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

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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 Intermitencias da Morte, 2005.

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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]. Pathophysio-logical 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 Ca^{2+} channel closure takes place at higher DA concentrations (~1 μM). Phasic activity involves the inhibitory, depressive mediation of D_2 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-patho-physiological 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 neurotropic factor (BDNF) and its receptor trKB activate CREB via Cγ-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.

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