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical-trial agreements with industry. *N Eng J Med* 2005; 352: 2202-2210.
35. Steinbrook R. Gag clauses in clinical-trial agreements. *N Eng J Med* 2005; 352: 2160-2162.
36. Imai K, Zhang P. Integrating economic analysis into clinical trials. *The Lancet* 2005; 365: 1749-1750.
37. Steinbrook R. Registration of clinical trials – voluntary or mandatory? *N Eng J Med* 2004; 351: 1820-1822.
38. Sheridan DJ. Reversing the decline of academic medicine in Europe. *The Lancet* 2006; 367: 1698-1701.
39. Sim I, Chan AW, Gulmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword; Horton R. Trial registers: protecting patients, advancing trust; Rockhold FW, Krall RL. Trial summaries on results databases and journal publication. *The Lancet* 2006; 367: 1633-1636.
40. Tugwell P, Petticrew M, Robinson V, Kristjansson E, Maxwell L. Cochrane and Campbell collaborations, and health equity. *The Lancet* 2006; 367: 1128-1130.
41. Liu JLY, Altman DG. Conduct and reporting of clinical research. *Science* 2005; 308: 201-202.
42. Frantz JA. Comparative studies of drug efficacy. *Science* 2005; 308: 202-203.
43. Harris R. Does the dose make the poison?. *Science* 2005; 308: 203.
44. Wang YL, Burrige K, Dembo M, Gabbiani G, Hanks SK, Hosoya H, Janmey P, Karlsson R, Lindberg U, Mabuchi I, Otey C, Rottner K, Small JV, Wang C-LA, Zigmond S. Biomedical research publication system. *Science* 2004; 303: 1974-1975.
45. Svetlov V. The real dirty secret of academic publishing. *Nature* 2004; 431: 897.
46. Stenflo L. Intelligent plagiarists are the most dangerous. *Nature* 2004; 427: 777.
47. Keusch GT, Medlin CA. Tapping the power of small institutions. *Nature* 2003; 422: 561-562.
48. Knight J. Null and void. *Nature* 2003; 422: 554-555.
49. *Legal status of traditional medicine and complementary-alternative medicine: A worldwide review*, WHO/EDM/TRM/2001.2. World Health Organization, Geneva 2001: 1-189.
50. Horton R. WHO: strengthening the road to renewal. *The Lancet* 2006; 367: 1793-1795.
51. McCarthy M. Critics slam draft WHO report on homeopathy. *The Lancet* 2005; 366: 705-706.
52. Shang A, Huviller-Müntener K, Nartey L, Jüni P, Dörig S, Sterne JAC, Pewsner D, Egger M. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *The Lancet* 2005; 366: 726-732.
53. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedgesw FE, Jonas WB. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *The Lancet* 1997; 350: 834-843.
54. Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. *J Clin Epidemiol* 1999; 52: 631-636.
55. Skrabanek P. Is homeopathy a placebo response?. *The Lancet* 1986; 2: 1107.
56. Braillon A. Should we trust results of meta-analyses?. *The Lancet* 2004; 364: 1401-1402.
57. Nicolucci A, Tognoni G. Should we trust results of meta-analyses?. *The Lancet* 2004; 364: 1401.

58. Khalida I. Author's reply. *The Lancet* 2004; 364: 1402-1403.
59. Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-blind clinical trials: a review of interactions with medications. *The Lancet* 1994; 344: 1347-1349.
60. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ* 1995; 311: 485.
61. Walach H, Jonas W, Lewith G. Are the clinical effects of homoeopathy placebo effects?. *The Lancet* 2005; 366: 2081.
62. Linde K, Jonas W. Are the clinical effects of homoeopathy placebo effects?. *The Lancet* 2005; 366: 2081-2082.
63. Fisher P, Berman B, Davidson J, Reilly D, Thompson T. Are the clinical effects of homoeopathy placebo effects?. *The Lancet* 2005; 366: 2082-2083.
64. Dantas F. Are the clinical effects of homoeopathy placebo effects?. *The Lancet* 2005; 366: 2083.
65. Shang A, Jüni P, Sterne JAC, Huwiler-Müntener K, Egger M. Author's reply. *The Lancet* 2005; 366: 2083-2084.
66. Skandhan KP, Amith S, Avni S. Author's reply. *The Lancet* 2005; 366: 2085.
67. Raoult D. Author's reply. *The Lancet* 2005; 366: 2085.
68. Editorial. The end of homoeopathy. *The Lancet* 2005; 366: 690.
69. Vandembroucke JP. Homoeopathy and the growth of truth. *The Lancet* 2005; 366: 691-692.
70. Ball P. Memory of water biologist dies after heart surgery. *Nature* 2004; 431: 729.
71. Federspil G, Vettor R. Il problema dell'omeopatia nella medicina contemporanea. *Ann Ital Med Int* 1999; 14: 172-184.
72. Kahn MF. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 365.
73. Seed P. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 365.
74. Paterson C. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 365-366.
75. Vallance AK, Jobst KA. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 366.
76. Ernst E, Barnes J. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 366.
77. Koch A. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 366-367.
78. Benveniste J. Meta-analysis of homoeopathy trials. *The Lancet* 1998; 351: 367.
79. Linde K, Jonas WB. Author's reply. *The Lancet* 1998; 351: 367-368.
80. Bobak M, Donald A. Author's reply. *The Lancet* 1998; 351: 368.
81. Vandembroucke JP. Homoeopathy trials: going nowhere. *The Lancet* 1997; 350: 824.
82. Langman MJS. Homoeopathy trials: reason for good ones, but are they warranted? *The Lancet* 1997; 350: 825.
83. Ernst E. Homoeopathy: past, present and future. *J Clin Pharmacol* 1997; 44: 435-437.
84. Reilly D, Taylor MA, Beattie NGM, Campbell JH, McSharry C, Aithohison TC, Carter R, Stevenson RD. Is evidence for homoeopathy reproducible?. *The Lancet* 1994; 344: 1601-1606.
85. Macri F, Bernardini S, Marinelli G, Minelli E, Piloni S. Raccomandazioni per la pratica della omeopatia in medicina integrata. *La Professione* 2004; 7-8: 11.
86. Wu J. Could evidence-based medicine be a ranger to progress? *The Lancet* 2005; 366: 122.
87. Leonard JV, Colquhoun D, Cooke R, Hachinski V. Evidence-based medicine. *The Lancet* 2005; 366: 972.
88. Burns E. Evidence-based searching. *The Lancet* 2005; 366: 979-980.
89. Ernst E. Is homeopathy a clinically valuable approach?. *Trends Pharmacol Sci* 2005; 26: 547-548.
90. Saxton J. Homeopathy: the case in favour. *Trends Pharmacol Sci* 2006; 27: 237-238.
91. Ernst E. Response to Saxton: homeopathy is not evidence based. *Trends Pharmacol Sci* 2006; 27: 238-239.
92. Prelec D. A bayesian truth serum for subjective data. *Science* 2004; 306: 462-466.

93. Rothwell PM, Metha Z, Howard SC, Gutnikov SA, Warlow CP. From subgroups to individuals: general principles and the example of carotid endarterectomy. *The Lancet* 2005; 365: 256-265.
94. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials. Comparison of protocols to published articles. *JAMA* 2004; 291: 2457-2465.
95. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Int Medicine* 2004; 256: 91-100.
96. Hróbjartsson A, Gøtzsche PC. Unreliable analysis of placebo analgesia in trials of placebo pain mechanism. *Pain* 2003; 104: 714-715.
97. Price DD, Riley JL, Vase L. Reliable differences in placebo effects between clinical analgesic trials and studies of placebo analgesia mechanisms. *Pain* 2003; 104: 715-716.
98. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Eng J Med* 2001; 344: 1594-1602.
99. Campbell MJ. Commentary: Statistical aspects. *BMJ* 2004; 328: 506.
100. Editorial. Single patient trials may guide treatment. *BMJ* 2004; 328: 7438.
101. Peile E. Commentary: n of 1 learning. *BMJ* 2004; 328: 505.
102. Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003; 326: 472-474.
103. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560.
104. Pich J, Carnè X, Arnaiz JA, Gómez B, Trilla A, Rodés J. Role of a research ethics committee in follow-up and publication of results. *The Lancet* 2003; 361: 1015-1016.
105. Evans S. Commentary: matched cohorts can be useful. *BMJ* 2003; 326: 360.
106. Cardon LR, Palmer LJ. Population stratification and spurious allelic association. *The Lancet* 2003; 361: 598-604.
107. Ioannidis JPA, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. *The Lancet* 2003; 361: 567-571.
108. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; 326: 219.
109. Osterberg L, Blaschke T. Adherence to medication. *N Eng J Med* 2005; 353: 487-497.
110. Lew MJ. Principles: when there should be no difference – how to fail to reject the null hypothesis. *Trends Pharmacol Sci* 2006; 27: 274-278.
111. Nietzsche FW. *Umano, troppo umano*. See: Galimberti U, Prefazione. In: Ferrari A, *Dizionario di Mitologia, I°*, Gruppo editoriale L'Espresso S.p.A. Roma, 2006.
112. Coggon DIW, Martyn CN. Time and chance: the stochastic nature of disease causation. *The Lancet* 2005; 365: 1434-1437.
113. Nee S, Colegrave N, West SA, Grafen A. The illusion of invariant quantities in life histories. *Science* 2005; 309: 1236-1239.
114. Skinner BF. *The behavior of organisms*, Appleton-Century Crofts, 1938.
115. Wise RA. In: *The Neuropharmacological Basis of Reward*, Lieberman JM, Cooper SJ, Eds, Oxford Univ Press, 1989: 377-424.
116. White L, et al. *Placebo theory, research and mechanisms*, Guilford Press, 1985.
117. Pincock S. Binge drinking on rise in UK and elsewhere. *The Lancet* 2003; 362: 1126-1127.
118. Gøtzsche PC. Is there logic in the placebo?. *The Lancet* 1994; 344: 925-926.
119. Chaput de Saintonge PM, Herxheimer A. Harnessing placebo effects in health care. *The Lancet* 1994; 344: 995-998.
120. Kumar A. Effetti indesiderati da eccipienti farmaceutici. *Adverse Drug Reaction Bulletin*, It Ed 2003; 155: 619-622.

121. Rossini P, Galeazzi G, Rossini L. Considerazioni di aggiornamento alle attuali conoscenze base in tema di tossicoassunzioni e tossicomanie. *Adria Medica* 1998; 23: 13-43.
122. Di Sarra B. Physio-pharmaco-toxicological *in vivo* read-out: an interuniversity integrated analytical center. Issues, results and perspectives. *Quad March Med* 1989; 5: 183-185.
123. De la Fuente-Fernández R, Stoessl J. The placebo effect in Parkinson's disease. *Trends Neurosci* 2002; 25: 302-306.
124. De la Fuente-Fernández R. Uncovering the hidden placebo effect in deep-brain stimulation for Parkinson's disease. *Parkinsonism & Related Disorders* 2004; 10: 125-127.
125. Dionne RA, Bartoshuk L, Mogil J, Witter J. Individual responder analyses for pain: does one pain scale fit all?. *Trends Pharmacol Sci* 2005; 26: 125-131.
126. Stoessl AJ, de la Fuente-Fernández R. Willing oneself better on placebo-effective in its own rights. *The Lancet* 2004; 364: 227-228.
127. Levine RJ, Carpenter WT, Appelbaum PS. Clarifying standards for using placebos. *Science* 2003; 300: 1659-1661.
128. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Raniero I. Conscious expectation and unconscious conditioning in analgesic, motor and hormonal placebo/nocebo responses. *J Neurosci* 2003; 23: 4315-4323.
129. De la Fuente-Fernández R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. *The Lancet* 2002; 1: 85-91.
130. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004; 303: 1162-1167.
131. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science* 2004; 303: 1158-1162.
132. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms?. *Trends Neurosci* 2003; 26: 696-705.
133. Holden C. Imaging studies show how brain thinks about pain. *Science* 2004; 303: 1121.
134. Rizzolatti G, Sinigaglia C. *So quel che fai. Il cervello che agisce e i neuroni specchio*. Raffaello Cortina Editore, 2006: 1-216.
135. Gross CG, Ghazanfar AA. A mostly sure-footed account of the hand. *Science* 2006; 312: 1314.
136. Nelissen K, Luppino G, Vanduffei W, Rizzolatti G, Orban GA. Observing others: multiple action representation in the frontal lobe. *Science* 2005; 310: 332-335.
137. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science* 2005; 308: 662-666.
138. Nakahara K, Miyashita Y. Understanding intentions: through the looking glass. *Science* 2005; 308: 644-645.
139. Baars BJ, Ramsøy TZ, Laureys S. Brain, conscious experience and the observing self. *Trends Neurosci* 2003; 26: 671-675.
140. Scalfari E. Noi stretti tra passato e futuro. *Il vetro soffiato*, *L'Espresso* 2006; LII: 170.
141. De la Fuente-Fernández R, Phillips AG, Zamburlini M, Sossi V, Calne DB, Ruth TJ, Stoessl AJ. Dopamine release in human ventral striatum and expectation of reward. *Behavioural Brain Research* 2002; 136: 359-363.
142. De la Fuente-Fernández R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 2001; 293: 1164-1166.
143. Sulzer D, Galli A. Dopamine transport currents are promoted from curiosity to physiology. *Trends Neurosci* 2003; 26: 173-175.
144. Ingram SL, Balakrishna MP, Amara SG. Dopamine transporter mediated conductances increase excitability of midbrain dopamine neurons. *Nature Neurosci* 2002; 5: 971-978.

145. Guttman M, Steward D, Hussey D, Wilson A, Houle S, Kish S. Influence of l-dopa and pramipexole on striatal dopamine transporter in early PD. *Neurology* 2001; 56: 1559-1564.
146. Phillips PEM, Stuber BD, Helen MLAV, Wightman RM, Carelli RN. Subsecond dopamine release promotes cocaine seeking. *Nature* 2003; 422: 614-618.
147. Self D. Dopamine as chicken and egg, *Nature* 2003; 422: 573-574.
148. Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JrJB. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology* 1995; 120: 10-20.
149. Staal RGW, Mosharov EV, Sulzer D. Dopamine neurons release transmitter via a flickering fusion pore. *Nature Neurosci* 2004; 7: 341-346.
150. Fiorillo CD, Tobler PN, Schultz W. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 2003; 299: 1898-1902.
151. Shizgal P, Arvanitogiannis A. Gambling on dopamine. *Science* 2003; 299: 1856-1858.
152. Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM. It could be habit forming: drugs of abuse and striatal synaptic plasticity. *Trends Neurosci* 2003; 26: 184-192.
153. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 1991; 41: 1-24.
154. Cragg SJ. Meaningful silences: how dopamine listens to the Ach pause. *Trends Neurosci* 2006; 29: 125-131.
155. Buccafusco JJ, Letchworth SR, Bencherif M, Lippiello PM. Long-lasting cognitive improvement with nicotinic receptor agonists: mechanisms of pharmacokinetic-pharmacodynamic discordance. *Trends Pharmacol Sci* 2005; 26: 352-360
156. Rice ME, Cragg SJ. Nicotine amplifies reward-related dopamine signals in striatum. *Nature Neurosci* 2004; 7: 583-584.
157. Zhang H, Sulzer D. Frequency-dependent modulation of dopamine release by nicotine. *Nature Neurosci* 2004; 7: 581-582.
158. Yang G. Muscarinic receptors: a novel therapeutic target for drug addiction. *Trends Pharmacol Sci* 2002; 23: 551.
159. Grant SGN. AMPA receptor trafficking and GluR1. *Science* 2005; 310: 234-235; Malinow R, Rumpel S, Zador A, Ledoux J. Response. *Science* 2005; 310: 234.
160. Popescu G, Robert AQ, Howe JR, Auerbach A. Reaction mechanism determines NMDA receptor response to repetitive stimulation. *Nature* 2004; 430: 790-793.
161. Kenny PJ, Markou A. The ups and downs of addiction: role of metabotropic glutamate receptors. *Trends Pharmacol Sci* 2004; 25: 265-272.
162. Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, Auberson YP, Wang YT. Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. *Science* 2004; 304: 1021-1024.
163. Fremeau Jr RT, Kam K, Qureshi T, Johnson J, Copenhagen DR, Storm-Mathisen J, Chaundhry FA, Nicoll RA, Edwards RH. Vesicular glutamate transporters 1 and 2 target to functionally distinct synaptic release sites. *Science* 2004; 304: 1815-1819.
164. Carlezon Jr WA, Nestler EJ. Response: What role do GluR1 subunits play in drug abuse?. *Trends Neurosci* 2003; 26: 182-183.
165. Stephens DN, Mead AN. What role do GluR1 subunits play in drug abuse?. *Trends Neurosci* 2003; 26: 181-182.
166. Carlezon Jr WA, Nestler EJ. Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse?. *Trends Neurosci* 2002; 25: 610-615.
167. The Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson's disease. A randomized dose-ranging study. *J Am Med Ass* 1997; 278: 125-130.
168. Diamond SG, Markham CH, Treciokas LJ. Double-blind trial of pergolide for Parkinson's disease. *Neurology* 1985; 35: 291-295.

169. Shetty N, Friedman JH, Kieburtz K, Marshall FJ, Oakes D. The placebo response in Parkinson's disease Parkinson Study Group. *Clin Neuropharmacol* 1999; 22: 207-212.
170. Goetz CG, Leurgans S, Raman R, Stebbins GT. Objective changes in motor function during placebo treatment in PD. *Neurology* 2000; 54: 710-714.
171. Bezard B, Gross CE, Brotchie JM. Presymptomatic compensation in Parkinson's disease is not dopamine-mediated. *Trends Neurosci* 2003; 26: 215-221.
172. Taylor JP, Mata IF, Farrer MJ. LRRK2: a common pathway for parkinsonism, pathogenesis and prevention?. *Trends Mol Med* 2006; 12: 76-82.
173. Linazasoro G. New ideas on the origin of l-dopa-induced dyskinesias: age, genes and neural plasticity. *Trends Pharmacol Sci* 2005; 26: 391-397.
174. Mercuri NB, Bernardi G. The "magic" of l-dopa: why is it the gold standard Parkinson's disease therapy?. *Trends Pharmacol Sci* 2005; 26: 341-344.
175. Walton-Hadlock JL. Levodopa and the progression of Parkinson's disease. *N Eng J Med* 2005; 352: 1386; Fahn S, Kieburtz K, Tanner CM. The authors reply. *N Eng J Med* 2005; 352: 1386.
176. Press DZ. Parkinson's disease dementia. A first step?. *N Eng J Med* 2004; 351: 2547-2549.
177. The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Eng J Med* 2004; 351: 2498-2508.
178. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Askenazi Jews. *N Eng J Med* 2004; 351: 1972-1977.
179. Smith PD, O'Hare MJ, Park DS. CDKs: taking on a role as mediators of dopaminergic loss in Parkinson's disease. *Trends Mol Med* 2004; 10: 445-451.
180. Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nature Neurosci* 2004; 7: 726-735.
181. Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nature Neurosci* 2004; Advance online publication 16 May; doi:10.1038/nn1250.
182. Valente EM et al. Hereditary early-onset Parkinson's disease caused by mutations in *PINK1*. *Science express* 15 April 2004: 1-3.
183. Paolini M, Sapone A, Gonzales FJ. Parkinson's disease, pesticides and individual vulnerability. *Trends Pharmacol Sci* 2004; 25: 124-129.
184. Bonifatti V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MCJ, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, Oostra BA, Heutink P. Mutations in the *DJ-1* gene associated with autosomal recessive early-onset parkinsonism. *Science* 2003; 299: 256-259.
185. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998 ; 80: 1-27.
186. Garris PA, Kilpatrick M, Bunin MA, Michael D, Walker QD, Wightman RM. Dissociation of dopamine release in the nucleus accumbens from intracranial self-stimulation. *Nature* 1999; 398: 67-69.
187. Peir I, Ansoms C, Leheret P. The European NEAT program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol dependent patients with statistical modeling of therapy success prediction. *Alcohol Clin Exp Res* 2002; 26 : 1529-1538.
188. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache ID, Lawson K, Javors MA, Ma JZ. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *The Lancet* 2003; 361: 1677-1685.
189. Swift RM. Topiramate for the treatment of alcohol dependence: initiating abstinence. *The Lancet* 2003; 361: 1666-1667.

190. Marsden CA. In vivo voltammetry-present electrodes and methods. *Neuroscience* 1988; 25: 389-400.
191. Ungless MA, Magill PJ, Bolam JP. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 2004; 303: 2040-2042.
192. Rossini L, Bernardi M, Cavalieri L, Cintolesi F, Concettoni C, Fulgenzi G, Galeazzi G, Graciotti L, Jacussi M, Lamura E, Maurelli E, Moretti V, Moroni L, Pettinari F, Pignini P, Rossi C, Rossini P, Tonnini C, Violet CA, Violet G. Dinamiche dei cicli cellulari e dell'apoptosi: attuali riferimenti biomedici. In: *I tumori della mammella*, Le Monografie di Adria Medica, 1988: 32-56. .
193. Rossini L. Domini del tempo e di frequenza in fenomeni biomedici, I°. Lettere dalla Facoltà 1999; 2: (6)21-25, (9)23-26.
194. Rossini L, Bernardi M, Galeazzi G, Moroni L, Pettinari F, Pignini P, Rossini P, Tonnini C, Vagionis G, Violet C. Domini del tempo e di frequenza in fenomeni biomedici, II°. *Memorie Accademia Marchigiana Scienze, Lettere ed Arti* 2005; 38: 187-232.
195. Montague PR, Hyman SE, Cohen JD. Computational roles for dopamine in behavioural control. *Nature* 2004; 431: 760-767.
196. Pelli DG, Farell B, Moore DC. The remarkable inefficiency of word recognition. *Nature* 2003; 423: 752-756.
197. Geisler W, Murray R. Practice doesn't make perfect. *Nature* 2003; 423: 696-697.
198. Calabrese EJ, Baldwin LA. Applications of hormesis in toxicology, risk assessment and chemotherapeutics. *Trends Pharmacol Sci* 2002; 23: 331-337.
199. Calabrese EJ, Baldwin LA. Hormesis: U-shaped dose responses and their centrality in toxicology. *Trends Pharmacol Sci* 2001; 22: 285-291.
200. Koester HJ, Johnston D. Target cell-dependent normalization of transmitter release at neocortical synapses. *Science* 2005; 308: 863-866.
201. Bhattacharjee Y. A timely debate about the brain. *Science* 2006; 311: 596-598.
202. Irizarry KJL, Licinio J. An explanation for the placebo effect ?. *Science* 2005; 307: 1411-1412.
203. Tobler PN, Fiorillo CD, Schultz W. Adaptive coding of reward value by dopamine neurons. *Science* 2005; 307: 1642-1645.
204. Redish AD. Addiction as a computational process gone awry. *Science* 2004; 306: 1944-1947.
205. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism : relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacol* 2004; 29: 1943-1961.
206. Szabadics J, Varga C, Molnar G, Olan S, Barzó P, Tamás G. Excitatory effect of GABAergic axo-axonic cells in cortical microcircuits. *Science* 2006; 311: 233-235.
207. Cruz HG, Ivanova T, Lunn M-L, Stoffel M, Slesinger PA, Lüscher C. Bi-directional effects of GABA_B receptor agonists on the mesolimbic dopamine system. *Nature Neurosci* 2004; 7: 153-159.
208. Laviolette SR, Gallegos RA, Henriksen SJ, van der Kooy D. Opiate state controls bi-directional reward signalling via GABA_A receptors in the ventral tegmental area. *Nature Neurosci* 2004; 7: 160-169.
209. Olson VG, Heusner CL, Bland RJ, During MJ, Weinshenker D, Palmiter RD. Role of noradrenergic signaling by the nucleus tractus solitarius in mediate opiate reward. *Science* 2006; 311: 1017-1020.
210. Landis SC. Quick-change artist: from excitatory to inhibitory synapse in minutes, *Nature Neurosci* 2002; 5: 503-504.
211. Kalueff AV, Augustinovich DF, Kudryavtseva NN, Murphy DL. BDNF in anxiety and depression. *Science* 2006; 312: 1598; Berton O, Krishnan V, Nestler EJ. Response. *Science* 2006; 312: 1598-1599.

212. Scharfman HE, MacLusky NJ. Similarities between actions of estrogen and BDNF in the hippocampus: coincidence or clue?. *Trends Neurosci* 2005; 28: 79-85.
213. Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 2006; 311: 864-868.
214. Picciotto MR. Nicotine as a modulator of behavior: beyond the inverted U. *Trends Pharmacol Sci* 2003; 24: 493-499.
215. Coggan JS, Bartol TM, Esquenazi E, Stiles JR, Lamont S, Martone ME, Berg DK, Ellisman MH, Sejnowski TJ. Evidence for ectopic neurotransmission at a neuronal synapse. *Science* 2005; 309: 446-451.
216. Lučić V, Baumeister W. Monte Carlo places strong odds on ectopic release. *Science* 2005; 309: 387-388.
217. Cline H. Sperry and Hebb: oil and vinegar? *Trends Neurosci* 2003; 26: 655-661.
218. Marsicano G, Goodenough S, Monory K, Herman H, Eder M, Cannich A, Azad SC, Cascio MG, Gutierrez SO, van der Stelt M, Lopez-Rodriguez ML, Casanova E, Schütz G, Zieglgänsberger W, Di Marzo V, Behl C, Lutz B. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science* 2003; 302: 84-88.
219. Brown SP, Brenowitz SD, Regehr WG. Brief presynaptic bursts evoke synapse-specific retrograde inhibition mediated by endogenous cannabinoids. *Nature Neurosci* 2003; 6: 1048-1057.
220. Rossini L, Bernardi M. Cannabinoidi, vanilloidi e razionale farmacologico. *Lettere dalla Facoltà* 2001; 4: 15-20.
221. Robbins TW, Murphy ER. Behavioural pharmacology: 40+ years of progress, with a focus on glutamate receptors and cognition. *Trends Pharmacol Sci* 2006; 27: 141-148.
222. Samaha A-N, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction?. *Trends Pharmacol Sci* 2005; 26: 82-87.
223. Choi D-S, Cascini M-G, Maillard W, Young H, Paredes P, McMahon T, Diamond I, Bonci A, Messing RO. The type 1 equilibrative nucleoside transporter regulates ethanol intoxication and preference. *Nature Neurosci* 2004; 7: 855-861.
224. Ito R, Robbins TW, Everitt BJ. Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. *Nature Neurosci* 2004; 7: 389-397.
225. Bassareo V, De Luca MA, Aresu M, Aste A, Ariu T, Di Chiara G. Differential adaptive properties of accumbens shell dopamine responses to ethanol as a drug and as a motivational stimulus. *Eur J Neurosci* 2003; 17: 1465-1472.
226. Ito R, Dalley JW, Howes SR, Robbins TW, Everitt BJ. Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J Neurosci* 2000; 20: 7489-7495.
227. Jones DT. Learning to speak the language of proteins. *Science* 2003; 302: 1347-1348.
228. Armillotta G. La fisica e lo sconvolgimento di filosofia e storia. *L'Indipendente* 2006, July 9, p 2.
229. Di Fiorillo CD, Tobler PN, Schultz W. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 2003; 299: 1898-1902.
230. Shizgal P, Arvanitogiannis A. Gambling on dopamine. *Science* 2003; 299: 1856-1858.
231. Jones R. Gambling on dopamine. *Nature Review Neurosci* 2003; 4: 332.
232. Pulvirenti L, Massotti M. The neuroscience of drug addiction: Rome built in a day. *Trends Pharmacol Sci* 2002; 23 : 543-544.
233. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. *Science* 1997; 278: 52-58.
234. Gold JJ. Linking reward expectation to behavior in the basal ganglia. *Trends Neurosci* 2003; 26: 12-16.

235. Cabib S, Orsini C, Le Moal M, Piazza PV. Abolition and reversal of strain differences in behavioral responses to drugs of abuse after a brief experience. *Science* 2000; 289: 463-465.
236. Landisman CE, Connors BW. Long-term modulation of electrical synapses in the mammalian thalamus. *Science* 2005; 310: 1809-1813.
237. Hsu M, Bhatt M, Adolphs R, Tranel D, Camerer CF. Neural systems responding to degrees of uncertainty in human decision-making. *Science* 2005; 310: 1681-1683.
238. Rustichini A. Emotion and reason in making decisions. *Science* 2005; 310: 1624-1625.
239. Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, Mayhew JEW, Overton PG, Redgrave P. How visual stimuli activate dopaminergic neurons at short latency. *Science* 2005; 307: 1476-1479.
240. Brebner K, Wong TP, Liu L, Liu Y, Campsall P, Gray S, Phelps L, Phillips AG, Wang YT. Nucleus accumbens long-term depression and the expression of behavioural sensitization. *Science* 2005; 310: 1340-1343.
241. Shannon CE. A mathematical theory of Communication. *Bell Syst Tech J* 1948; 27: 379-423.
242. Rescorla RA, Wagner AR. In: *Classical Conditioning II: Current Research and Theory*, Black AH, Prokasy WS Eds, Appleton-Century-Crofts, 1972: 64-69.
243. Pearce JM, Hall GA. A model for pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psycholog Rev* 1980; 87: 532-552.
244. Koechlin E, Ody C, Kounehier F. The architecture of cognitive control in the human prefrontal cortex. *Science* 2003; 302: 1181-1185.
245. Berridge KC, Robinson TE. Parsing reward. *Trends Neurosci* 2003; 26: 507-513.
246. Berridge KC, Robinson TE. Erratum to: "parsing reward". *Trends Neurosci* 2003; 26: 581.
247. Montague PR, Dayan P, Seynowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *J Neurosci* 2006; 16, 1936-1947.
248. Crabbe JC, Phillis TJ, Buck KJ, Cunningham CL, Belknap JK. Identifying genes for alcohol and drug sensitivity: recent progress and future directions. *Trends Neurosci* 1999; 22: 173-179.
249. McGinty JF, Ed. Advancing from the ventral striatum to the extended amygdala. *Ann New York Acad Sci* 1999; 877: 1-832.
250. Bonci A, Bernardi G, Grillner P, Mercuri NB. The dopamine-containing neuron: maestro or simple musician in the orchestra of addiction? *Trends Pharmacol Sci* 2003; 24: 172-177.
251. Svenningsson P, Tzavara ET, Carruthers R, Rachleff I, Wattler S, Nehls M, McKinzie DL, Fienberg AA, Nomikos GG, Greengard P. Diverse psychotomimetics act through a common signalling pathway. *Science* 2003; 302: 1412-1415.
252. Matoba S, Kang J-G, Patino WD, Wragg A, Bohem M, Gavriloova O, Hurley PJ, Bunz F, Hwang PM. P53 regulates mitochondrial respiration. *Science* 2006; 312: 1650-1653.
253. Uno K, Katagiri H, Yamada T, Ishigaki Y, Ogihara T, Imai J, Hasegawa Y, Gao J, Kaneco K, Iwasaki H, Ishiara H, Sasano K, Inukai K, Mizuguchi H, Asano T, Shiota M, Nakazato M, Oka Y. Neuronal pathway from the liver modulates energy expenditure and systemic insulin sensitivity. *Science* 2006; 312: 1656-1659.
254. Boill e S, Yamanaka K, Lobsiger CS, Copeland NG, Jenkins NA, Kassiotis G, Kollias G, Cleveland DW. Onset and progression in inherited ALS determined by motor neurons and microglia. *Science* 2006; 312: 1389- 1392.
255. L eopold P, Layalle S. Linking nutrition and tissue growth. *Science* 2006; 312: 1317-1318.
256. Olsen A, Vantipalli MC, Lithgow GJ. Checkpoint proteins control survival of the postmitotic cells in *Caenorhabditis elegans*. *Science* 2003; 312: 1381-1385.
257. Conti F. Il cervello sconosciuto. *Darwin* 2006; 13: 62-63.
258. Balleine BW, Killcross S. Parallel incentive processing: an integrated view of amygdala function. *Trends Neurosci* 2006; 29: 272-279.

259. Weinstein LS, Chen M, Xie T, Liu J. Genetic diseases associated with heterotrimeric G proteins. *Trends Pharmacol Sci* 2006; 27: 260-266.
260. Silling RA, Venter H, Velamakanni S, Bapna A, Woebking B, Shai S, van Veen HW. New light on multidrug binding by an ATP-binding-cassette transporter. *Trends Pharmacol Sci* 2006; 27: 195-203.
261. Grubb Tesmer JJ. Hitting the hot spots of cell signaling cascades. *Science* 2006; 312: 377-378.
262. Raymond J, Segrè D. The effect of oxygen on biochemical networks and the evolution of complex life. *Science* 2006; 311: 1764-1767.
263. Bozzi Y, Borrelli E. Dopamine in neurotoxicity and neuroprotection: what do D₂ receptors have to do with it?. *Trends Neurosci* 2006; 29: 167-174.
264. Schoenbaum G, Roesch MR, Stalnaker TA. Orbitofrontal cortex, decision-making and drug addiction. *Trends Neurosci* 2006; 29: 116-124.
265. Carlsson A. Nerves as chemical messengers. *Science* 2005; 310: 1120-1121.
266. Pascual O, Casper KB, Kubera C, Zhang J, Revilla-Sanchez R, Sul J-Y, Takano H, Moss SJ, McCarthy K, Haydon PG. Astrocytic purinergic signaling coordinates synaptic networks. *Science* 2005; 310: 113-116.
267. Fetler L, Amigorena S. Brain under surveillance: the microglia patrol. *Science* 2005; 309: 392-393.
268. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* 2005; 308: 1314-1318.
269. Huber D, Veinante P, Stoop R. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science* 2005; 308: 245-248.
270. Perez DM, Karnik SS. Multiple signaling states of G-protein-coupled receptors. *Pharmacol Reviews* 2005; 57: 147-161.
271. Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* 2004; 306: 1940-1943.
272. Ungless MA. Dopamine: the salient issue. *Trends Neurosci* 2004; 27: 702-706.
273. Siekevitz P. Producing neuronal energy; Kasischke KA, Webb WW. Response: Siekevitz raises an interesting point. *Science* 2004; 306: 410-411.
274. Tanaka SC, Doya K, Okada G, Ueda K, Okamoto Y, Yamawaky S. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nature Neurosci* 2004; 7: 887-893.
275. Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion. *Science* 2004; 304: 878-880.
276. Purcell AL, Carew TJ. Tyrosine kinases, synaptic plasticity and memory: insights from vertebrates and invertebrates. *Trends Neurosci* 2003; 26: 625-630.
277. Cami J, Farrè M. Drug Addiction. *N Eng J Med* 2003; 349: 975-986.
278. Gold JJ. Linking reward expectation to behaviour in the basal ganglia. *Trends Neurosci* 2003; 26: 12-14.
279. Jacobs EH, Smit AB, De Vries T, Schoffelmeer ANM. Neuroadaptive effects of active versus passive drug administration in addiction research. *Trends Pharmacol Sci* 2003; 24: 566-573.
280. Krekelberg B, Boynton GM, van Wezel RJA. Adaptation: from single cells to BOLD signals. *Trends Neurosci* 2006; 29: 250-256.
281. Walker MJA, Soh MLM. Challenges facing pharmacology – the *in vivo* situation. *Trends Pharmacol Sci* 2006; 27: 125-126.
282. Gresham D, Ruderfer DM, Pratt SC, Schacherer J, Dunham MJ, Botstein D, Kruglyak L. Genome wide detection of polymorphisms at nucleotide resolution with a single DNA microarray. *Science* 2006; 311: 1932-1936.

283. Yu J, Xiao J, Ren X, Loa K, Xie XS. Probing gene expression in live cells, one protein molecule at time. *Science* 2006; 311: 1600-1603.
284. Thorpe MJ, Moll KD, Jones RJ, Safdi B, Ye J. Broadband cavity ringdown spectroscopy for sensitive and rapid molecular detection. *Science* 2006; 311: 1595-1599.
285. Wightman RM. Probing cellular chemistry in biological system with microelectrodes. *Science* 2006; 311: 1570-1574.
286. Cooks RG, Ouyang Z, Takats Z, Wiseman JM. Ambient mass spectrometry. *Science* 2006; 311: 1566-1570.
287. Bosh X. Linking neurons and ethics. *Science* 2006; 311: 339.
288. Enriquez J. Deconstructing biotechnology. *Science* 2005; 309: 384.
289. Ioannidis JPA. Microarrays and molecular research: noise discovery? *The Lancet* 2005; 365: 454-455.
290. Lipton P. Testing hypotheses: prediction and prejudice. *Science* 2005; 307: 219-221.
291. Scher S. Was Watson and Crick's model truly self-evident?. *Nature* 2004; 427: 584.
292. Ozbay E. Plasmonics: merging photonics and electronics at nanoscale dimension. *Science* 2006; 311: 189-193.
293. Perlman ZE, Slack MD, Feng Y, Mitchison TJ, Wu LF, Altshuler SJ. Multidimensional drug profiling by automated microscopy. *Science* 2004; 306: 1194-1198.
294. Salwinski L, Eisenberg D. In silico simulation of biological network dynamics. *Nature Biotech* 2004; 22: 1017-1019.
295. Takats Z, Wiseman JM, Gologan B, Cooks RG. Mass spectrometry sampling under ambient conditions with desorption electrospray ionization. *Science* 2004; 306: 471-473.
296. Pilcher H. MRI machine tracks brain's metabolism. [News@nature.com](http://www.nature.com/news@nature.com) 21 September 2004/040920-4.
297. Donaldson DI. Parsing brain activity with fMRI and mixed designs: what kind of a state is neuroimaging in?. *Trends Neurosci* 2004; 27: 442-444.
298. Yang H, Luo G, Karnchanaphanurach P, Louie TM, Rech I, Cova S, Xun L, Xie XS. Protein conformational dynamics probed by single-molecule electron transfer. *Science* 2003; 302: 262-266.
299. Orrit M. The motions of an enzyme soloist. *Science* 2003; 302: 239-240.
300. Van Oijen AM, Blainey PC, Crampton DJ, Richardson CC, Ellenberger T, Xie XS. Single-molecule kinetics of λ exonuclease reveal base dependence and dynamic disorder. *Science* 2003; 301: 1235-1238.
301. Tiang P, Keusters D, Suzaki Y, Warren SW. Femtosecond phase-coherent two-dimensional spectroscopy. *Science* 2003; 300: 1553-1555.
302. Jonas DM. Optical analogs of 2D NMR. *Science* 2003; 300: 1515-1517.
303. Larson DR, Zipfel WR, Williams RM, Clark SW, Bruchez MP, Wise FW, Webb WW. Water-soluble quantum dots for multiphoton fluorescence imaging in vivo. *Science* 2003; 300: 1434-1436.
304. Stephens DJ, Allan VJ. Light microscopy techniques for live cell imaging. *Science* 2003; 300: 82-86.
305. Lippincott-Schwartz J, Patterson GH. Development and use of fluorescent protein markers in living cells. *Science* 2003; 300: 87-91.
306. Grant F. Recognising the future. *Scientific Computing World* 2006; 88: 14-19.
307. Buhl J, Sumpter DJT, Couzin ID, Hale JJ, Despland E, Miller ER, Simpson SJ. From disorder to order in marching locusts. *Science* 2006; 312: 1402-1406.
308. Aradi I, Erdi P. Computational neuropharmacology: dynamical approaches in drug discovery. *Trends Pharmacol Sci* 2006; 27: 240-243.
309. Sachs K, Perez O, Pe'er D, Lauffenburger DA, Nolan GP. Causal protein-signaling networks derived from multiparameter single-cell data. *Science* 2005; 308: 523-529.

310. Knill DC, Pouget A. The Bayesian brain: the role of uncertainty in neural coding and computation. *Trends Neurosci* 2004; 27: 712-719.
311. Eddy SR. What is hidden Markov model? *Nature Biotech* 2004; 22: 1315-1316.
312. Eddy SR. What is Bayesian statistics?. *Nature Biotech* 2004; 22: 1177-1178.
313. Körding KP, Wolpert DM. Bayesian integration in sensorimotor learning. *Nature* 2004; 427: 244-247.
314. Qin ZS, McCue LA, Thompson W, Mayerhofer L, Lawrence CE, Liu JS. Identification of co-regulated genes through Bayesian clustering of predicted regulatory binding sites. *Nature* 2003; 21: 435-439.
315. Orlitsky A, Santhanam NP, Zhang J. Always good Turing: asymptotically optimal probability estimation. *Science* 2003; 302: 427-431.
316. Jansen R, Yu H, Greenbaum D, Kluger Y, Krogan NJ, Chung S, Emili A, Snyder M, Greenblatt JF, Gerstein M. A Bayesian networks approach for predicting protein-protein interaction from genomic data. *Science* 2003; 302: 449-453.
317. Swedlow JR, Goldberg I, Brauner E, Sorger PK. Informatics and quantitative analysis in biological imaging. *Science* 2003; 300: 100-102.
318. Shermer M. The demon of determinism. *Science* 2003; 300: 56-57.
319. Bruno RM, Sakmann B. Cortex is driven by weak but synchronously active thalamocortical synapses. *Science* 2006; 312: 1622-1627.
320. Alonso JM. Neurons find strength through synchrony in the brain. *Science* 2006; 312: 1604-1605.
321. Brown CH, Bourque CW. Mechanism of rhythmogenesis: insights from hypothalamic vasopressin neurons. *Trends Neurosci* 2006; 29: 66-67.
322. Gilbert PFC. Response to Kitazawa and Wolpert: rhythmicity, randomness and synchrony in climbing fiber signals. *Trends Neurosci* 2006; 29: 66-67; Kitazawa S, Wolpert DM. Rhythmicity, randomness and synchrony in climbing fiber signals. *Trends Neurosci* 2005; 28: 611-619.
323. Yin L, Wang J, Klein PS, Lazar MA. Nuclear receptors rev-erba is a critical lithium-sensitive component of the circadian clock. *Science* 2006; 311: 1002-1003.
324. Maret S, Franken P, Dauvilliers Y, Ghyselink NB, Chambon P, Tafti M. Retinoic acid signaling affects cortical synchrony during sleep. *Science* 2005; 310: 111-113.
325. Kussell E, Leibler S. Phenotypic diversity, population growth, and information in fluctuating environments. *Science* 2005; 309: 2075-2078.
326. Werner S, Barken D, Hoffmann A. Stimulus specificity of gene expression programs determined by temporal control of IKK activity. *Science* 2005; 309: 1857-1861.
327. Covert MW, Leung TH, Gaston JE, Baltimore D. Achieving stability of lipopolysaccharide-induced NF- κ B activation. *Science* 2005; 309: 1854-1857.
328. Cardone L, Hirayama J, Giordano F, Tamaru T, Palvimo JJ, Sassone-Corsi P. Circadian clock control by SUMOylation of BMAL1. *Science* 2005; 309: 1390-1394.
329. Baldini G, Cannone F, Chirico G. Pre-unfolding resonant oscillations of single green fluorescent protein molecules. *Science* 2005; 309: 1096-1100.
330. Gillette MU, Sejnowski TJ. Biological clocks co-ordinately keep life on time. *Science* 2005; 309: 1196-1198.
331. Niessing J, Ebish B, Schmidt KE, Niessing M, Singer W, Galuske RAW. Hemodynamic signals correlate tightly with synchronized gamma oscillation. *Science* 2005; 309: 948-951.
332. Yamamoto Y, Verma UN, Prajapati S, Kwak YT, Gaynor RB. Histone H3 phosphorylation by IKK- α is critical for cytokine-induced gene expression. *Nature* 2003; 423: 655-659.
333. Israël A. A regulator branches out. *Nature* 2003; 423: 596-597.
334. Anest V, Hanson JL, Cogswell PC, Steinbrecher KA, Strahl BD, Baldwin AS. A nucleosomal function for I κ B kinase- α in NF- κ B-dependent gene expression. *Nature* 2003; 423: 659-663.

335. Brown SA, Ripperger J, Kadener S, Fleury-Olela F, Vilbois F, Rosbash M, Schibler U. PERIOD1-associated proteins modulate the negative limb of the mammalian circadian oscillator. *Science* 2005; 308: 693-696.
336. Schoffelen JM, Oostenveld R, Fries P. Neuronal coherence as a mechanism of effective corticospinal interaction. *Science* 2005; 308: 111-113.
337. Van Oers NSC, Chen ZJ. Kinasing and clipping down the NF- κ B trail. *Science* 2005; 308: 65-66.
338. Rosenfeld N, Jonathan WY, Alon U, Swain PS, Elowitz MB. Gene regulation at the single cell level. *Science* 2005; 307: 1962-1965.
339. Isaacs FJ, Blake WJ, Collins JJ. Signal processing in single cells. *Science* 2005; 307: 1886-1888.
340. Winslow MM, Crabtree GR. Decoding calcium signaling. *Science* 2005; 307: 56-57.
341. Olesen C, Lykke-Møller Sørensen TL, Nielsen RC, Møller JV, Nissen P. Dephosphorylation of the calcium pump coupled to counterion occlusion. *Science* 2004; 306: 2251-2255.
342. Barken D, Wang CJ, Kearns J, Cheong R, Hoffmann A, Levchenko A. Comment on "Oscillations in NF- κ B signaling control the dynamic of gene expression"; Nelson DE, Horton CA, See V, Johnson JR, Nelson G, Spiller DG, Kell DB, White MRH. Response to "Oscillations in NF- κ B signaling control the dynamic of gene expression". *Science* 2005; 308: 52; Nelson DE, Ihekweaba AEC, Elliott M, Johnson JR, Gibney CA, Foreman BE, Nelson G, See V, Horton CA, Spiller DG, Edwards SW, McDowell HP, Unitt JF, Sullivan E, Grimley R, Benson N, Broomhead D, Kell DB, White MRH. Oscillations in NF- κ B signaling control the dynamics of gene expression. *Science* 2004; 306: 704-707.
343. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, Teng KK, Yung W-H, Hempstead BL, Lu B. Cleavage of proBDNF by tPA/plasmin is essential for long term hippocampal plasticity. *Science* 2004; 306: 487-491.
344. Buzsàki G, Draguhn A. Neuronal oscillations in cortical networks. *Science* 2004; 304: 1926-1929.
345. Gwinner E. Life's daily beat. *Science* 2004; 304: 1906-1907.
346. Magee JC. A prominent role for intrinsic neuronal properties in temporal coding. *Trends Neurosci* 2003; 26: 14-16.
347. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?. *Brain Res Rev* 1998; 28: 309-369.
348. McClure SM, Daw ND, Montague PR. A computational substrate for incentive salience. *Trends Neurosci* 2003; 26: 423-428.
349. Pandey SC. Anxiety and alcohol abuse disorders: a common role for CREB and its target, the neuropeptide Y gene. *Trends Pharmacol Sci* 2003; 24: 456-460.
350. Ernfors P, Bramham CR. The coupling of a trkB tyrosine residue to LTP. *Trends Neurosci* 2003; 26: 171-173.
351. Ge W-P, Yang X-J, Zhang Z, Wang H-K, Shen W, Deng Q-D, Duan S. Long-term potentiation of neuron-glia synapses mediated by Ca²⁺-permeable AMPA receptors. *Science* 2006; 312: 1533-1537.
352. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms?. *Trends Neurosci* 2003; 26: 696-705.
353. Zhou O, Tao HW, Poo M. Reversal and stabilization of synaptic modifications in a developing visual system. *Science* 2003; 300: 1953-1957.
354. Arshavsky YI. Long-term memory: does it have a structural or chemical basis?. *Trends Neurosci* 2003; 26: 465-468.
355. Nader K. Response to Arshavsky: Challenging the old views. *Trends Neurosci* 2003; 26: 466-468.

356. Dinse HR, Ragert P, Pleger B, Schwenkreis P, Tegenthoff M. Pharmacological modulation of perceptual learning and associated cortical reorganization. *Science* 2003; 301: 91-94.
357. Kerns JG, Cohen JD, MacDonald III AW, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science* 2004; 303: 1023-1026.
358. Anders S, Birbaumer N, Sadowski B, Erb M, Mader I, Grodd W, Lotze M. Parietal somatosensory association cortex mediates affective blindsight. *Nature Neurosci* 2004; 7: 339-340.
359. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science* 2004; 303: 1157-1162.
360. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen J. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004; 303: 1162-1167.
361. Lau HC, Rogers RD, Haggard P, Passingham RE. Attention to intention. *Science* 2004; 303: 1208-1210.
362. Baars BJ, Ramsøty TZ, Laureys S. Brain, conscious experience and the observing self. *Trends Neurosci* 2003; 26: 671-675.
363. Critchley HD, Wiens S, Rotschtein P, Öhman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nature Neurosci* 2004; 7: 189-195.
364. Li RW, Levi DM, Klein SA. Perceptual learning improves efficiency by re-tuning the decision 'template' for position discrimination. *Nature Neurosci* 2004; 7: 178-183.
365. Connolly JD, Goodale MA, Menon RS, Munoz DP. Human fMRI evidence for the neural correlates of preparatory set. *Nature Neurosci* 2002; 5: 1345-1352.
366. Otten LJ, Henson RNA, Rugg MD. State-related and item-related neural correlates of successful memory encoding. *Nature Neurosci* 2002; 5: 1339-1344.
367. Coull JT, Vidal F, Nazarian B, Macar F. Functional anatomy of the attentional modulation of time estimation. *Science* 2004; 303: 1506-1508.
368. Ugurbil K, Toth L, Kim D-S. How accurate is magnetic resonance imaging of brain function?. *Trends Neurosci* 2003; 26: 108-113.
369. Giot L, Bader JS, Brouwer C, Chaundhuri A, Kuang B, Li Y, Hao YL, Ooi CE, Godwin B, Vitols E, Vijayadamodar G, Pochart P, Machinemi H, Welsh M, Kong Y, Zerhusen B, Malcolm R, Varrone Z, Collis A, Minto M, Burgess S, McDaniel L, Stimpson E, Spriggs F, Williams J, Neurath K, Ioime N, Agee M, Voss E, Furtak K, Renzulli R, Aanensen N, Carrola S, Bickelhaupt E, Lazovatsky Y, DaSilva A, Zhong J, Stanyon CA, Finley jr RL, White KP, Braverman M, Jarvie T, Gold S, Leach M, Knight J, Shimkets RA, McKenna MP, Chant J, Rothberg JM. A protein interaction map of *Drosophila melanogaster*. *Science* 2003; 302: 1727-1736.
370. Pennisi E. Tracing life's circuitry. *Science* 2003; 302: 1646-1648.
371. Rossini L, Bernardi M, Conchettoni C, De Florio L, Deslauriers R, Moretti V, Piantelli F, Pigini P, Re L, Rossini P, Tonnini C. Some approaches to the pharmacology of multisubstrate enzyme systems. *Pharmacol Res* 1994; 29: 313-334.
372. Cingolani ML, Re L, Rossini L. The usefulness, in pharmacological classification, of complementary pattern-recognition techniques and structure modelling as afforded by the iterative collation of multiple-trial data in data banks. *Pharmacol Res Commun* 1985; 17: 1-22.
373. Festing MFW. Principles: The need for better experimental design. *Trends Pharmacol Sci* 2003; 24: 341-345.
374. Whittaker PA. What is the relevance of bioinformatics to pharmacology. *Trends Pharmacol Sci* 2003; 24: 434-439.

375. Gurwitz D, Weizman A, Rehavi M. Education: Teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. *Trends Pharmacol Sci* 2003; 24: 122-125.
376. Porter R. *The greatest benefit to mankind*. Harper Collins, London, 1998.
377. Le Fanu J, *The rise & fall of modern medicine, 1999: Ascesa e declino della medicina moderna*. Transizioni 18, Vita e Pensiero, Milano, 2005 : 1-510.
378. Tomlin D, Kayali MA, King-Casas B, Anen C, Camerer CF, Quartz SR, Montague PR. Agent-specific responses in the cingulate cortex during economic exchanges. *Science* 2006; 312: 1047-1050.
379. Mulcahy NJ, Call J. Apes save tools for future use. *Science* 2006; 312: 1038-1040.
380. Padoa-Schioppa C, Assad JA. Neurons in the orbitofrontal cortex encode economic value. *Nature* 2006; 441: 223-226.
381. Berns GS, Chappelow J, Cekic M, Zink CF, Pagnoni G, Martin-Skurski ME. Neurobiological substrates of dread. *Science* 2006; 312: 754-758.
382. Pompilio L, Kacelnik A, Behmer ST. State-dependent learned valuation drives choice in an invertebrate. *Science* 2006; 311: 1613-1615.
383. Shuler MG, Bear MF. Reward timing in the primary visual cortex. *Science* 2006; 311: 1606-1609.
384. Blaisdell AP, Sawa K, Leising KJ, Waldmann MR. Causal reasoning in rats. *Science* 2006; 311: 1020-1022.
385. Dijksterhuis A, Bos MW, Nordgren LF, van Baaren RB. On making the right choice: the deliberation without attention effects. *Science* 2006; 311: 1005-1007.
386. Chamberlain SR, Müller U, Blackwell AD, Clark K, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 2006; 311: 861-863.
387. Salganik MJ, Dodds PS, Watts NJ. Experimental study of inequality and unpredictability in an artificial cultural market. *Science* 2006; 311: 854-856.
388. Tsao DY, Freiwald WA, Tootell RBH, Livingstone MS. A cortical region consisting entirely of face-selective cells. *Science* 2006; 311: 670-674.
389. Krakauer JW, Shadmehr R. Consolidation of motor memory. *Trends Neurosci* 2006; 29: 58-64.
390. Williams ZM, Bush G, Rauch SL, Cosgrove GR, Eskander EN. Erratum: human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nature Neurosci* 2005; 8: 121.
391. Polyn SM, Natu VS, Cohen JD, Norman KA. Category-specific cortical activity precedes retrieval during memory search. *Science* 2005; 310: 1963-1966.
392. Samejima K, Ueda Y, Doya K, Kimura M. Representation of action-specific reward values in the striatum. *Science* 2005; 310: 1337-1340.
393. Millar JK, Pickard BS, Mackie S, James R, Christie S, Buchanan SR, Malloy MP, Chubb JE, Huston E, Baillie GS, Thomson PA, Hill EV, Brandon NJ, Rain J-C, Camargo LM, Whiting PJ, Houslay MD, Blackwood DHR, Muir WJ, Porteous DJ. DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. *Science* 2005; 310: 1187-1191.
394. Sawa A, Snyder SH. Two genes link two distinct psychoses. *Science* 2005; 310: 1128-1129.
395. Hung CP, Kreiman G, Poggio T, DiCarlo JJ. Fast readout of object identity from macaque inferior temporal cortex. *Science* 2005; 310: 863-866.
396. Nussey DH, Postma E, Gienapp P, Visser ME. Selection of heritable phenotypic plasticity in a wild bird population. *Science* 2005; 310: 304-306.
397. Johansson P, Hall L, Sikström S, Olsson A. Failure to detect mismatches between intention and outcome in a simple decision task. *Science* 2005; 310: 116-119.

398. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. *Science* 2005; 309: 2228-2232.
399. De Schotten MT, Urbansky M, Duffau H, Volle E, Lévy R, Dubois B, Bartolomeo P. Direct evidence for parietal frontal pathway subserving spatial awareness in humans. *Science* 2005; 309: 2226-2228.
400. Gaffan D. Widespread cortical networks underlie memory and attention. *Science* 2005; 309: 2172-2173.
401. Miller G. Mutant mice reveal secrets of the brain's impressionable youth. *Science* 2005; 309: 2145.
402. Olsson A, Ebert JP, Banaji MR, Phelps EA. The role of social groups in the persistence of learned fear. *Science* 2005; 309: 785-787.
403. Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser M-B. Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* 2005; 309: 619-623.
404. Buzsáki G. Similar is different in hippocampal networks. *Science* 2005; 309: 568-569.
405. Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, Castiglioni I, Valler G, Paulesu E. Shared cortical anatomy for motor awareness and motor control. *Science* 2005; 309: 488-491.
406. Guo J, Guo A. Crossmodal interactions between olfactory and visual learning in *Drosophila*. *Science* 2005; 309: 307-310.
407. Miller G. What is the biological basis of consciousness?. *Science* 2005; 309: 79.
408. Minamimoto T, Hori Y, Kimura M. Complementary process to response bias in the centromedian nucleus of the thalamus. *Science* 2005; 308: 1798-1801.
409. Hammock EAD, Young LJ. Microsatellite instability generates diversity in brain and sociobehavioral traits. *Science* 2005; 308: 1630-1634.
410. Eagleman DM. Comment on "The involvement of the orbitofrontal cortex in the experience of regret"; Coricelli G, Camille N, Pradat-Diehl P, Duhamel J-R, Sirigu A. Response to comment on "The involvement of the orbitofrontal cortex in the experience of regret". *Science* 2005; 308: 1260.
411. Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J. Attractor dynamics in the hippocampal representation of the local environment. *Science* 2005; 308: 873-876.
412. Sack AT, Camprodon JA, Pascual-Leone A, Goebel R. The dynamics of interhemispheric compensatory processes in mental imagery. *Science* 2005; 308: 702-704.
413. Guimerà R, Uzzi B, Spiro J, Amaral LAN. Team assembly mechanism determine collaboration network structure and team performance. *Science* 2005; 308: 697-702.
414. King-Casas B, Tomlin D, Anen C, Camerer CF, Quartz SR, Montague PR. Getting to know you: reputation and trust in a two person economic exchange. *Science* 2005; 308: 78-83.
415. Jensen O, Lisman JE. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends Neurosci* 2005; 28: 69-71.
416. Abraham WC, Robins A. Memory retention – the synaptic stability versus plasticity dilemma. *Trends Neurosci* 2005; 28: 73-78.
417. Brown JW, Braver TS. Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 2005; 307: 1118-1121.
418. Ridderinkhof KR, van den Wildenberg WPM. Adaptive coding. *Science* 2005; 307: 1059-1060.
419. Emery NJ, Clayton NS. The mentality of crows: convergent evolution of intelligence in corvids and apes. *Science* 2004; 306: 1903-1907.
420. Miyashita Y. Cognitive memory: cellular and network machineries and their top-down control. *Science* 2004; 306: 435-440.
421. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science* 2004; 306: 443-447.

422. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural system value immediate and delayed monetary rewards. *Science* 2004; 306: 503-507.
423. Ainslie G, Monterosso J. A marketplace in the brain?. *Science* 2004; 306: 421-423.
424. Gordon P. Numerical cognition without words: evidence from Amazonia. *Science* 2004; 496-499.
425. Ehrsson HH, Spence C, Passingham RE. That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science* 2004; 305: 875-877.
426. Maviel T, Durkin TP, Menzaghi F, Bontempi B. Sites of neocortical reorganization critical for remote spatial memory. *Science* 2004; 305: 96-99.
427. Krupa DJ, Wiest MC, Shuler MG, Laubach M, Nicolelis MAL. Layer-specific somatosensory cortical activation during active tactile discrimination. *Science* 2004; 304: 1989-1992.
428. Sugrue LP, Corrado GS, Newsome WT. Matching behavior and the representation of value in the parietal cortex. *Science* 2004; 304: 1782-1787.
429. Seymour B, O'Doerthy JP, Dayan P, Koltzenburg M, Jones AK, Dolan RJ, Friston KJ, Frackowiak RS. Temporal difference models describe higher-order learning in humans. *Nature* 2004; 429: 664-667.
430. Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ. The involvement of the anterior cortex in remote contextual rear memory. *Science* 2004; 304: 881-883.
431. Lee JLC, Everitt BJ, Thomas KL. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* 2004; 304: 839-843.
432. Alberini CM. Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci* 2005; 28: 51-56.
433. Roesch MR, Olson CR. Neuronal Activity related to reward value and motivation in primate frontal cortex. *Science* 2004; 304: 307-310.
434. Poggio T, Rifkin R, Mukherjee S, Niyogi P. General conditions for predictivity in learning theory. *Nature* 2004; 428: 419-422.
435. Coull JT, Vidal F, Nazarian B, Macar F. Functional anatomy of the attentional modulation of time estimation. *Science* 2004; 303: 1506-1508.
436. Eagleman DM. The where and when of intention. *Science* 2004; 303: 1144-1146.
437. Matsumoto K, Tanaka K. Conflict and cognitive control. *Science* 2004; 303: 969-970.
438. Holden C. The practical benefits of general intelligence. *Science* 2003; 299: 192-193.
439. Dohlmans HG. Diminishing returns. *Nature* 2002; 418: 591.
440. Goldman D, Barr CS. Restoring the addicted brain. *N Eng J Med* 2002; 347: 843-844.
441. Shidara M, Richmond BJ. Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 2002; 296: 1709-1711.
442. Peoples LL. Will, anterior cingulate cortex, and addiction. *Science* 2002; 296: 1623-1624.
443. Brembs B, Lorenzetti FD, Reyes FD, Baxter DA, Byrne JH. Operant reward learning in *Aplysia*: neuronal correlates and mechanisms. *Science* 2002; 296: 1706-1709.
444. Rankin CH. A bite to remember. *Science* 2002; 296: 1624-1625.
445. WHO. *The safety of medicines in public health programmes: pharmacovigilance an essential tool*. World health organization - The Uppsala monitoring centre, May 16, 2006 : 1-60.
446. Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, Fireman B, Newhouse JP, Selby JV. Unintended consequences of caps on medicare drug benefits. *New Eng J Med* 2006; 354: 2349-2359.
447. Bach PB, McClellan. The first months of the prescription-drug benefit – A CMS update. *N Eng J Med* 2006; 354: 2312-2314; Slaughter LM. Medicare part D – The product of a broken process. *N Eng J Med* 2006; 354: 2314-2315.
448. Rodham Clinton H, Obama B. Making patient safety the centerpiece of medical liability reform. *N Eng J Med* 2006; 354: 2205-2208.

449. Mehran R, Leon MB, Feigal DA, Jefferys D, Simons M, Chronos N, Fogarty TJ, Kunz RE, Baim DS, Kaplan AV. Mini-Review : Expert opinions. Post-market approval surveillance. A call for a more integrated and comprehensive approach. *Circulation* 2004; 109: 3073-3077.
450. Colquhoun D. The quantitative analysis of drug-receptor interactions: a short history. *Trends Pharmacol Sci* 2006; 27: 149-157.
451. Barrera NP, Morales B, Torres S, Villalon M. Principles: mechanisms and modelling of synergism in cellular responses. *Trends Pharmacol Sci* 2005; 26: 526-532.
452. Alvan G, Paintaud G, Wakelkamp M. The efficiency concept in pharmacodynamics. *Clin Pharmacokinet* 1999; 36: 375-389.
453. Rossini L. Per una ricerca di messa a punto di un programma statistico-modellistico per il rilevamento dei consumi e la valutazione dei benefici e risorse di alcuni gruppi di farmaci, utilizzando i dati della banca dati O.M.S. di Uppsala. *Convenzione MINSAN - Centro Studi* 13.1'89. Handed over September 1, 1991 : 1-309.