The problems of inattention: methods and interpretations
(Editorial)

R.D. Oades1, G. Sartory2

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1. Introduction

This volume brings together the work from a group of laboratories who have in common a psychobiological approach to one particular paradigm in the study of the mechanisms of associative learning, namely ‘learned inattention’. The paradigm aims by detailed trial by trial analysis and the use of very specific stimulus exposure conditions to elucidate the mechanisms by which a given CS–US association can be acquired, maintained and changed. These investigations are attempted (although not always successfully) in the rarefied air where state and motivation, usually so important in day-to-day learning, are controlled. Thus, with this paradigm, one is seeking a description purely in terms of information processing, a cognitive strategy.

Of necessity this process must be applying selective mechanisms; hence the use of the term selective attention; but this descriptive use of the term is, at the outset, without many of the usual implicit assumptions, such as whether the processing is effortful and controlled or automated. But the primary question that concerned those who gathered at the European Neuroscience Forum in September 1996 in Strasbourg was the nature of the underlying biological substrate that mediates these mechanisms, in terms of the contributions of defined regions of the brain and the neurotransmitters used.

The primary contrast between participants were the two major types of approach, the comparative study of the neurobiology in animals and the clinical study of various human psychopathologies to see how differences in physiology and cognitive style map on to expectations deriving from the animal model. In animal work we saw a concentration of study on the dopaminergic and serotonergic modulation, in particular in terms of the types of terminal receptor involved. Nicotinic and noradrenergic influences received brief mention, but, the amino-acid transmitters undoubtedly involved in bringing information to the nodes where it is registered and compared were not examined here. Interest in the mediating structures the ‘nodes’ concentrated on the hippocampal complex (in its broadest sense) and the mesolimbic nucleus accumbens septi in particular, though reference will be found to contributions from tertiary and primary neocortices. The clinical contributors provided data from a rich assortment of conditions including schizophrenia, obsessive compulsive disorder, Parkinsonism, attention-deficit hyper-activity disorder and Tourette’s syndrome. All of these reflected the influences of various permutations and combinations of monoaminergic abnormalities one would expect from the animal models.

2. The tasks: an historical perspective

Attention, ‘the selective aspect of perception’ [53], is the mechanism, the pre-requisite for adaptive response, and part and parcel of the process of learning. Selection of perceived information for further analysis (the attentional mechanism) is achieved by the
allocation of appropriate channels and resources for analysis and registration. The costs and benefits of attention vs. inattention, a particular strategy of information selection, are biologically adaptive for further cognitive function. They provide the basis for invoking, then maintaining or shifting attention that is at the centre of study here.

The method used here for studying the control of attention: inattention involves the precise measure of the progress of learning. The element in common between the tasks used in the study of learned inattention is the speed with which an organism will acquire a new UCS-CS connection under the influence of a previous such connection. The specifications of this previous connection are defined within each task form. In latent inhibition (LI)\(^1\), the two ‘zero’ conditions for a new CS connection are compared: the ‘to-be-CS’ that has not been followed by any consequences over a number of trials is compared with one that has not had the chance to become associated with anything. In conditioned (Kamin) blocking (CB) the competition of two CSs for a given association is recorded: the comparison is between one condition where the elements are contiguous in time with one where the ‘blocking stimulus’ has received experiential priority for the exposure that allows conditioning. In the non-reversal-shift (NR) the degree of relationship of the new association to the old one is compared with a condition where a complete break with the previous association is required, as in a reversal (i.e. a change within and between stimulus dimensions is presented). Historically each task had its separate origins, each designed for its specific purpose (e.g. LI [25]; CB [17]; NR [19]) before various learning theorists described the potential communalities [26, 44].

Paradigms of inattention were of great interest to learning theorists because they demonstrated that it was not only temporal or spatial contiguity that were influential for associative learning about two stimuli but also previous experience. A number of models were advanced to account for the effects of ‘learned inattention’. One group of such models proposed, (i) that the CS was differentially processed according to previous experience [26], another (ii) that the changing effectiveness of the US accounted for learned inattention [54] and finally, (iii) that contextual cues acted as an occasion setter during the original learning thereby preventing learning of new stimulus contingencies [43].

(i) Attentional and stimulus processes were introduced as an explanatory concept at an early stage. CB, for example, was thought to be the result of poor processing of the new stimulus element because the previously conditioned stimulus was preferentially attended [50]. Thus, given limited attentional capacity and competition between stimuli for the organism’s attention, the previously conditioned stimulus dominates attention leaving little processing capacity for the additional stimulus. Mackintosh [26] specified this position further by arguing that the previously conditioned stimulus derived its salience from having become the predictor of important consequences, such as the US. An additional CS element will be initially attended to on account of its novelty but consequently ignored as it does not add to the predictability of the US.

(ii) Kamin [17] originally suggested that CB was due to the diminishing effectiveness of the US after having been associated with a CS. A new and unexpected CS is more powerful than a well-signalled one; but through the

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\(^1\) Definitions: LI (latent inhibition), non-contingent repeated presentations of a stimulus retard the subsequent association of that stimulus with a consequence [25]; CB (conditioned blocking), the amount of conditioning accruing to one element of a compound conditioned stimulus is affected [blocked] by the subject’s prior experience with the other element [17]; NR (non-reversal shift), a previously irrelevant stimulus present in a discrimination task is shifted [within or between stimulus dimensions] to become the sole relevant predictor of reinforcement [19,27]; PPI (prepulse inhibition), if a weak stimulus [prepulse] occurs immediately prior to a ‘significant’ stimulus, then the amplitude of the response [startle] to the salient [relevant] stimulus alone is reduced [12]; MMN (mismatch negativity), is the frontal negativity occurring about 150–250 ms after an event derived by subtracting the potential elicited by a standard from that elicited by a deviant stimulus [32,34].
association of stimulus elements the association with the new CS element can no longer be learned. Pearce and Hall [41] attempted to reconcile the two positions by arguing that the ‘conditionability’ of CSs depends on their being followed by surprising consequences which will elicit an attentional response. The additional CS element in the CB experiment cannot be conditioned because, being predicted by the initial CS element, the US has lost its power to surprise.

(iii) Wagner [54] proposed that contextual cues were as important for associative learning as the CS and US. According to this view the context primes CS events in the same manner that the latter signal the US. LI thus develops because an association is learned between the pre-exposed stimulus and the context in which it took place. Following that, the context serves as a prime for accessing the pre-exposed stimulus from long to short term memory. Being predictable, the CS is not further processed and therefore fails to establish new associative learning. As data emerged that failed to support the notion of a context extinction effect, Rescorla [43] and Lubow [22] suggested instead that the context acted as an occasion setter for a certain learned stimulus association, i.e. in case of the pre-exposed stimulus, a stimulus-no consequence association. Disruption of context attenuates LI and its maintenance is therefore thought to contribute to it.

In the present volume, contributors were scrutinising the biological features that influence and mediate the adaptive change from UCR to CR. As the system is biological, the key word is ‘adaptive’. In the case of each of these tasks the change is slowed by experience. It is as if the intuitive benefit of rapid new learning is retarded by previous learning, by inattention. The slowness is not a result of a limit to resources as the pharmacological and psychopathological studies reveal.

The physiological mechanisms reveal a complex interplay of inhibition, and if necessary their disinhibition, in guarding against perceptual confusion where the consequences of misinterpretation and inadequate planning of response over time may be costly.

The fruit of the psychobiological approach lies in the confirmation of the crucial role of the nucleus accumbens in the initiation of processing integral to the LI measure of acquiring associations. Here the activity of dopamine, modulated by nicotinic and serotonergic sites, is critical for the effective switching between available influences [57]. But, as has been articulated before for both cognitive and response control systems, switching by dopaminergic (DA) systems will depend on the volume control exerted by serotonergic (5-HT) activity and, in the case of the competition between two or more ongoing processes (e.g. CB and NR), the tuning role exerted by noradrenergic (NA) activity [31,32]. Perhaps for the first time we are starting to see biological bases for the marginally different operations afforded by the different tasks studied in this paradigm. Studies with the electron microscope show that the substrate is there. For example, a recent Japanese-French cooperative study found a dense accumulation of DA immunoreactive fibres in the medial nucleus accumbens of the monkey with 94% of DA synapses on the shafts or spines of the neurons [15]. Significant for the putative switching role of DA as well as for considerations of the sources of information involved, they reported a number of synaptic triads. On these dendrites there was not only DA input, but input from the hippocampus and prefrontal cortex.

In contrast to the attention paid to the mesolimbic anatomy, it is surprising to find three areas that have received relatively little attention in the psycho-biological approach. The first reflects a certain lack of rigour in consideration of the stages of information processing represented by the conditions compared in learned inattention tasks (see the points raised in [21] on transmitter activity during the conditioning phase and [23] on the role of perceptual ‘pop-out’ phenomena in the non-pre-exposed LI condition). The second concerns the relationship between the constituent tasks of LI, CB and NR, touched on in [33], and their relationship to several
closely related paradigms. What are the correlates of comparing common and unusual stimuli (cf. the Mismatch Negativity of the event-related potential [32 footnote 1])? Are there different biological mediators for the effect of a learned association on the processing of a superfluous relevant stimulus (e.g. CB) and the effect of an irrelevant stimulus on the processing of a salient or target stimulus (Prepulse Inhibition1 [5, 47])? Third, what does the ontogeny of learned inattention tell us about its constitution? Is it not extraordinary that, while classic-al conditioning can be accomplished in infants, trace conditioning awaits years of development [62] or that several stages are apparent in the acquisition of LI abilities in children [18]? Developmental aspects are but touched upon here [7, 36].

Let us first briefly consider some of the problems in the study of learned inattention, the solution of which lies within the grasp of the methods available.

3. Attention: methods and problems

First, what the three task forms have in common is a comparison between (at least) two learning situations. In all three there is the pre-exposed vs. the non-pre-exposed stage (with respect to the critical stimulus conjunction). The problem is that these two situations differ not only in the presence or absence of the influence under study, but with the specialness or novelty of the new stimulus exposure that renders comparisons misleading (cf. orienting and pop-out phenomena). This adds fuel to the arguments from abnormal psychology on the advantages of using a within rather than a between-subject design. The demonstration of the importance of the context in which stimuli are presented and the incorporation of this into attention theory underlines the importance of this aspect of design [24].

A second design problem continues to reflect the type of stimulus used. While the need for balancing for perceptual salience to avoid confounds with other phenomena such as overshadowing is widely appreciated, the learned inattention literature uses the whole range of forms of learning task, without the caveats customary in other branches of experimental psychology. The question relates not just to the conventional contrast between operant and classical conditioning, but between appetitive and aversive conditioning, taste avoidance and emotive conditioning. If the question can be raised in all seriousness that dopamine, for example, is involved in mediating incentive rather than classical conditioning [2], then, irrespective of whether it is true, it behoves experimentalists using the conditioned suppression of drinking method with animals to confirm their results with another form of learning. This is important if for no other reason that conditioned suppression of drinking is not the preferred method for studying LI in humans. The point has been made, with some effect, with the suggestion that motivational variables can explain LI phenomena without recourse to attentional explanations [20]. The point is not without its own interest: most psychologists will testify to the importance of motivation in learning. The special feature in the learned inattention paradigm is that one normally attempts to control for its influence.

A third problem concerns the number of pre-exposures. Within the narrow context of the need to demonstrate LI in the conditioned suppression task form, the technique has been honed to perfection. This allows for replication within drug studies and the performance of comparable investigations between drugs. As the reports below attest, if you want to see enhancement after a manipulation, pre-expose ten times, but if you want to demonstrate disruption, then pre-expose 40 times. But the constraints operating here are still naively ignored. What factors limit the demonstration of robust LI with ten pre-exposures and why can one not enhance the LI after 40 pre-exposures? Potentially relevant at this juncture is the procedural item relating to the so called ‘re-baseline’ phase of an experiment. In the conditioned suppression of eating or drinking it is usual to precede test stimulus presentations with a hundred or so responses (licks of a water bottle or lever presses). But, a feature that distinguishes between studies is whether or not a training phase is re-instituted between conditioning
and test. When present this consists of several hundred responses and hence exposures to the context. Accordingly this emphasizes the ‘occasion-setting’ nature of the context and the degree of contrast of the experience of the non-pre-exposed group. The actual consequences are not clear.

Far less satisfactory is the status of our understanding the basis of and constraints operating in CB or NR. One school of thought argues that the use of a within subject design controls for the slowness of learning that may be observed as a result of a drug, a lesion or an illness: another argues, on the basis of normal psychology, that the number of learning trials or exposures takes prescience. However, it is also clear that such arguments ignore the potential contribution to learning of other factors evident in individual differences, in Spearman’s ‘g’ or in subjects with widely differing etiological histories. So, for example, the question of over-training simply does not pertain to a group that is unable to reflect the potential CS–US association in their response pattern. However, the point is important for the selection of stimuli when separate groups of subjects are to be compared; in the NR task, for example, it would seem that a truly appropriate format has not yet been developed for studies of human performance. This problem raises its head again under the rubric of state-dependent learning in the interpretation of drug effects.

This question on the role of the degree of stimulus exposure throws a related problem into contrast, the relationship of learned inattention to similar paradigms. These questions have only been approached as yet by psycho-physiologists. If learned inattention researchers are interested in how exposure to one stimulus affects learn-ing about another, they should also know how an organism compares stimuli, with and without focused attention, when these stimuli have no association with a US (e.g. the Mismatch Negativity paradigm, MMN). In the one condition such stimuli may be the subject of focused (in)attention and in another condition ignored [34]. These conditions produce distinguishable biological states of activity and beg a comparison with the situation in, say, LI. This question stands on the one side of the LI paradigm: on the other side is the question of how an irrelevant stimulus affects making a simple discrimination or CS–US connection. Here we are thinking of the prepulse inhibition paradigm (PPI). In its simple form the prepulse interferes with a UCR, but in important variations attention can be focused on salient post-pulses that are targets or non-targets [47], or focused on the prepulse [48]. The physiological correlates vary with the condition, but there have been few reports comparing the situation with learned inattention.2 That there are informative comparisons to be made is indicated by the comparison of CB and NR in the same patients by Oades [33]. Performed on the same morning, performance in the one related more to the general status of catecholamine activity, but in the other indole amine activity was prominent among the correlates.

What is the nature of the similarity and difference between tasks in the learned inattention paradigm? We have already mentioned the similarity, that in one way or another, they each look at the influence of the formation of one CS–US connection on the formation of another. For LI this may not be explicitly obvious to all. But, it should be noted that the idea of learning that a stimulus is associated with no consequence occurs in a situation when it is phasic, and thus more salient than the tonic comparison stimulus, namely the context (cf. [45]). Disruption of the

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2 (a) Some selected similarities between LI and PPI: disrupted by indirect DA agonists, effect reversed by DA antagonists; disrupted by 5HT agonists and enhanced by 5HT antagonists; the glycine antagonist strychnine disrupts startle. PPI and LI; the adenosine antagonist caffeine has no effect on PPI or LI [1,9–11,40]. (b) Some reported differences between LI and PPI: apomorphine (indirect DA agonist), blocking mesocortical D1 and D2 sites, and PCP (non-competitive NMDA antagonist) decrease PPI but not LI (?); disruption of mesocortical DA projections may interfere with PPI but not LI; amygdaloid input may interfere with PPI but reportedly not LI; unlike the situation in animals, in healthy humans nicotine may not affect LI but it can normalise PPI in schizophrenic patients; PPI weakened more than LI by social isolation:deprivation during development [5,52,56,59,60].
context disrupts the associations with the phasic stimulus. The stimuli are contiguous and the situation is analogous to trace conditioning. Similarly, in CB there is the competition between two stimuli for an association, where one has temporal priority. Conceptually, CB has an advantage over LI in that the stimulus transiently hindering the new learning is closely defined. However the stimuli are only macroscopically contiguous (in the sense that presentations alternate more or less with each other); microscopically they usually are not presented together, but phasically alternate rapidly across time. (NR differs in having clearly separate temporal phases macroscopically, but microscopically is similar to CB with the emphasis on the comparison of elements, namely between intra- and extra-dimensional conditions). Finally CB has a practical disadvantage and that lies with the difficulty of exactly balancing the salience of the two stimuli in all four dimensions. In LI one attempts to control for this by keeping the context (or occasion setter) constant.

Which is more important the similarity or the difference between LI and CB? That LI researchers rarely compare their results with CB data suggests the difference is crucial. Perhaps they are right. Recent CB results imply rather different correlations with monoamine activity (e.g. role of 5-HT and NA [38]). However, the human studies point to more similarities between LI and CB in schizophrenic patients than is evident in animals (e.g. role of DA and sensitivity to illness state). But is this similarity an artifact, in that to study LI in humans usually a masking task is employed simultaneously: otherwise learning conditions are just too simple (pace Vaitl and Lipp’s autonomic measures [55]). As Lubow has remarked, CB has a built-in masking task. This brings us to the need to develop, as a control, some measure of information load. The effects of LI or CB are only evident if the information load is high enough; yet if too high, the experiment becomes less practicable.

4. Biology: methods and problems

As far as the areas of the brain involved in LI are concerned, there is to a first approximation some consensus. This has been provided by a series of lesion studies reviewed by Weiner and Feldon [58] and c-fos activation [49] and confirm the proposal of Gray et al. [8]. These show that function of the nucleus accumbens (especially via the input to the shell), in conjunction with the dentate gyrus and subiculum is crucial to normal LI. Other regions contribute to specific aspects of learning in the task form used (sensory perception, pain and motivation-sensory cortex, colliculus, periaqueductal gray, amygdala [28, 49, 59]). After processing in this core, it is assumed that the final common pathway for execution of response takes over. Integration of the input, relevant to learning but not unique to learned inattention involves pyramidal areas of the hippocampus. Some controversy remains on the role of the prefrontal, cingulate and entorhinal cortices where investigations overlap with studies of transmitter roles [3, 5, 58]. Studies of the substrates for CB and NR clearly implicate the nucleus accumbens and hippocampal complex but remain, by comparison, rare ([7] reviewed in [38]).

Problems and controversy accumulate when it comes to considering the transmitter systems involved. On the one hand dopamine (DA) systems play a crucial role in learned inattention both in animal studies of LI and CB [4,9,58] and in human investigations of all three task forms [10,14,23,33]. However a delineation of the mechanisms and their distribution gives rise to problems.

To be sure, a fine series of experiments has demonstrated the importance of DA activity in the nucleus accumbens [10,58]. The release of DA can interfere with and a DA antagonist can enhance LI. The release of accumbens DA by the prepulse in the PPI paradigm, interfering with subsequent processing, is here consistent [13]. However, novel stimuli can also transiently increase DA release in the medial prefrontal cortex and the accumbens shell [42]. This is less consistent with what some authors report about the mesocortical DA role in LI (see below). Thus, to go further, in terms of transmitters and brain regions, incurs
questions on the nature of the interactions of different DA systems and other transmitter systems in the fundamental mediation of learning within which attentional mechanisms operate. As a further illustration of this, toxic lesions of the DA system in the VTA disrupt conditioning completely, although selective application to the mesolimbic terminals enhances and the mesocortical terminal reduces CB [39]. While locally applied 5-HT and nicotinic agents affect LI in as much as they alter DA release in the nucleus accumbens of animals [9], systemic applications of serotonergic substances affect transmitter systems mediating the conditioning to be modified by exposure to the critical stimulus [11,21].

Confidence in what the DA mechanism and role really consists of is not rein-forced by the astonishing plasticity of the deficit in schizophrenia patients—now you see it now you don’t—being present in the first few weeks after an exacerbation, but not thereafter: or is there another explanation for the conflicting results of ([10,55] vs. [51,61]). Is the difficulty of finding an expected super LI effect resulting from hypodopaminergic activity in Parkinson’s patients due to the processing of novelty of the CS in the non-pre-exposed condition [23] or is there another reason, perhaps relating to compensatory homeostatic effects in other transmitter systems? It is unfortunate that the protagonists in this debate neglected to collect more data on the state and symptoms shown by their patients and signs of neurotransmitter or regional activity from plasma, urine, pharmacological challenge, and PET or fMRI studies. There are numerous reports of different neuropsychological profiles from Parkinson’s patients with:without the on-off features, depression or dementia-like symptoms and schizophrenic patients with negative, disorganized or positive symptomatology. Recent reports from Oades ([33] and references therein) with respect to CB indicate that this approach may be fruitful.

As far as other transmitter systems are concerned, there is sound reason to think that communication through the retro-hippocampal system is glutamatergic: aspartergic, and indeed the other limbic node receiving DA input, highlighted in the monograph on DA connectivity [35], namely the entorhinal cortex, is implicated in the integration of information that contributes to LI. NMDA lesion of this area attenuates LI in a haloperidol reversible way [63]. The function of the local DA innervation deserves more attention, particularly in view of the findings that DA efflux here is modulated by oestrogen [46], the levels of which are strikingly low in women with schizophrenia [37] and of numerous cytotoxic anomalies in postmortem studies of schizophrenic patients [16]. But what about the prefrontal mesocortical DA system?

If 6-OHDA in the prefrontal cortex interfered with CB in rodents [39] it might be expected that local D1 or D2 antagonists would interfere with LI. Not so, say Ellenbroek et al. [5] on the basis of their conditioned taste aversion test-form. However, comparison of conditions is complicated by the finding that low doses of the D2 antagonist sulpiride increased the amount of sucrose taken. Now it is well known that D2 antagonists like raclopride, at least after systemic administration affect sucrose intake, whereby the change depends on the concentration [29]. This is an annoying complication that suggests a different task form would be appropriate, particularly as in the presented form LI approached near maximal levels and any potential enhancement would not have been measurable. Broersen et al. [3] took this other approach and looked at the conditioned suppression of eating. They found that local flupenthixol interfered with LI whereas apomorphine did not. While this is not the same as the systemic effect of neuroleptic agents it is consistent with the CB effect described above and with the finding that blocking mesocortical DA activity often induces ‘compensatory’ increases in the mesolimbic system. Alas, despite the clear significance of the LI disruption the treatment decreased suppression ratios in the non-pre-exposed group to the level of placebo-treated pre-exposed controls. So the contrast could have been more convincing had the treatment
not exerted such a substantial effect on conditioning.

Last, but perhaps not the least perplexing of problems, pertains to the systemic administration of agents in learned inattention tasks. The problem concerns the timing and duration of the purported mechanism of action and the organizational system in the brain so affected. As Gray et al. relate [10], agents may be injected in the pre-exposure, in the conditioning or in both phases, but not usually at the time of testing. With regard to the time-point when the drug is administered, data should be reported for at least these three permutations, and then depending on the way they turn out discussed for their potential implication for attention, learning and the influence of the drug-induced state on performance: all these are of interest. With regard to the time-point when the data are taken, we refer to the experience of the London group with amphetamine (i.e. single:repeated administration with tests at 15 or 90 min after administration). One should not rely alone on reports in the literature on the length of time for which an effect is said to hold. Either one should measure it oneself in each study, or, analogous to the use of prepulses at 2, 4, 8, 19 dB) in PPI studies, LI researchers should titrate the effects with respect to time after administration. Lastly, it should be accepted that many potential medications are anxiolytic and decrease sensitivity to or perception of electric shock as pain and punishment and something to be avoided. Thus the anxiety reducing properties of the benzodiazepines, clozapine and serotonergic agents disrupt the conditioned emotional response [6,30] and may explain other reported inconsistencies in the learned inattention literature. Such state dependence can be clarified by comparison with performance in an appetitive paradigm.

5. Conclusions:

There remains a lot of work to be done to clarify the conditions that con-strain attention and the whole range of amine systems that contribute to the integration necessary. But the field has come a long way in the 15-20 years or so since it was first supposed that hippocampal and DA systems might be involved. We are at the stage of listing the participants and quantifying the degree of their contribution. Before 15 more years pass, it should be possible to describe the developmental time course for these contributions and describe which elements are substantially involved in the major forms of psychopathology already under study.

References


[33] Oades, R.D., Stimulus dimension shifts in patients with schizophrenia, with and without paranoid hallucinatory symptoms or obsessive compulsive disorder: strategies, blocking and


