PhD Thesis

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The role of expectancies in drug withdrawal

*“To sum up, I am suggesting that many of the reinforcing consequences and antecedents of drug addiction have no direct pharmacological basis. For a given individual the temporal pattern of drug use may be maintained almost entirely by secondary reinforcers.“*

Valliant, 1988

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# Chapter 1: Expectancy and the Placebo Effect

The context in which a stimulus is presented to us has an enormous influence on the way we perceive and react to that stimulus. Most people however are either unaware of or ignore this fact, as it introduces an uncomfortable element of doubt into their transactions with the world. If we question whether the expensive wine we drink actually tastes better, or if it merely tastes better because it is expensive, we may be forced to admit that all our perceptions are flawed, from the way we think our colleagues interpret what we say to the way we remember pivotal moments in our personal histories. Therefore most of the time we accept our perceptions of both internally and externally generated events as being accurate and in some sense true. These perceptions go on to guide both our volitional and non-volitional responses to the stimuli we encounter. One of the goals of psychology as a science is to explain the reasons for the gap between what we perceive as reality and what that reality actually is, and to use this knowledge to help develop ways to calibrate the two states so that individuals can base their future decisions on a view of the world undistorted by their beliefs, expectations, and predilections.

## Expectancies

Expectancies are important moderators of how we perceive and interact with the world and are central to influential theories in learning and in clinical, social, educational, and developmental psychology. Expectancies can be defined as schemas that are activated based on appraisals of the likelihood of a stimulus or response signaling the arrival of another stimulus (Bolles, 1972; Rescorla & Solomon, 1967). Thus the context preceding the occurrence of a stimulus can itself be considered a stimulus that gives us an indication of what to expect when the antecedent stimulus arrives. Schemas are organized patterns of stored information acquired by observing the relations between all the stimuli the organism has experienced. They are derived via the classification of stimuli into classes based on salient features that individuals within each class share (DiMaggio, 1997). Thus completely novel stimuli can still elicit expectancies if these stimuli are judged to belong to a class with which the organism has prior experience. Expectancies are useful in that they provide us with a heuristic that allows us to efficiently assimilate novel information into our existing worldview. However they can also alter the way we perceive and respond to any stimuli that occur after the schema that generates the expectancies has been activated. Most modern explanations for the placebo effect agree that it is a phenomena that arises as a result of expectancies.

## The Placebo Effect

The most archetypal example of a placebo effect is when an individual experiencing some form of pain is given a sugar pill under the guise of an analgesic and subsequently reports a reduction in pain. This canonical example, while instructive, does not adequately cover the scope of placebo effects. A more accurate definition of a placebo effect might be any change on an outcome that is brought about by the administration of a pharmacologically inert compound or therapeutically inert treatment. It is widely thought that placebo effects are brought about by expectancies held by the individual receiving the placebo treatment concerning the consequences of that treatment (G. H. Montgomery & I. Kirsch, 1997); however as yet there are no definitive answers as to which mechanisms are responsible for the phenomenon.

When no active treatment has been administered placebos can lead to observed effects that mimic the effects of the active treatment (Hull & Bond, 1986; Kirsch & Weixel, 1988; Marlatt & Rohsenow, 1980). Furthermore even when an active treatment *has* been administered, awareness of having ingested the drug and expectancies about the likely effects of ingesting the drug can elicit placebo effects that augment (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti, Maggi, et al., 2003; Neukirch & Colagiuri, 2015; Penick & Fisher, 1965; Penick & Hinkle, 1964) or inhibit (Aslaksen, Zwarg, Eilertsen, Gorecka, & Bjørkedal, 2015; Bingel et al., 2011; Flaten, Simonsen, & Olsen, 1999) the direct effects of the treatment itself. Because placebos are used widely in clinical trials to isolate the active effects of a treatment from the effect of expectancy, in medical settings the placebo effect has been considered a nuisance variable, a factor to be ‘controlled out’ in order to gauge the precise effects of the treatment alone. However new advances in placebo research suggest that patients’ expectations of treatment effects, far from being a nuisance, can in fact be harnessed in order to enhance treatment outcomes.

Placebo effects have been observed for a wide range of psychophysiological phenomena, including analgesia (Amanzio & Benedetti, 1999), improved motor function (Pollo et al., 2002), reduced insomnia/improved sleep (Neukirch & Colagiuri, 2015; Suetsugi, Mizuki, Yamamoto, Uchida, & Watanabe, 2007), bronchioconstriction (Butler & Steptoe, 1986) and immunosuppression (Longo et al., 1999). Placebo effects can be positive or negative, depending on what the patient is expecting from the treatment. Side-effects of a drug for example are sensitive to conditioning and expectancy manipulations in much the same way as the desired effects (Colagiuri, McGuinness, Boakes, & Butow, 2012; Shapiro, Chassan, Morris, & Frick, 1974). Possibly the most salient example of an aversive expectancy-induced effect (or nocebo effect) is the anticipatory nausea experienced by patients undergoing chemotherapy (G. H. Montgomery & Bovbjerg, 2001, 2004; Roscoe, Hickok, & Morrow, 2000).

The type and direction of the placebo effect elicited depends largely on the expectancies held by the individual who receives the placebo concerning the likely outcome of the treatment. Expectancies can be acquired directly through personal experience with the treatment or indirectly through social learning or generalization of stimuli.

## Sources of Placebo Effects: Expectancy vs Conditioning

That the placebo effect exists is universally agreed upon. However there is less agreement on the precise mechanisms that give rise to it. The following sections will examine the various theories concerning the psychological and physiological mechanisms behind placebo effects.

### Stimulus Substitution Model

The placebo effect is most often explained as a learning phenomena, specifically an example of classical conditioning. In classical or Pavlovian conditioning a neutral stimulus (conditioned stimulus or CS) paired with a non-neutral stimulus (unconditioned stimulus or US) that reliably elicits a response (unconditioned response; UR) acquires the ability to elicit the same or a similar response on its own in the absence of the US. This latter response to the solitary CS is known as the conditioned response (or CR). The archetypal example of classical conditioning is Pavlov’s (1927) famous experiment using a dog, its food, and a bell. Pavlov observed that the sight and smell of food (US) caused the dog to salivate (UR). Pavlov rang a bell (CS) each time the food was presented to the animal and did this over repeated feedings. Eventually ringing the bell on its own came to induce salivation (CR). For a long while this learning phenomenon was explained using a stimulus substitution model. ‘Stimulus-substitution’ in the model’s name refers to the fact that the CS comes to stand in for or substitute for the US in its ability to elicit the response in question. In this model the essential process that allows the substitution—and hence the conditioned response—to take place is the contiguous pairing of the CS with the US.

Following Pavlov’s discovery research began in earnest to determine what other unconditioned stimuli could be substituted with neutral stimuli. For example Pavlov and others found that the salivation that that followed morphine injection could also be conditioned to neutral stimuli (Collins & Tatum, 1925; Crisler, 1928; Pavlov, 1927). Conditioned responses that mimic unconditioned responses have also been found for atropine-induced pupil dilation (Korol, Sletten, & Brown, 1966) and morphine-induced hyperthermia (Eikelboom & Stewart, 1979, 1981) and gastric secretion (Rush, Pearson, & Lang, 1970).

Wickramasekera (1980) adapted the stimulus-substitution model of classical conditioning to explain placebo effects. According to this model the placebo effect is a conditioned response: The treatment itself is the US, the cues surrounding the treatment’s administration such as the vehicle of administration (e.g. pill, injection) or more general environmental cues (e.g. the room the treatment is administered in, the doctor who administers the treatment) are the CS, and the acute effects of the treatment on the central nervous system the UR. Repeated contiguous pairings of the effects of the treatment (US) and the context surrounding its administration (CS) eventually lead to a conditioned response (CR) that is similar to the UR, which can be elicited following the presentation of the CS alone. The reason an inert pill administered for the first time can produce a conditioned analgesic response is that all the patient’s prior experience with analgesics constitute conditioning trials that are generalized to the new pill and are thus able to produce a conditioned response to a novel stimulus. Thus through stimulus substitution inert treatments such as saline injections or sugar pills are able to evoke conditioned responses that mimic the responses to the active treatment.

The stimulus-substitution model was the dominant theory used to explain classical conditioning from Pavlov’s experiment until the early 1970’s. Eventually however the theory began to fall out of favour. This happened for several reasons.

The first reason was that the stimulus-substitution model is a descriptive model; it makes no attempt to explain the mechanisms by which the phenomenon occurs. This is not a fault with the theory *per se.* Many scientific models, such as the early models of the solar system, are descriptive only. However any model of such an important and widely applicable *cognitive* phenomenon needed an explanatory component if it was going to be widely accepted.

Secondly the stimulus-substitution model frames classical conditioning as a form of low-level mechanical process, something akin to a reflex; with the implication being that it occurs unconsciously. This contradicts evidence that learning is mediated as much by conscious processes as by unconscious (for a review see Mitchell, De Houwer, & Lovibond, 2009). For example one study found that when respondents had incorrect beliefs about the contingencies between events their responding was in line with these incorrect beliefs rather than actual contingencies (Parton & Denike, 1966). Another study found that that when attention and cognitive load were diverted away from conditioning trials (tone paired with shock) via a masking task it resulted in both diminished contingency knowledge AND reduced electrodermal conditioned responses (Dawson, 1970; Dawson & Biferno, 1973). If conditioning is in some way unconscious/automatic then we would expect it to be unaffected by tasks that divert conscious attention

Thirdly stimulus-substitution models are unable to explain the fact that some conditioned drug responses are opposite in direction to the unconditioned response (Crowell, Hinson, & Siegel, 1981; Lang, Brown, Gershon, & Korol, 1966; Lê, Poulos, & Cappell, 1979; Siegel, 1975). In their review of the drug-conditioning literature Eikelboom and Stewart (1982) show that, far from being a rare-exception, conditioned responses that are opposite in direction to the unconditioned response are more common across a wide range of drugs and bodily systems (e.g. salivatory, thermoregulatory, gastrointestinal) than responses that mimic the unconditioned response. If the conditioned stimulus comes to replace the function of the unconditioned stimulus, as the stimulus-substitution model maintains, then it should always evoke the same response. This problem takes on an extra dimension in stimulus-substitution models of placebo effects, where rodents’ conditioned response to a drug and humans’ placebo response to the same drug can be in opposite directions. For example in experiments on rodents, pairing morphine with a CS results in conditioned hyperalgesia and pairing a CS with a tranquiliser produces conditioned hyperactivity (i.e. CSs that oppose their respective US; Krank, Hinson, & Siegel, 1981; Siegel, 1975, 1976, 1983) whereas in human subjects placebo morphine reduces pain (Amanzio & Benedetti, 1999; Atlas et al., 2012; Benedetti, Amanzio, Rosato, & Blanchard, 2011; Evans, 1974) and placebo tranquilisers decrease activity levels (Frankenhaeuser, Järpe, Svan, & Wrangsjö, 1963; Frankenhaeuser, Post, Hagdahl, & Wrangsjoe, 1964). These inconsistencies in conditioned responses across drugs and between species are not easy to reconcile with the stimulus substitution model as it stands.

Lastly the stimulus-substitution model’s analysis of the essential associative processes behind classical conditioning is contradicted by evidence. For example the stimulus-substitution model postulated *contiguity* ofCS-US pairing as the necessary process in conditioning. However new findings showed that contiguous CS + US pairings do not always lead to conditioning if, for example, prior to the CS + US pairing, the CS occurred many times in the absence of the US (Rescorla, 1968). Thus while contiguity is the most common predictor of association formation it is by no means necessary.

The inability of the stimulus substitution model to provide an explanatory model of conditioning, or to adequately account for seemingly contradictory evidence, meant that a new theory of classical conditioning was needed.

### Revised Stimulus Substitution Model

Eikelboom and Stewart (1982) proposed a revision of the stimulus substitution model that addressed the apparent inconsistencies in direction of conditioned responses. They proposed that conditioned responses to drugs *do* in fact always resemble the unconditioned response, but that the unconditioned response is not always the *observed* response. They hypothesised that if a drug acts on the afferent arm of the system in question (e.g. thermoregulatory, salivatory) then the observed drug effect will be the UR and the conditioned drug effect will be in the direction of the observed effect. If on the other hand the drug in question acts on the efferent arm of the system then the observed effect is actually the US not the UR, and will evoke a compensatory UR that is in the opposite direction to the observed effect. Thus situations where the conditioned response seems to oppose the unconditioned response are really just the result of incorrect identification of the US. This model seemed to address the inconsistencies between theory and evidence in the existing stimulus substitution model. This revised stimulus substitution model is still generally well accepted, however there was still a problem for the stimulus-substitution model of *placebo effects.* The revised model now explained the inconsistencies in the evidence for conditioned responses in rodents, but offered no explanation for the contradictory evidence from human studies, where placebo responses most commonly act in the direction of the unconditioned stimulus. The inconsistency in the direction of the conditioned response to these drugs means either that: a) the revised stimulus substitution model of classical conditioning is true for rodents and humans but that the drugs in question act on different arms of the systems involved, or b) that placebo effects in humans do not involve classical conditioning as it was currently conceptualised.

### Expectancy Models

The need for a model of classical conditioning that was explanatory as well as descriptive and that took account of conscious learning led to researchers in the late 1960’s and early 1970’s to begin proposing theories of learning and classical conditioning that focused on the role of cognition and information processing. These theories framed classical conditioning as the learning of relations between events rather than a reflexive response to the repeated co-occurrence of stimuli. According to these models, conditioning is dependent not on contiguity but on the formation of expectancies, which are beliefs based on the perceived likelihood of one set of stimuli being followed or accompanied by another (Bolles, 1972; Rescorla & Wagner, 1972). The extent to which a CS is able to produce a conditioned response depends on the information the CS provides about the likelihood of the arrival of the US and subsequent UR (Rescorla, 1988). In expectancy models of classical conditioning both the UR and, eventually, the CR, are *preparatory* responses, the organism’s reaction to the anticipated arrival of the US. Viewed in this context, the bell that caused Pavlov’s dog to salivate—the same bell that in the past had accompanied the delivery of food—over repeated feedings became a predictive cue signaling that the food was about to arrive. The salivation that occurred when the bell was rung was therefore its body’s reflexive preparation for receiving that food. Thus the bell provides information that food is likely to soon be consumed, just as seeing the food or smelling the food would, and produces the same anticipatory salivation response. In the expectancy model of classical conditioning, while the conditioned *response* is still reflexive, the *learning* that leads to it is not, but is instead the product of observation, generalisation and an appraisal of likelihoods. In this model conditioning is no longer opaque, but is instead dependent on the processing of information.

Just as with the stimulus-substitution model before it, the expectancy model of classical conditioning was adapted to form the basis of a model of placebo effects. The Expectancy model of placebo effects attempted to explain the mechanisms behind placebo effects, by which expectancy alone can cause changes in psychophysiological states. According to the expectancy model, placebo effects result from the activation of *response expectancies* (Kirsch, 1999)*.* Response expectancies are defined as “the anticipation of nonvolitional responses” (Montgomery & Kirsch, 1997, p. 108). These are to be distinguished from the *stimulus* expectancies that are the focus of information theories of classical conditioning. Stimulus expectancies are the anticipation of external consequences such as food, money, praise, and punishment. Expectancies of nonvolitional responses are also distinct from expectancies of *voluntary* responses, which are more like intentions.

Similarly to the revised stimulus substitution model of classical conditioning, Expectancy theories of placebo effects suggest that for a stimulus to act as a US, and thus be able to be associated with a CS, it must be perceived. Therefore the drug itself cannot be a US, only the body’s response to it—the *effects of the drug*—can be, for it is only this response that can be perceived by the organism to whom the drug is administered. What the organisms who ingests a drug learns is that the drug makes it feel a certain way: analgesics produce pain relief, alcohol produces disinhibition, amphetamines produce arousal and so on. Therefore, for the organism being conditioned, the *response* to the active effects of the drug on the central nervous system acts as the unconditioned stimuli with which neutral cues are paired and which the expectancies of a nonvolitional response form around. Thus in a sense, according to expectancy theories of placebo effects, placebo effects are anticipatory responses to URs masquerading as USs and the reason why drug-oppositional placebo effects are not as common in humans is because tolerance develops without our perceiving it, and thus we form no expectations around it.

According to expectancy theorists such as Kirsch, classical conditioning is only one way that we come to acquire response expectancies. Other ways are through third party accounts such as reading or watching television, or through direct observation of others’ reactions to stimuli.

Both Kirsch’s account of placebo effects and Rescorla’s account of classical conditioning: a) emphasise *what* is learned and the *strength* of what is learned over the *source* of that learning; b) say that what is learned is the relationship between the *observed* effect and the CS.

The reason why an expectancy model of placebo effects was necessary was to explain the repeated findings that placebo responses are in the same direction as the observed effects of the active treatments they are disguised as, that is to say, in the same direction as the expected reaction. By talking of response expectancies Kirsch was attempting to separate expectancy effects from conditioning effects. Doing so allowed him to propose that conditioned responses and expectancy effects behave in an independent fashion. Thus, he says “when conditioning produces effects that are contrary to people’s expectancies, the effect of expectancy may be powerful enough to reverse the conditioning effect.” (Kirsch, 1999, p 172). Thus cf. the reason why human placebo effects seem to differ from animals’ conditioning effects is that the effect of expectancy reverses or counteracts the effect of conditioning. Whether this happens in an additive, multiplicative, or non-linear fashion Kirsch himself is unclear.

There are several strands of evidence to back up the theory that expectancies and conditioning are separate processes.

The first is that responses to placebos are often unrelated to the actual drug’s effects. For example while caffeine tends to improve motor performance, if participants expectancies are manipulated by experimenters so that they expect caffeine to impair their performance then their performance is impaired irrespective of whether they are given caffeine or placebo (Fillmore & Vogel-Sprott, 1992). The same holds if they are told to expect improved performance.

The second is that conditioning can be blocked by providing verbal information. For example Montgomery and Kirsch (1997) found that the placebo effects attributed to a topical analgesic cream but really brought about by a surreptitious shock reduction conditioning procedure (see Voudouris, Peck, & Coleman, 1985) could be eliminated if participants were told that the pain reduction they experienced was brought about by actual shock-level reduction.

The third is that placebo effects involving both instruction and conditioning are more pronounced than placebo responses that are elicited by either on their own (Amanzio & Benedetti, 1999). In general conditioning procedures seem to bring about stronger placebo effects than expectancy (Amanzio & Benedetti, 1999; Colloca et al., 2008; Voudouris et al., 1985), but Kirsch argues that while both conditioning procedures and verbal instruction generate expectancies, direct experience with the effects of a treatment (i.e. conditioning trials) generate stronger expectancies—and hence expectancy effects—than the mere assertions of a third party.

The last is that placebo effects can be resistant to extinction. Montgomery and Kirsch (1997) found that placebo analgesia increased rather than decreased across extinction trials. According to conditioning theory, conditioned responses should extinguish eventually if repeatedly unaccompanied by unconditioned stimuli. Therefore if placebo effects are caused by conditioning they should extinguish over time. The results of Montgomery and Kirsch’s (1997) study on the other hand would seem to suggest that placebo effects caused by expectancy are self-sustaining—because the expectancy itself produces a response that further reinforces the expectancy. On the whole however the evidence is mixed, with some studies confirming the resistance of expectancy effects to extinction (Boissel, Philippon, Gauthier, Schbath, & Destors, 1986; Traut & Passarelli, 1957) but more recent studies finding that placebo effects extinguish in the absence of direct reinforcement (Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010; Yeung, Colagiuri, Lovibond, & Colloca, 2014).

According to Kirsch it is clear that expectancy effects behave in a way that is different from conditioning. The problem is that in hypothesizing a separate phenomenon, it is also necessary provide a separate mechanism to explain *how* this phenomenon occurs. Kirsch does this via his ‘immediacy hypothesis’. He acknowledges that some expectancy effects may be mediated by other variables (e.g. trust, faith, hope, anxiety reduction, endorphin release, the therapeutic relationship); however he suggests that these variables cannot account for the full range of expectancy effects, and that some therefore some expectancies must affect the responses they anticipate in an *immediate* way, that is, directly and unmediated by other variables. So expectancies of pain-relief produce the changes in the nervous system that reduce pain, expectancies of alcohol ingestion produce arousal and so on. His principle evidence for this immediacy is from Montgomery and Kirsch (1996), where applying a placebo cream presented as a site-specific topical analgesic produced analgesia in the area it was applied to but not to another site where the same painful stimuli had been applied but without the cream. According to Kirsch’s interpretation such a specific placebo response cannot be explained via any global mechanism, therefore the expectancy of pain in that site only must have produced analgesia *directly* on that site only. This he says rules out the hypothesis that placebo analgesia is mediated by a conditioned release of endogenous opiates (Benedetti, 1996).

Kirsch’s expectancy model of placebo effects is a compelling attempt to update models of placebo effects with modern thinking on classical conditioning and with current evidence on placebo effects. While there is general agreement that people’s beliefs and expectations *are* responsible for placebo effects there are several problems with the expectancy model that warrant further discussion.

Firstly Kirsch suggests that “the occurrence of a subjective experience may be an immediate consequence of its expectation.” (Kirsch, 1997, p. 179). This is more understandable with fear or depression or anxiety, where anticipation of panic may make one panicked, or anticipation of sadness might make one sad, and hence the expectation directly induce the emotion. However, as Kirsch himself acknowledges, it is harder to imagine how anticipation of nausea can *directly* make one nauseous (i.e. via a constriction of the stomach wall?), or how anticipation of pain relief might *directly* relieve pain (i.e. reversing tissue damage?). Furthermore the site-specific placebo analgesia observed in Montgomery and Kirsch (1997) that is the cornerstone of his evidence for immediacy could just as easily be explained by response shift or demand characteristics as by immediate and direct topical analgesia.

Secondly Kirsch does not identify a neurological, neurochemical or physiological mechanism that may be responsible for the implementation of these unmediated effects. In place of a mechanism he offers evidence for the immediacy hypothesis in findings showing that placebos have produced physiological changes, such as bronchioconstriction in response to instruction about placebo asthma medication (Butler & Steptoe, 1986), penile tumescence in response to placebo alcohol (Briddell & Wilson, 1976), and blood pressure and heart rate in response to instruction about receiving caffeine (Kirsch & Rosadino, 1993; Kirsch & Weixel, 1988). However penile tumescence, asthma attacks (Lehrer, Isenberg, & Hochron, 1993), heart rate, and blood pressure are all physiological symptoms that can be brought about by changes in subjective state, making Kirsch’s citing of them as evidence that placebo effects are unmediated by psychological variables seems misplaced. Kirsch also cites examples where tumours (Klopfer, 1957) and skin rashes (Ikemi & Nakagawa, 1962) were altered by information alone, but concedes that neither of those findings were replicated.

Thirdly the expectancy model is still unable to explain the dissociation between the direction of conditioned responses in animals and placebo responses in humans. Kirsch explains this anomaly as follows: “Thus when conditioning produces effects that are contrary to people’s expectancies, the effect of expectancy may be powerful enough to reverse the conditioning effect.” (Kirsch, 1997, p. 172). However this assertion would seem to imply either that rats do not experience expectancies or that their expectancy response is attenuated and thus results in an observed ‘expectancy + conditioning’ *net* response to drugs that is opposite to humans’. The holding of expectancies is not predicated on language or abstract reasoning. All it implies is that the organism is able to learn the relations between events and hold beliefs about the predictive value of CSs. Even behaviourists would be unwilling to assert these days that rats’ learning is *entirely* unconscious.

Lastly it is not immediately clear what response expectancies contribute to our understanding over and above stimulus expectancies. In expectancy theory the CR is a preparatory response, preparing the organism for the arrival of the US. In the expectancy theory of *placebos*, the CR is a preparatory response in anticipation of the *effects* of the drug, which are themselves a response to the active drug’s effects on the central nervous system. So as mentioned in Kirsch’s schema the conditioned placebo response is to a UR masquerading as a US. However Kirsch does not specify what the conditioned response to that response consists of. Without specifying what the CR consists of, the expectancy theory of placebo effects no longer resembles the expectancy theories of classical conditioning upon which it is based.

The expectancy theory of placebo effects was an attempt to reconcile contradictions in the placebo and conditioning literature, specifically the ability of humans to show placebo effects to novel stimuli based on instruction only and with no prior conditioning. Whether it achieved its goal is questionable. However the term expectancy has showed some utility as a euphemism for these unconditioned, instruction-only placebo effects.

## Expectancy vs Conditioning: Need there be a debate?

While there has been much debate about whether learning generally and placebo effects specifically are due to expectancy or conditioning, as Stewart-Williams and Podd (2004) point out, there is no reason why these two explanations of the placebo effect need be mutually exclusive. According to their model, both subjective and physiological placebo effects can be caused by instruction, classical conditioning, or a combination of both. The difference between the two is that classically-conditioned placebo effects can be mediated either consciously or unconsciously whereas placebo effects induced by instruction only *must* be mediated consciously. The evidence is largely consistent with this integrative model.

### Placebo Effects Induced by Instruction Only

According to Stewart-Williams and Podd’s model placebo effects induced by verbal manipulations only *must* be consciously mediated. Placebo effects brought about by instruction tend to be less pronounced than those brought about by conditioning (Amanzio & Benedetti, 1999); however instruction-only manipulations can often produce the most interesting findings, where placebo and nocebo responses can be induced by the same inert substance with different accompanying instructions, or where instruction can override the reported effects of an active drug. Butler and Steptoe (1986) found that the same placebo inhaler could either induce or prevent bronchioconstriction in asthmatics, depending on which outcome researchers led participants to expect via verbal instruction. Flaten (1988) similarly found that the lactose powder led to either sedation or arousal depending on the instructions given to participants. His laboratory also found that patients who were given a muscle relaxant but who were told it was a stimulant reported greater muscle tension than those who were truthfully told it was a muscle relaxant (Flaten, 1999). One multi-centre placebo-controlled trial testing the effects of aspirin on unstable angina listed “gastrointestinal irritation” as a possible side-effect in the information statements supplied by 2 of the 3 centres but not in the third. Patients at the former centres reported significantly higher rates of gastrointestinal problems than those at the latter, and were 6 times more likely to drop out of the study due to gastrointestinal distress (Myers, Cairns, & Singer, 1987). Fillmore and Vogel-Sprott (1992) found that participants who were informed that caffeine improved motor performance demonstrated a greater improvement in performance following administration of a caffeine placebo than participants who were told caffeine would impair performance. The examples above suggest that some placebo and nocebo responses to drugs appear to be entirely mediated by conscious verbal expectancies, occurring in the absence of any prior pairings of the drug with its effects. Furthermore when subjects are told that there is a possibility that they will receive a placebo the placebo response is lessened or eliminated (Kirsch & Weixel, 1988). These results appear to show that a verbal manipulation, even without prior pairings of a vehicle to a treatment or drug, can lead to a placebo response. Whether placebo effects induced by instruction only represent a separate phenomenon to conditioning or are a special form of conditioned response is unknown. One school of thought suggests that expectancies induced by instruction still respresent a form of conditioning—a *conditioned response to a completely new stimulus*. Humans are unusual in that we have the power to communicate abstract ideas through language (e.g. ‘this pill is an analgesic’), extract salient features of one set of stimuli (e.g. the pill), place those features within a general class whose properties we are aware of through experience with other members of that class (e.g. ‘analgesics reduce pain’), and then generate expectancies based on this generalization (e.g. ‘if I take this pill my pain will be reduced’). Thus, provided we believe what we are told about the pill, we are able in a sense to superimpose a response conditioned to one class of stimuli onto a novel stimuli of the same class and obtain the same conditioned response to that new stimuli.

### Placebo Effects without Awareness

There is evidence that classical conditioning can occur without awareness in humans (Esteves, Parra, Dimberg, & Öhman, 1994; Öhman & Soares, 1994; Soares & Öhman, 1993a, 1993b; Wong, Shevrin, & Williams, 1994). Similarly there are examples of placebo effects that occur in the absence of awareness. For example Benedetti et al. (1998) were able to induce a placebo respiratory depression response following conditioning with buprenorphine (a partial opiate agonist) that, though objectively measurable, was unnoticed by participants and which had not been mentioned as a consequence of the administration of the drug. The control group, who had not received any prior pairings of the active drug with the placebo pill, showed no such respiratory depression. Since conditioning was achieved without awareness this result would seem to indicate a completely unconsciously mediated placebo response. Another study found that an immune-activation response could be conditioned to a neutral taste stimulus in human participants (Longo et al., 1999). Because the immune-suppression response produced no changes in physical or psychological symptoms that could be perceived by the subjects, this finding could truly be called a conditioned placebo effect without awareness. In another experiment Benedetti et al. (2003) injected participants with sumatriptan, a drug that increases human growth hormone levels, during pre-test training. On test a saline injection caused an increase in growth hormone levels. Once again the changes in growth-hormone levels both during training and test were unable to be detected by participants, indicating a nonconscious conditioning effect.

### Effect of Expectancy vs Effect of Conditioning

Often the effects of conditioning and expectancy do not operate in the same direction. As mentioned above the CR to morphine conditioning in rodents is hyperalgesia whereas in humans it is analgesia. Stewart-Williams and Podd (2004) suggest that this contradiction can be resolved by considering the types of learning involved. Conditioned compensatory responses can take place only when the learning is of the non-conscious, reflexive sort, whereas if learning is more declarative and consciously mediated—either through conditioning or instruction or both—then the conditioned response to placebo will always operate in the same direction as the unconditioned.

It is difficult to assess the independent contribution of expectancy and conditioning to placebo effects. This is because most conditioning procedures, through the organism’s feeling the effects of the treatment, result in the formation of conscious expectancies. In general however it is thought that instruction on its own leads to weaker expectancies than expectancies obtained through direct experience, where it is likely that expectancy and contribute additively to the final response. In a meta-analysis Vase, Riley, and Price (2002) compared effect sizes of placebo analgesia from studies that used conditioning-only procedures to those that used instruction only. They found that conditioning-only procedures produced effect sizes of 0.85 whereas studies that used instruction yielded 0.83. Thus the placebo effects from the two different methods seem to produce similar sized placebo effects. However the only study included in their analysis that used a conditioning-only procedure was Amanzio & Benedetti (1999), compared to fourteen studies that used instruction-only procedures. Though Amanzio and Benedetti did have two conditioning-only procedures with adequate sample sizes, it seems difficult to make a reliable comparison of the difference between methods when so few conditioning-only studies were used. Furthermore in Amanzio and Benedetti (1999) the ‘conditioning-only’ group were merely told their saline injection on the test day was an inert antibiotic. The training days where they were given morphine that constituted their conditioning trials would have led to the development of expectancies during these trials due to their perception of the effects of the drug. Even if the researchers effectively removed expectancy on test day via their instruction they could not retroactively erase the expectancies that developed during training. Thus to what extent *any* drug whose effects are perceptible can be conditioned in the absence of expectancy is doubtful.

Indirect evidence that conditioning leads to stronger placebo effects than instruction comes from crossover designs. In a training phase Laksa and Sunshine (1973) gave participants an injection of either one of three doses of a synthetic opiate or placebo. This was followed by a second injection where all participants received a placebo. The level of analgesia was predicted by dose level of the first injection, with the group that received placebo during training showing the smallest level of analgesia throughout, though they did still experience a small analgesic effect in after both injections. Moulin et al. (1996) also used a crossover design to test the effect of morphine on chronic pain. Order of two injections, morphine and placebo, were counterbalanced across participants. The participants who received morphine first experienced effective analgesia with the second placebo injection. Interestingly the participants who received placebo first did not experience effective analgesia following either the first placebo injection *or* the subsequent morphine injection. These studies suggest that the reason why conditioning procedures produce stronger placebo effects is that they produce stronger expectancies. This interpretation is confirmed by Montgomery and Kirsch (1997) where the placebo analgesia in one group brought about by a surreptitious shock-reduction procedure were not present in another group who were told prior to the procedure that shocks were being reduced by experimenters, and thus not a result of the cream applied to their arm.

### Effect of Expectancy and Conditioning on Subjective vs Objective Outcomes

It has been demonstrated above that placebo effects for subjective outcomes can be influenced by instruction only and by conditioning only procedures, or both (see Amanzio & Benedetti, 2005). In the section on conditioning without awareness it was also shown that conditioning using hidden administration of drugs can induce placebo effects for a range of physiological symptoms. There is also evidence, discussed above, that instruction alone influenced objectively measurable symptoms such as bronchioconstriction (Luparello, Lyons, Bleecker, & McFadden, 1968), penile tumescence (Briddell et al., 1978), and blood pressure and heart rate (Kirsch & Weixel, 1988), however these are all physiological changes that can be heavily dependent on mindset and can occur in the absence of any drug. Expectancies derived from instruction only can also influence nonconscious *cognitive* processes such as implicit learning. Colagiuri, Livesey, and Harris (2011) asked participants to inhale a bubblegum odour while performing a contextual cueing task. Contextual cueing tasks are often cited as evidence for unconscious learning because reaction times on cued trials are consistently lower than to uncued trials despite participants being unable to consciously recognise the configurations in the cued trials. Participants were assigned to three different instructional sets: that the odour would improve their performance, that the odour would hinder their performance, or were given no instruction. Participants given positive instructions showed improved performance on the cueing task compared to the other conditions. Thus expectancy without conditioning was able to influence an unconsciously-mediated cognitive outcome in an analogous way to the unconsciously-mediated physiological outcomes already mentioned.

### Placebo Effects Induced by Both Expectancy and Conditioning

Expectancy and conditioning can act in isolation to produce placebo effects. However Stewart-Williams and Podd (2004) suggest that outside the laboratory most placebo effects will contain elements of both conditioning and expectancy. As long as the effects of the treatment are perceivable in some way by the recipient, most conditioning procedures will lead to a conscious awareness of the relationship between a treatment and its effects. That unconsciously conditioned responses to drugs can co-occur in conjunction with, but separate to, conscious expectancies is most obvious when conditioned responses and expectancies contradict one another. For example smelling a plastic rose or being shown a sealed jar filled with dust can induce asthma attacks in asthmatics (Dekker & Groen, 1956; Dekker, Pelser, & Groen, 1957; Luparello et al., 1968). The participants in these studies were aware that the stimuli could not cause an asthma attack—dust causes asthma but in a jar there is no way of inhaling it and a plastic rose contains no pollen—and thus should have had no expectation. It of suffering an attack, yet the visual resemblance to stimuli that had caused attacks in the past was enough to evoke an attack. A similar phenomenon is when long-abstinent heroin addicts suffer physical tolerance/withdrawal symptoms such as runny nose, goose-bumps and lachrymation upon merely witnessing the tools of heroin administration or another addict shooting up (Valliant, 1988). In both examples the sufferers are aware that they have not ingested the agent in question and thus do not have a conscious expectancy of a response, but nevertheless suffer a physiological reaction to the visual stimulus that they have come to associate with that agent.

There is general agreement that conditioning and verbal instruction lead to larger effect sizes than either on their own. In two similar experiments Voudouris et al. (1985) and Montgomery and Kirsch (1997) told participants that an inert cream was a powerful analgesic and would reduce the pain from a painful stimulus. There were three phases. In the pre-test phase participants were shocked with and without the cream at the same shock level. The placebo response was measured by subtracting pain ratings when the cream was not applied from pain ratings when the cream was not applied. In the training phase a conditioning procedure was applied whereby the shock level administered when the cream was applied was reduced surreptitiously but increased again when the cream was removed—thereby creating the illusion that the cream was reducing the pain. In the test phase the shock level during the trials when the cream was applied was increased to match that of shock levels without the cream and the difference between pain ratings with and without the cream calculated. Though placebo analgesia was higher following the conditioning procedure there was still a placebo effect in the first phase. This implies that both instruction only and conditioning with instruction can produce placebo effects, but that conditioning with instruction produces more pronounced placebo effects. Montgomery and Kirsch’s (1997) experiment differed from Voudouris et al.’s (1985) only in that during the test phase half the participants were told that the shock level had been reduced. The finding that placebo effects brought about by both conditioning and verbal suggestion are stronger than either alone has been well replicated (Amanzio & Benedetti, 1999; Benedetti, Durando, Giudetti, Pampallona, & Vighetti, 2015; Quinn, MacDougall, & Colagiuri, 2015).

In summary placebo effects can sometimes be induced without expectancy via hidden conditioning procedures, by expectancy only without conditioning procedures, or can incorporate elements of both. Generally placebo effects brought about by a conditioning procedures are more pronounced than those brought about by expectancy because most often conditioning procedures will result in the formation of expectancies. But, as Stewart-Williams and Podd (2004) contend, in the world beyond the laboratory it is likely that in most cases both conditioning and expectancy mediate placebo effects.

### Neurobiological Theories

Neurobiological theories pertain more to the physical mechanisms that produce different forms of placebo effects than to the associative processes themselves. The foremost researcher and theorist in this area is Fabrizio Benedetti and his colleagues, however the first major discovery that led to this theory was made by Levine, Gordon, & Fields (1978). In this seminal study, patients suffering from postoperative dental pain were given a placebo injection administered by intravenous catheter 3 hours after their operation, and then 1 hour after the operation, were given either placebo or the opiate antagonist naloxone. After the second injection the patients given naloxone’s pain ratings increased at a significantly higher rate than those given placebo, indicating that the placebo effect had been attenuated in those receiving the opiate antagonist. The authors concluded that the fact that a drug that blocks opiate receptors reduced the placebo effect proves that placebo analgesia acts via the conditioned release of endogenous opioids. This result has been replicated several times, by Benedetti and others (Amanzio & Benedetti, 1999; Amanzio et al., 2001; Benedetti, 1996; Eippert et al., 2009; Grevert, Albert, & Goldstein, 1983).

Interestingly there are indications that subsystems other than the endogenous opioid system may be responsible for some placebo analgesic effects. Naloxone attenuates placebo effects brought about by expectancy or by conditioning with morphine or a combination of the two; however when conditioning is performed with non-steroidal anti-inflammatories it seems as if the endocannabanoid system is recruited for placebo pain-relief. This was shown in a series of influential studies by Benedetti and Colleagues. Amanzio and Benedetti (1999) found that the naloxone-induced blocking of placebo analgesia only occurred if conditioning procedures were performed with morphine. If conditioning was performed with the non-steroidal anti-inflammatory ketorolac naloxone was unable to fully block the placebo effect. This result was confirmed by Guo et al. (2010) who showed that naloxone blocked a morphine-conditioned increase in pain tolerance in mice, but failed to increase tolerance if the mice were conditioned with aspirin, another non-steroidal anti-inflammatory. These established that different systems and drugs could be responsible for placebo analgesia. That endocannabanoids were involved in non-opiate placebo analgesia was confirmed in a subsequent study by Benedetti, Amanzio, Rosato, & Blanchard (2011) who were able to effectively block ketorolac-conditioned analgesia with the cannabinoid antagonist rimonabant.

A different neurochemical has been identified as being involved in placebo *hyper*algesia: the peptide cholecystokinin or CCK. Benedetti et al. (1997) induced hyperalgesia by suggestion in postoperative pain patients. This was blocked by proglumide, the CCK antagonist, in a dose-dependent manner but not by Naloxone. It was hypothesised that since CCK is involved in anxiety mechanisms that perhaps proglumide prevented anticipatory anxiety and this is what prevented placebo hyperalgesia. This possibility was investigated further by Benedetti, Amanzio, Vighetti, & Asteggiano (2006). They found that a placebo administered with the suggestion of hyperalgesia induced both hyperalgesia and HPA-Axis activation, a measure of stress or anxiety. Both were blocked by benzodiazepam; however the CCK receptor antagonist proglumide blocked hyperalgesia but not HPA-Axis activation. This suggests that CCK is involved in the hyperalgesic but not the anxiety component of the nocebo effect and that proglumide does not abolish nocebo hyperalgesia by blocking anticipatory anxiety as previously hypothesized. Rather it interrupts a CCK-ergic between anxiety and pain. Therefore the anxiety is the catalyst that activates the downstream CCK-mediated nocebo hyperalgesia response. Thus if the anticipatory anxiety is blocked so too is the nocebo hyperalgesia; however if the downstream CCK is blocked only the hyperalgesia is affected but not the anxiety.

The neurobiological theory of placebo effects is very persuasive to those who believe that there must be a non-cognitive mechanism for placebo analgesia. Furthermore the studies that support the theory are well-replicated and well-designed. However there are several flaws with the approach that warrant mention.

The first flaw is in the logic of the evidence for placebo analgesia being mediated by endogenous opioids. It is assumed that because naloxone is an opiate antagonist and because naloxone abolishes placebo analgesia that therefore placebo analgesia must be caused by an expectancy-induced release of endogenous opioids that dull the pain in a way that mimics the analgesic effect of administration of exogenous opiates. However since no studies have yet measured the release of endogenous opioids inside participants’ central nervous systems *directly* following their being given a placebo painkiller, it is impossible to be certain that naloxone does not have effects on some other non-nociceptive system that mediates the effect of expectancy on pain perception. Endogenous opioids have multiple functions within the brain and central-nervous system beyond analgesia, such as regulation of mood, and, importantly for the current discussion, learning. For example it has been shown that naloxone enhances learning of second-order fear conditioning in rodents. When testing the effect of a drug such as morphine on fear conditioning, a stimulus such as a tone (CS­­1) is paired with a shock so that the shock comes to elicit a fear response. If rats given morphine during this procedure show an attenuated conditioned fear response compared to controls when presented with the CS1, it is difficult to know whether the effect is due to analgesia or to a failure to learn the CS1–shock contingency. In second-order fear conditioning once the conditioned fear response has been established a second stimulus such as a light (CS2) is paired to CS1 until a conditioned fear response is elicited by CS2 in the same way as it was to CS1. If morphine is administered to half the subjects after the CS1–shock pairing but *before* the CS1–CS2 pairing and the morphine group show attenuated fear response then there can be some certainty that morphine affected the *learning* of the association between the stimulus and the shock rather than the perception of pain from the shock itself. Cicala, Azorlosa, Estall, and Grant (1990) found that naloxone administered after CS1 –shock pairing but before the CS1–CS2 pairing enhanced learning of the second-order association, as measured by suppression of licking. It has also been shown that naloxone affects extinction learning. McNally, Pigg, and Wiedemann (2004) and McNally and Westbrook (2003) found that injections of naloxone into the periacqueductal grey of rats resulted in slower abolition of the conditioned fear response during extinction than saline-injected controls. A failure to learn a new relationship between the CS and US—that the CS no longer predicts the US—is analogous to a placebo effect which could be framed as a failure to learn that the drug vehicle no longer contains any active ingredients. That naloxone would impair the ability of rats to learn a new non-association between a CS and a US seems to contradict the fact that in humans naloxone seems to enhance extinction learning in that it blocks the placebo effect. There are also problems with the fact that naloxone enhances one type of learning in rodents, second-order fear conditioning, but impairs another, extinction learning. Irrespective of these inconsistencies, it appears as if there are grounds for thinking that naloxone affects learning itself in some way. Since the placebo effect is thought to be learning phenomenon, even by neurobiological theorists, it might be that naloxone’s ability to attenuate placebo effects might be due to its influence on learning rather than its blocking of the expectancy-induced release of analgesic endogenous opioids. The naloxone studies mentioned above are the foundation upon which neurobiological theories of placebo effects are based. If the logic of the evidence for these assumptions is questionable then so must be the theories that are based on them.

The second problem with neurobiological theories of placebo effects is that the evidence for them only comes from studies of placebo analgesia. Even if one accepts the assumptions made about how naloxone abolishes placebo analgesia, placebo effects can be observed across a range of sensory modalities, not just nociception. It is unlikely that all forms of placebo effect will have a readily identifiable neurochemical mechanism to mimic the effects of the active treatment in the same way as placebo analgesia is thought to mimic the analgesia brought about by exogenous analgesics.

## Other explanations of placebo effects

Though expectancy and conditioning, and models that integrate the two concepts, tend to dominate the discourse in placebo research, there are other explanations for placebo effects that warrant mention.

### Response Shift, Perceptual Shift, or ‘Recalibration’

The theories discussed above concerning the source of placebo effects discussed above all carry assumptions, either implicit or explicit, that a mistaken impression about the likely effect of a treatment can cause some *real* objective change in the relevant system within the organism. For example pain can be caused by tissue damage or inflammation or, in the case of headache, dilation of blood vessels. Pain signals travelling from the site of the tissue damage travel via the peripheral nervous system to the central nervous system where they are detected by the brain and registered as the subjective experience of pain. The conditioned response of the brain upon registering this pain is to produce endogenous opioids, which then attenuate the strength of the pain signals. However these endogenous opiates only attenuate the sensation of pain so far. A *voluntary* response to pain is to take an analgesic. Analgesic medicines contain chemical agents that work by suppressing either the chemicals that produce the inflammation themselves, in the case of prostaglandin suppression by non-steroidal anti-inflammatories, or the pain *signal*, by binding to relevant receptors in the central nervous system in the case of opioid-based drugs. The need for theories of placebo effects is to explain fact that placebo groups perceive less pain than controls who receive the same painful stimuli. The assumption in the theories discussed above is that the mistaken belief that one has ingested a painkiller causes an additional release of the chemical agents that ameliorate pain, *over and above* the endogenous opioids already released by the central nervous system as a compensatory response to the sensation of pain. That is, the belief that one will be receiving pain relief causes a *direct* change in the systems responsible for pain relief. This direct change is then perceived by the individual and reported back to the researcher.

There are other theories about how placebo effects work.

Four possible explanations for placebo effects.

a) Neurobiological theories:bona fide psychophysiological mimicry of an unconditioned response by a conditioned response (e.g analgesia, immunosuppression, bronchioconstriction)

b) smudging/ignoring of bodily cues which contradict our expectancies

c) Somatic focus/interpretive frame causes ambiguous and incidental symptoms (e.g. headache, fatigue etc.), which overlap with symptom profile of drug, to be interpreted as instances of drug effects

d) Anticipatory anxiety/worry over onset of negative symptoms of drug either:

i) carry over post drug-administration and resemble the unconditioned symptoms so that they are once again misinterpreted as instances of drug effects.

ii) and/or triggers bona fide symptoms which resemble drug effects.

### Response Shift: Demand Characteristics (delusion, contextual responding, impression management) Interoceptive smudging (assimilation), misattribution (symptomatic overlap, attentional shift, windfarms etc.)

The idea that our expectancies influence the way we perceive the world has been studied for many years across many different disciplines and under many different names. The Gestalt Psychologist Solomon Asch conducted research into the effect positively- or negatively-valenced trait descriptors can have on the perception of subsequent behaviour (Asch, 1946). He found that certain descriptors were more central than others and that the valency of these central trait descriptors change the way that other more ‘peripheral’ traits were perceived by the observer. Participants were given vignettes to read which described a hypothetical person. Prior to reading the vignettes the hypothetical person was labeled with a trait descriptor. Asch found that labeling this person with the words ‘warm’ or ‘cold’ prior to participants reading the vignette could have fundamental and predictable effects on the overall impression people formed of the hypothetical individual’s character. Importantly, identical peripheral traits could be perceived vastly differently depending both on the valency of the central trait descriptor and the order in which the subsequent trait descriptors were presented.

Social information processing theory states that ambiguous social cues can be encoded in a way that is consistent with the pre-existing schemas held by the observer of those cues. The nature of these schema influence the way the observer perceives the valency, intensity, and meaning of the cue. For example the cognitive model of social phobia (Clark & Wells, 1995) proposes that sufferers of social anxiety tend to interpret ambiguous social cues negatively, in line with the way they feel about themselves. The focus on negative interoceptive information concerning the way they feel then shifts attentional focus away from the true features of the external situation and makes the sufferer feel like they are the centre of attention, which exacerbates their anxiety. This theory has been confirmed by findings from clinical studies where participants with social anxiety were more likely to interpret ambiguous descriptions of social events (e.g., “someone you are dating says ‘hello’ to you”) as being negative than either nonpatient controls or controls with other anxiety disorders (Amin, Foa, & Coles, 1998; Stopa & Clark, 2000). Furthermore participants with social anxiety were more likely to interpret mildly negative social events as being catastrophic than either of the two control groups (Stopa & Clark, 2000). The theory and findings imply that individuals with social phobia have a cognitive schema that biases them to interpret otherwise ambiguous social cues as reflecting others’ disapproval and dislike. The second part of this theory that follows from the first is that is that the bias in interpretation causes a shift of attention away from the objective features of the situation inward towards interoceptive stimuli (see Clark & McManus for a review). This has also been backed up by experimental findings that show that individuals with social anxiety exhibit an attentional bias away from faces when under conditions of social threat (Mansell, Clark, Ehlers, & Chen, 1999) and poorer recall of details of recent social interactions (Daly, Vangelisti, & Lawrence, 1989; Hope & Heimberg, 1988; Kimble & Zehr, 1982; Mellings & Alden, 2000).

There is evidence that information processing biases may be involved in the maintenance and aetiology of other disorders. Analogous to individuals with social anxiety disorder, individuals with conduct disorder (Dodge & Crick, 1990) and eating disorders (McFillin et al., 2012) have been shown to be more likely interpret ambiguous social cues as signaling hostile intent. In the different disorders studied the stimuli are the same; ambiguous social cues.

What differs between the disorders mentioned is a) the pre-existing schema held by the individual concerning the meaning and intentions of the other people in the social situation from whom these cues originate and b) the concomitant response that is elicited by the resulting misinterpretation. What is common in all these disorders is that individuals with the disorder interpret the ambiguous information in line with their own pre-existing schema.

So in the case of both the effects of labeling on perception of personality traits and in the way individuals with various mental disorders perceive threat in social situations we can extract commonalities in the underlying processes of each:

the existence of a schema or belief elicits an attentional bias which, when a certain class of stimuli is presented, results in a misinterpretation of the objective features of the situation which in turn elicits an emotional, cognitive, behavioural, or somatic response.

The previous examples pertain to perceptions of unobservable phenomena (i.e. personality and intent of others in social situations), both of which would appear to be a more indirect, subjective, and hermeneutic exercise than perception of the senses, since it involves inferring unobservable constructs (the ‘traits’) from direct or third-party observations of behaviour. However even more ‘direct’ perceptions can be biased by contextual information. For example when white wine is coloured red with food dye it is perceived as having the odour of red wine (Morrot, Brochet, & Dubourdieu, 2001). Also experienced wine tasters rated white wine coloured the same colour as Rosé as being sweeter than uncoloured white wine (Rose M Pangborn, Berg, & Hansen, 1963). Furthermore accuracy in judging the taste of nectars was found to be reduced when the nectar was coloured than when it was uncoloured (Rose Marie Pangborn & Hansen, 1963). These results and others from the smell and taste perception literature led Morrot et al. (2001) to state: “Our results tend to confirm that sense of smell is, by itself, unlikely to provide sufficient information to allow for a consciously reasoned decision, as it is for other sensory modalities.”

The findings from these disciplines seem to confirm that expectancies derived from context influence the way we perceive stimuli as varied as traits, the taste of beverages or the meaning of social cues.

## Sources of Expectancies

The expectancies of drug or treatment effects that are tested in the lab can be grouped broadly into three categories. These modes of acquisition of the expectancies can effect which sub-systems of the brain are responsible for the resulting placebo effects. For example expectation triggers endogenous opioids whereas conditioning activates specific subsystems (Amanzio & Benedetti, 1999)

### Verbally-Induced Expectancies

Firstly there are those expectancies concerning the effects of a drug or treatment which participants do not hold prior to the experiment and which are induced verbally by the experimenter. As mentioned earlier expectancies are derived from the information an organism receives about the contingency between events. Many animals possess the ability to generalise the information gained from one set of CS-US associations to a new set. This allows them to generate expectancies about the imminent arrival of a familiar US, based on the perceived similarity of certain features of a novel CS to a familiar CS that had reliably signalled the US in the past. Humans however are unique in that we are able to generate these expectancies not based solely on the physical and/or environmental features of the new CS, but on verbal information alone.Humans are unusual in that we have the ability, mainly through language, to abstract information (i.e. isolate salient features of particular instances from their specific context in order to form generalisations). Thus expectancies can be induced verbally in the absence of direct experience with a contingency between events (unlike in non-literate animals for whom contingencies can only be obtained through direct observation of events). Humans are unusual in that we have the ability, mainly through language, to abstract information (i.e. isolate salient features of particular instances from their specific context in order to form generalisations)

This abstract information can serve as a cue, an abstract cue, which can elicit placebo responses not possible in creatures who do not have language.

Thus merely by providing credible information about the likely effects of a drug to participants it is possible to have:

1. a conditioned response being elicited by a novel stimulus

e.g. analgesia can be caused by a placebo masquerading as a new treatment

b) a novel response (though the response itself can never be novel) being elicited by a familiar stimulus. For example omitting gastrointentinal irritation as a side effect on boxes containing aspirin in one group of participants led to significantly decreased reports of gastrointestinal complaints compared to a who received identical aspirin except packaged in boxes where the side effect was listed (Myers, Cairns and Singer, 1987).

c) The same inert substance leading to opposing effects. For example inert lactose pill causes sedation or arousal depending on what participants are told it was (Flaten, 1998).

Because we are able to abstract information from language we are able to produce conditioned responses in the absence of direct observation of a contingency between events. In other words, by **decontextualising** a previously acquired contingency between a drug and its unconditioned response and then **superimposing** that contingency onto a new drug we are able to produce what amounts to a conditioned response to a novel stimulus.

For verbal information alone to be able to induce conditioned responses participants must: a) be previously unaware that the effects in question are associated with the drug or treatment they think they are about to receive[[1]](#footnote-1); b) believe that the experimenter is a credible source of information about the likely effects of the drug and that the vehicle they are given actually contains an active agent.

For example participants with food allergies who were told that a saline injection was an allergen developed allergic symptoms (Jewett, Fein, & Greenberg, 1990). Luparello, Lyons, Bleecker and McFadden (1969) gave asthmatic patients nebulised saline to inhale and told them it was an allergen. Approximately half of all participants developed dyspnea, decreased vital capacity, and increased airway resistance.

Arguably these purely verbally induced expectancies still rely, for their ability to induce placebo effects, on some familiarity with the physical or psychological symptoms that experimenters suggest will follow administration of that drug. Thus even verbally induced expectancies may be mediated to some extent by prior conditioning. ???????? reference

### Expectancies Acquired from Personal Experience

Secondly there are those expectancies about a drug or treatment which have been derived prior to the experiment, either from participants’ first-hand personal experience of the association between the drug and its effects or from observation of others reactions to the drug (i.e. social learning; Bandura, 1977). As with purely verbally induced expectancies harnessing long-held expectancies in the lab also requires credulity on the part of participants that any vehicle they are given by experimenters does actually contain an active agent.

Here you need to give evidence of expectancy and suggestion vs evidence of conditioned negative placebo responses (see Barsky et al for a review, look in Side effects file in Lit Review Section). Paragraph below is the start of expectancy & Suggestion bit.

### Experimentally-Conditioned Expectancies

Lastly there are expectancies which are acquired by direct experience but where this experience is acquired during the conditioning phase of laboratory trials. These can be induced without any prior awareness or ignorance of likely outcomes of administration of the drug or treatment, nor need there be any belief in the experimenters trustworthiness, for the unconditioned effects of the drug are paired with the conditioned stimulus over repeated trials/administrations during the experiment. Expectancies conditioned in the lab are typically stronger than those acquired by simple verbal suggestion (Pollo, Carlino, & Benedetti, 2008), and those which have been acquired by first hand experience over a lifetime in naturalistic settings and, of course, stronger than either.

## Chains of Expectancies

Fillmore and Vogel-Sprott (1992) have identified four types of events that are relevant to expectancies: the stimulus accompanying the administration of a drug (S); the stimulus effect of the drug (Sd); the particular effect of the drug on a response (Rd); and the environmental outcome of this effect (S\*). These four events can lead to three sets of expectancies. The first is when the stimulus of administration lead to the expectancy of the drug’s effect (S–S­d). This expectancy is assumed to produce the effects observed in double-blind and balanced placebo studies, where the learned association between, for example, a bottle labeled with a familiar brand of alcoholic beverage, a taste that resembles this beverage, and (therefore) the belief that it *is* this alcoholic beverage lead to an expectancy that the beverage will cause bodily sensations which have been caused by this type of liquor in the past. The second set of expectancies occurs in relation to the connection between the effects of the drug and the responses to those effects (Sd–Rd). Expectancies of this sort are evoked by the past associations of the drug stimuli—the bodily sensations of alcohol in our example—with the behaviour that these sensations have produced (disinhibition, aggression, or sexual arousal in the case of alcohol). Lastly there is the set of expectancies known as response expectancies, between the response to the drug and the environmental outcomes of the behavioural effect of the drug (Rd–S\*). This expectancy is important because if the environmental outcome is desirable (because it leads to some form of catharsis in the case of aggression leading to a fight or sexual arousal leading to coupling) it may increase the incentive to display Rd (Sdao-Jarvie & Vogel-Sprott, 1991). Placebo responses rely on all three of these expectancies occurring in sequence.

# Chapter 2: The Role of Expectancies in Drug Withdrawal

Drugs of abuse also show expectancy effects. For example, expectations of receiving alcohol (Fillmore, Carscadden, & Vogel-Sprott, 1998), THC (Kirk, Doty, & deWit, 1998), Caffeine (Lotshaw, Bradley, & Brooks, 1996), and d-Amphetamine (Mitchell, Laurent, & de Wit, 1996) have all been shown to mimic effects of the drugs themselves.

It has been suggested that many of the effects of the long-term abuse of drugs such as tolerance (Siegel, 2000) and sensitivity (Schenk & Partridge, 1997), may in part be learned responses due to repeated pairings of environmental and/or endogenous affective stimuli with the acute effects of the drugs themselves. Tolerance and withdrawals are hallmark symptoms of drug dependence according to the Diagnostic and Statistical Manual of Mental Disorders (5th Ed.; DSM-V, American Psychiatric Association, 2013) description of substance abuse disorders. Tolerance is a neuroadaptive homeostatic response of the organism to repeated exposures to a substance, whereby the required dose to achieve the same psychophysiological effects increases over time. Tolerance has been shown to be comprised of a significant learned component, shown by the fact that it can be reduced in novel locations and that treatments that retard learning ­- such as Actinomycin D, electroconvulsive shock therapy, and frontal cortical stimulation - also inhibit the development of tolerance (see Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000, for a review). Given that many of the effects of drugs of abuse, including tolerance, have been shown to be sensitive to expectancy manipulations, there is no *a priori* reason why withdrawals should not also have a significant placebo component.

## Drug Withdrawals

Withdrawals are a suite of mostly aversive psychophysiological phenomena that occur upon discontinuation or reduction of dose of a substance that has come to be relied upon for maintaining affective, cognitive and physiological equilibrium. Withdrawal symptoms can be divided into two categories: physical and psychological. Physical withdrawal symptoms are more likely to be specific to particular drugs, begin rapidly upon cessation of drug-taking, generally peak within the first 1-3 days of abstinence, and dissipate within 7-21 days (Hughes, Higgins, & Bickel, 1994). Psychological symptoms on the other hand tend to be common among all drugs of abuse (West & Gossop), and persist considerably longer (Hughes et al. 1994; Martin et al. 1963; Maurer & Vogel, 1967; Goldberg & Schuster, 1969; Gawin & Kleber, 1986; O’Brien et al. 1992). In fact addicts report these withdrawal symptoms as more distressing than physical withdrawal symptoms (Cohen, Klett, & Ling, 1983). These symptoms, such as anxiety, depression, insomnia, irritability, lack of energy, restlessness, decreased appetite, and craving for drugs do not tend to be as salient as physical symptoms during the acute stage of withdrawal (though addicts still rate the level of distress caused by them more highly than clinicians) but are usually much longer lasting. This is born out by the fact that: a) patients on methadone maintenance programs report psychological symptoms as relatively more distressing than physical symptoms (Cohen et al, 1983) and b) most relapses occur well after the physical symptoms have dissipated. Withdrawal symptoms are certainly not the only factor determining duration of abstinence and relapse. Long-term motivational factors, such as commitment to treatment outcome (Miller, 1985), abstinence goal (Elal-Lawrence, Slade, & Dewey, 1987), desire to abstain (Best, 1975), expectation of success (Mothersill, McDowell, & Rosser, 1988), expected difficulty of quitting (Rosen & Shipley, 1983), perceived self-efficacy (Annis & Davis, 1988), and perceived costs and benefits of change (Hall, Rugg, Tunstall, & Jones, 1984) also have been shown to predict successful attempted abstinence. In all likelihood there is an interaction between withdrawal symptoms and motivational goals, particularly during times of significant stress (Benfari & Eaker, 1984; Cronkite & Moos, 1980; Krueger, 1981; Rosenberg, 1983).

## Expectancy and Withdrawals

If expectancies of changes in psychophysiological state, caused by the repeated pairings of environmental stimuli surrounding the administration of a drug with the drug’s pharmacological effects, are enough to cause placebo effects that mimic or augment the active effects of the drug, it also follows that repeated pairings of the stimulus surrounding discontinuation or reduction of a drug with the concomitant withdrawal symptoms could also produce expectancies of withdrawal that lead to placebo withdrawal responses.

The symptoms that follow abstinence are very similar across many different types of drugs: headache, irritability, fatigue, depression, difficulty concentrating. These symptoms are also present in non-medicated, non-addicted persons in everyday life (Reidenberg & Lowenthal, 1968; Khosla, Bajaj, Sharma, & Mishra. 1992). The overlap in symptom profile between abstinent addicts experiencing withdrawal, and normal non-addicted, non-medicated individuals suggests that at least a portion of the withdrawal symptoms reported by abstinent addicts may be the result of the misattribution in the mind of the addict of the vague, incidental physical or psychological symptoms which occur commonly simply as a part of everyday life to withdrawal symptoms. It is expectancy of experiencing these withdrawal symptoms which cause this misattribution.

Solomon and Corbit (1974), in their opponent-process theory of motivation, suggest that drug withdrawals, initially, are a slave process, which can only be evoked indirectly via the absence of the primary process, which is the drug. In time however this slave process, the opponent process, ‘can, under proper conditions, be activated by events in memory, as a consequence of Pavlovian conditioning procedures.’ According to the theory the opponent process—withdrawals in this case—acquire more power if frequently elicited. Applying this idea to withdrawal expectancy we could make predictions such as that addicted individuals who have been addicted longer and who have thus had more experience with withdrawals will have a greater expectancy-induced withdrawal response.

Kleber 1981 (as cited in Phillips, Gossop, & Bradley) cumulative effect of expectancies on withdrawal as pronounced as any pharmacological factors.

Need to go over F& V-S’s model of expectancies in more detail.

If the environmental and verbal/cognitive stimuli surrounding the administration of a drug can be considered S1, which then evokes a chain of expectancies concerning the physiological, behavioural and environmental effects of the drug, then the presence of stimuli signaling the absence or reduction of maintenance dose of the drug can be thought of as S­­2 , a stimulus which signals a different chain of expectancies[[2]](#footnote-2). Thus applying Fillmore and Vogel-Sprott’s (1992) schema above to withdrawals: the absence of the drug (S2) elicits a physical withdrawal response (S2d) which in turn evokes a behavioural response (R2d) and an environmental consequence (S2\*). In case of drug addiction, the behavioural response to the physical discomfort, boredom, depression etc. of withdrawals is to obtain the drug, the environmental consequence of which is relief from withdrawals. The more the process is repeated the stronger, more automatic, less goal-directed and more habitual become the links between these steps, and the more difficult it becomes to break the drug-seeking behaviour. With enough reiterations of this chain of stimulus-response contingencies, the same three sets of expectancies that occur with respect to the presence of the drug (S–Sd: Sd–Rd: Rd–S\*) come to form around its absence. It is the anticipation that the absence of the drug (S2) will lead to withdrawals (S2d)followed by obtaining the drug (R2d)to seek relief that causes the habitual use of drugs that are otherwise detrimental to the wellbeing of the addicted individual. If it is this chain of stimulus and their expected consequences that sustains drug-seeking behaviour then it is possible that altering either the valence of steps (eg. if the environmental consequence of obtaining drugs became considerably more negative to the point where it outweighed the relief caused by eliminating withdrawals) or the degree of automaticity/contingency between the steps (eg. if an alternative method of coping with withdrawals, other than obtaining the drug, became available) could conceivably lead to a change in the behaviour.

The expectancy that one set of stimulus will reliably lead to another is thought to be the cause of placebo responses to drug treatment (Kirsch, 1997). Placebo responses rely on all three of the above expectancy sets occurring in sequence. However it is likely that knowledge of the contingency between S and Sd is not the only association made. It seems probable that when the individual senses the initial stimulus relating to drug administration (S), this causes them not only to anticipate the physical effects of the drug (Sd), but also the behavioural (Rd) and environmental consequences (S\*). This is also most likely true of the absence of the drug. Thus what begins as a slave process, withdrawals, which can only be initiated indirectly by the presence of the primary process, drug use, eventually becomes a conditioned response, able to be elicited in the absence of the drug, by environmental cues or expectancy alone.

Schema theory (see pdf ‘Expectancy and side effects in cancer patients’ in ‘Nocebo\_Side Effects’ folder)

## Evidence for Placebo Withdrawals: Tolerance vs Withdrawal

The notion of conditioned withdrawals is not a new one. There is ample evidence of withdrawal-like conditioned responses, both physiological and psychological, to stimuli that have been paired with drug use in the past. For example men on research wards who have been abstinent for months can experience acute craving and signs of withdrawal, such as goose-flesh, lacrimation, runny nose etc. upon merely seeing another man receive an injection of morphine (Valliant, 1988). (also see Childress, McLellan and O’Brien, 1986 for conditioned withdrawal evidence). In addition, addicts maintained on such high doses of methadone they did not feel the effects of heroin, still reported symptoms of withdrawal when they experienced psychological stress (Dole and Nyswander, 1965). Both these examples show that visual and/or affective triggers can induce cravings and physical withdrawal symptoms in individuals who should not have any physiological reason for feeling them — in Valiant (1988) because they had been abstinent for months and were no longer experiencing physical withdrawals, and in Dole and Nyswander (1965) because they were on a very high dose of methadone.

Not only can withdrawal symptoms be induced by expectancy alone, they can be reduced by the expectancy of receiving the drug needed to relieve them, even if that drug is actually a placebo. Thompson & Schuster (1964) for example, found that withdrawal symptoms of monkeys could be effectively relieved by injections of saline administered in settings where morphine was given in the past. Findings such as the above led Valliant (1988) to suggest that ‘even withdrawal symptoms themselves are not simple physiological responses to the withdrawal of a biologically active substance.’

However a distinction needs to be made between conditioned tolerance and conditioned withdrawal. Conditioned tolerance is a homeostatic/allostatic response that occurs in response to stimuli surrounding the impending *presence* of a drug. It can occur even in the absence of expectancy (in much the same way as the jar of dust in asthmatics) of receiving the drug (e.g. addicts in Childress et al. and Valliant.). There is ample evidence, both in humans and animals, of conditioned tolerance (see Siegel). While O’Brien etc. have written many papers based on what they call conditioned withdrawal in humans what they are likely observing is conditioned tolerance. However perhaps this internally-generated tolerance response itself becomes conditioned to presence of drug-related stimuli, so that over time what initially was a conditioned tolerance response (an unconscious physiological response preparing the body for the impending ingestion of the drug) becomes a expectancy-induced withdrawal response (i.e. over repeated exposures to drug-related stimuli *without a corresponding ingestion of the drug* the conditioned negative withdrawal-like tolerance response becomes an expectancy-induced bona fide expectancy-induced withdrawal response to the presence of drug-stimuli *combined* with the and expectancy of actually recieiving no drug.

Experimental studies dealing with conditioned withdrawal proper (as opposed to conditioned tolerance) have dealt mostly with pharmacologically-induced withdrawal pairing antagonist drugs such as naloxone with compound stimuli (Kenny et al.) Well-run studies in animals have shown good evidence for conditioned withdrawal. Evidence in humans using similar designs has however been hampered by small sample sizes, an understandable problem given the complexities of accessing a sample size of sufficient statistical power in a population of addicted individuals (O’brien et al). Both these studies (O’Brien and Kenny) show that bona fide withdrawal responses can be conditioned to occur in the absence of a pharmacological agent in response to environmental stimuli that had been paired with withdrawals in the past and in organisms who had sufficient drug levels in their system for there to be no physiological reason for withdrawals.

The designs mentioned above tested a conditioned withdrawal response to the presence of a signaling stimuli. If there is such a thing as *in vivo* conditioned withdrawal however, it would have to occur in response to stimuli that signal the impending *absence* of a drug. To prove this would require conditions where participants have a pre-existing expectancy that discontinuation or reduction of dose of a drug will lead to adverse symptoms. The challenge to experimenters who wish to test this notion is that separating the conditioned or expectancy-induced component of withdrawals from the physiological component would require surreptitious reduction or interruption of the dose of a drug in one group of participants, in other words, convincing participants that they are still taking their expected dose of a drug when in fact it has been reduced.

The reason that conditioned tolerance and conditioned withdrawal are confused is that the physiological symptoms of acute withdrawal (e.g. in opiate addiction: lachrymation, rhinorrhea, myoclonus, piloerection, dilation of pupils, craving etc.) strongly resemble conditioned tolerance responses. Tolerance responses however are relatively ephemeral whereas chronic withdrawal can last 6 months or more and is characterized by symptoms that are more psychological in nature: insomnia, depression, anxiety, dysphoria, boredom, irritability. I would argue that real-world expectancy-induced withdrawal responses, if they exist, can only occur in response to cues which signal the *absence* of a drug. (i.e. removing an aversive stimulus – withdrawals - by administering a placebo (i.e. signalling *presence* of a drug) is different to removing aversive withdrawal symptoms by omitting absence of a drug.)

Expectancy

Expectancy

Expectancy

Expectancy

S­2\*

Environmental consequence of drug-seeking: eg. relief from withdrawal but also social/financial problems

S1\*

Environmental consequence of behaviour: eg. violence, sex, criminality, socializing etc.

***Figure 1.* Chain of Expectancies involved in Repeated Drug Taking (adapted from Fillmore and Vogel-Sprott, 1992)**

Expectancy

Expectancy

Expectancy

Expectancy

Expectancy

Expectancy

S1d­

Bodily and Cognitive/Affective effects of drug e.g. euphoria,

R2d

Behavioural response to withdrawals: eg. drug-seeking

R1d

Behavioural response to drug: eg. arousal, disinhibition etc.

S2d

Bodily effects of absence of drug. i.e. withdrawals

Presence of Drug

Absence of Drug

S2

Cues surrounding absence of drug

S1

Cues surrounding administration of drug

Perhaps the ‘placebo’ euphoria etc, observed when people believe they have received a drug (the left arm of the above diagram) is *not* after all a conditioned behavioural response to a conditioned *physiological* reaction (i.e. the chain S+:S+d:R+d) but a conditioned behavioural response to a stimulus (which would be represented by the chain S+:R+d) where the physiological S+d is ‘manufactured’ ad hoc via an over-willingness to be in a ‘high’ state, and therefore an intentional misperception or ‘smudging’ of bodily cues.

Following on from this: perhaps the efficacy of a placebo is enhanced with drugs or dosing regimens whose physical effects are very mild and/or whose target symptomatology is mostly psychological. For example ‘cravings’, though they may have a physiological cause, that is the absence of active drug in the system, do not *manifest* in the perception of the addict as a physical symptom but rather as a ‘strong desire’. Though this desire can be very intense it is easy to imagine how this response, since it has a purely psychological manifestation could be mediated (i.e. either induced or reduced) entirely by expectancy in some cases, whereas more physiological withdrawal symptoms (lachrymation, piloerection, diarrhea) may be much harder to induce by expectancy alone.

Is it possible to condition ‘positive’ physical symptoms of drugs (eg. dilation of eyeballs) in a convincing manner? i.e. behaviourial symptoms may not be convincing evidence for a placebo effect. Surely conditioned ‘positive’ drug effects are ephemeral.

### Open/Hidden Designs

There have been several studies that have looked at the effect that removal of information about timing of dose and magnitude of change of dose have on subjective effects of treatment. This paradigm, known as the open/hidden paradigm can estimate the extent to which expectations of treatment efficacy influence perceived treatment effects over and above direct effects by comparing the DV of interest – in this case withdrawals but it really could be any expected consequence, positive or negative, of treatment – in a group who knows they are receiving a treatment (or treatment change) with a group who do not.

This design can be contrasted with the placebo-controlled trial, which attempts to isolate the effects expectancy have on treatment outcome by comparing a group who receive active treatment with a group who think they are receiving an active treatment but who are actually receiving an inert substance. Placebo-controlled trials measure psychological effects in the absence of the active treatment whereas open/hidden paradigms measure treatment effects in the absence of psychological effects (see Figure 1). Furthermore most placebo-controlled trials do not measure expectancy effects accurately because they do not contain a no-treatment group, which allows for the effects of natural history upon treatment outcome to be compared against placebo effects (Hróbjartsson & Gøtzsche, 2001).

|  |  |  |  |
| --- | --- | --- | --- |
|  | In Clinical and Commercial Setting | Placebo Arm of Placebo-Controlled Trial | Hidden Arm of open-hidden Design |
| Expectation About Drug | ✓ | ✓ |  |
| Active Effects of Drug | ✓ |  | ✓ |

***Figure 2. Combination of Expectancy and Active Effects of Drug in Different Settings***

***(based on Benedetti, Carlino, & Pollo, 2011)***

Benedetti et al., (2003) showed that perceived postoperative pain increased less following interruption of morphine delivery in patients who were not informed about the interruption compared with those who were informed. The same result was shown for perceived anxiety in patients who were informed their diazepam was interrupted vs those who were not.

  
 ***Figure 2. Open vs Hidden Interruption of Morphine and Diazepam (from Benedetti et al., 2003)***

## The Central Questions

The central questions of this thesis are:

1. Do people addicted to a drug and coming off it suffer lower withdrawal symptoms if they are unaware they are coming off it than people who are aware.
2. Related to the first question, might it be easier for people to quit a drug if their dose is tapered without their knowledge
3. Does uncertainty about dose result in more or less withdrawal relative to certainty about a false maintenance schedule?

## Caffeine as Model of Processes of Addiction

## Blah de blah caffeine a good drug for modeling addiction. All experiments in this PhD are on caffeine. Good to use because

1. 90% of population (hence not underpowered)
2. Ethical problems with deceptive administration or discontinuation of a class-A drug (which is only way to truly measure placebo effects
3. Most caffeine users are not seeking to quit so in a sense you can study pure withdrawals uncorrupted by the self-deception that accompanies quit attempts (e.g. ‘no I’m not feeling bad, I feel great’ )

# Chapter 3

## Experiment 1

Attempting to establish if caffeine withdrawal can be manipulated by information alone.

Attempting to establish if manipulating information about whether they have received caffeine or not can alter the way individuals addicted to caffeine perceive their withdrawal symptoms.

# Chapter 4

## Experiment 2

Replication of experiment 1 with more salient prime.

# Chapter 5

## Treatment of Addiction with Drug Replacement Regimens

There are many ways of treating addiction to drugs of abuse: counseling or psychotherapy; non-profit fellowship societies such as Narcotics Anonymous or Alcoholics Anonymous; total ‘cold turkey’ abstinence, either unsupervised or in an inpatient rehabilitation facility; or pharmacological drug replacement/maintenance therapies. Drug replacement therapies involve controlled administration of either an agonist or the drug itself but in a different form. For example heroin addicts are given methadone or buprenorphine orally instead of injecting and nicotine addicts are given nicotine gum, patches or nasal spray instead of smoking. Drug maintenance/replacement therapies allow the patient to focus on coping with the sudden discontinuation of the habitual behaviours, emotions, and cognitions surrounding their drug dependence without having to deal with the physical withdrawal symptoms. When a stable maintenance dose has been achieved the patient can either discontinue use of the replacement therapy completely, which once again is likely to induce a withdrawal response, or a reduction regimen can begin. Reduction regimens involve the replacement dose being reduced in discrete stages down to a zero dose.

If the increase in pain following interruption of morphine can be seen as a related phenomenon to the onset of withdrawal symptoms following the discontinuation or reduction of the normal dose of a drug in an addicted individual, then, based on Benedetti et al. (2003), there does seem to be some grounds for expecting that removal of information concerning the timing and magnitude of dose reduction may serve to ameliorate subjective withdrawal symptoms in addicted individuals on a drug-reduction regimen.

If withdrawal symptoms, whether physical or psychological, relate directly to likelihood of relapse, and if placebo withdrawal symptoms contribute to total perceived withdrawal symptoms over and above actual withdrawals, then any intervention that can minimise placebo withdrawal symptoms in patients on a drug reduction regimen may help to reduce subjective distress and the likelihood of relapse.

In long-term, dependent drug users a discontinuation or reduction of dose will have been paired many times in the past with aversive physical and psychological withdrawal symptoms. Thus any cues that suggest such a discontinuation or reduction should produce an expectancy of aversive withdrawal symptoms and a concomitant placebo withdrawal response. Removing all cues that may allow the generation of such an expectancy should therefore also remove the placebo withdrawal response that follows. These cues can be perceptual (such as the size/shape/volume/colour/taste of the vehicle), environmental (the location where the drug is administered/purchased, the identity of the administrator/vendor of the drug) or verbal. Arguably the most important of these in drug reduction/maintenance regimens is the verbal information concerning the dose, supplied by the doctor, pharmacist or on the packaging (if it is a commercially available, over-the-counter replacement therapy).

## Hypotheses

Hypothesis one is that by removing information concerning the schedule and magnitude of dose titrations, and by masking any changes in the physical attributes of the vehicle following dose reduction, it should be possible to eliminate the placebo component of subjective withdrawal symptoms in drug reduction regimens, thereby reducing total withdrawal symptoms and potentially preventing relapse.

Hypothesis two is that if it is conditioning that leads to a placebo response then the placebo withdrawal response should be more pronounced in individuals who have been drug dependent for longer and/or who have attempted to quit on more occasions prior to the trial.

## Experiment 3: Proposed Drug Reduction Intervention

The experimental design by which we propose to test hypothesis one and two will be a one way, between-subjects design with an open/hidden manipulation. There will be four levels of the independent variable Reduction Condition. The dependent variables will be subjective ratings of both physical and psychological withdrawal symptoms, number of cigarettes smoked, and duration of abstinence both during and subsequent to the reduction intervention comprised by the study. In order to assess hypothesis two, a classification variable will be included: Number of Previous Quit Attempts. The vehicle will be the same in all physical/perceptual characteristics regardless of dose.

***Conditions/Instruction/Consent***

For the conditions where dose is being reduced there will be a fixed titration period. Withdrawal symptom inventories will be completed at the beginning and halfway through each titration period for all conditions. Ss in the no reduction conditions will go from full dose (same throughout the study) to no dose/no vehicle on the day after the last day of the test period. Prior to random allocation Ss will be informed that they are taking part in a study designed to assess the effects of knowledge and dosing schedule on withdrawal symptoms. They will be asked to give consent to having information about their dosing schedule withheld if need be.

*Blind Reduction*: Ss actual dose will be reduced at the beginning of each titration but they will not be given any information about the timing or magnitude of dose reduction. Ss in the Blind Reduction condition will be told that their dose will be reduced but that they will not know when. This is important since this condition represents the particular expectancy conditions that would be present were this regimen to be made available to addicted individuals in a real-world setting, i.e. the participant wishes to enroll in a drug replacement-therapy reduction regimen and thus wishes to reduce their dose gradually, but gives their consent to have the information about when or by how much their dose will be reduced withheld in order to minimise withdrawal symptoms.

*Informed Reduction/Reduction*: Ss dose will be reduced at the beginning of each titration period and Ss will be informed when and by how much.

*Informed Reduction/No Reduction:* Ss will be informed that their doses are being reduced but their actual dose will not be reduced.

*Informed No Reduction/No Reduction:* Ss will be informed that their dose is being maintained at the same level across the entire study and their actual dose will not be reduced.

A balanced placebo version of this design would consist of, instead of a Blind Reduction condition, actually generating an expectancy of no dose-reduction, while surreptitiously titrating dose. However theoretically interesting this situation is it has little external validity. The goal of this experiment is to model a possible real-world intervention that could minimise withdrawals in a drug-replacement therapy dose-reduction regimen. There is no real-world situation that can be envisaged visage where a person would enroll in a drug-replacement dose-reduction regimen with a view to eventual discontinuation while not expecting that their dose is actually being reduced. Therefore, rather than generating an expectancy of no dose-reduction-related withdrawals, participants in the Bind Reduction condition will have a *general* expectation of dose-reduction but will receive no information concerning the timing or magnitude of withdrawals.

**Experiment 1: Brief Proof of Concept Study Using Nicotine Patches**

The above design, which could in theory apply to any drug of abuse, will be tested first on smokers who wish to quit smoking using nicotine patches as nicotine replacement therapy.

Transdermal nicotine patches have been shown to be effective at aiding smoking cessation (Stapleton et al., 1995; Shiffman, Ferguson, Gwaltney, Balabanis, & Shadel, 2006).

Withdrawal symptoms are a significant predictor of relapse to smoking (West, Hajek, & Belcher, 1989; Piasecki et al., 2000; Shiffman et al., 1997a, Killen & Fortmann 1997; Patten & Martin, 1996). Physical withdrawal symptoms include decreased adrenaline, cortisol, heart rate, orthostasis, thyroid function and tremor and increased taste for sweets, metabolic rate, weight and slowing of the EEG. Psychological symptoms include anxiety, craving for cigarettes, depression, irritability, restlessness, difficulty concentrating, hunger and nocturnal awakenings. These symptoms are highly reproducible, observable by others, and can be clinically significant (Hughes, 1992a; Hughes & Hatsukami, 1987). Cravings for cigarettes are generally held to be the most salient of the nicotine withdrawal symptoms and the most significant predictors of relapse (West & Schneider, 1987; Russell, 1988) and can continue up to 6 months after the acute physical symptoms have disappeared (Hughes et al., 1994), however their subjective nature has led to confusion about whether they can be considered a physical or a psychological symptom of abstinence.

However in order to prove that removal of the opportunity to anticipate the precise timing or magnitude of a withdrawal response can ameliorate subjective withdrawal symptoms, and that this concept can apply to smoking and transdermal nicotine patches, it is first necessary to prove that expectancies regarding timing of onset of nicotine replacement alone are enough to affect withdrawal symptoms in a group of medium to heavy smokers given placebo drug replacement therapy compared to a no-treatment group. Several studies have shown that expectancies about nicotine can influence therapeutic outcome.

Juliano and Brandon (2002) used a balanced placebo design to assess the effects of nicotine and instructional set on anxiety reduction in smokers given either nicotine or de-nicotinised cigarettes. They found that being instructed that the cigarette had nicotine in it produced a pronounced anxiolytic effect in those who believed that nicotine reduced anxiety and not in those who didn’t. In addition they found that urge to smoke/cravings were significantly lower in the group who were told they had smoked a nicotinised cigarette, regardless of whether they had actually smoked on or not. Balanced placebo designs are more powerful than placebo-controlled designs as they allow the separation of expectancy effects from effects due to active treatment effects. Dar, Stronguin and Etter (2005) also used a balanced placebo design, measuring reduction in cigarette consumption in smokers on either nicotine gum, patches or inhaler, and found that subjects who believed they had received active treatment had larger reductions in cigarette consumption than those who believed they had received placebo regardless of whether they had received active treatment or not. Bailey, Fong, Bryson, Fortmann, and Killen (2010) compared the assignment beliefs of those participants in a nicotine patch dose-reduction regimen with a group receiving equivalent placebo patches and found that those who believed they had received active avoided relapse for longer than those who believed they had received placebo, regardless of actual assignment condition (see Figure 3). This was not true of abstinence status at 12 months, where assignment beliefs predicted abstinence in only the active patch group. Lastly Gottlieb, Killen, Marlatt & Taylor, 1987, found, using a balanced placebo design, that expectation of receiving nicotine gum predicted significant decreases in physical symptoms and less smoking in the first week after quitting, and that, compared with the effects of expectancy, the *actual* gum that subjects received, either nicotine or placebo, seemed to have no effect on either withdrawal symptoms or smoking behavior. Thus there seems to be grounds for the hypothesis that the expectancy that a nicotine replacement therapy will ameliorate nicotine withdrawal symptoms is enough to produce a reduction in these withdrawal symptoms even in the absence of actual nicotine.



***Figure 3. Time to Relapse Based on Belief of Treatment Assignment and Actual Assignment (from Bailey et al., 2010)***

**Design**

This will be a one-way, between-subjects design designed to test whether instructions regarding the timing of onset of active nicotine dose in a transdermal nicotine patch are enough on their own to affect both level and timing of withdrawal symptoms in a sample of heavy smokers. There will be three levels of the independent variable Dose: Fast-Dose (told is fast acting), Low-Dose (told is slow acting) and No-Dose (given no patch). Dependent variable will be withdrawal symptoms, measured using the Withdrawal Rating Form (Shiffman & Jarvik, 1976). This is a 25-item self-report measure of smoking withdrawal symptomatology with five subscales: Craving, Psychological Discomfort, Stimulation/Sedation, Physical Symptoms and Appetite. In addition subjects will be asked to rate how long after the administration of the patch their withdrawal symptoms began to reduce. In order to assess whether subjects’ beliefs mediated the effect of the patches on perceived withdrawal symptoms, subjects will be asked, upon completion of the 24-hour abstinence period, whether they believed a) they were assigned a placebo or an active patch, b) whether they were assigned a fast-or slow-acting patch. In addition to the experimental manipulation, a classification variable will be included: number of previous attempts to quit.

**Hypotheses**

If expectancy alone can generate a placebo withdrawal-reduction effect then we would anticipate that an expectation of a fast-acting withdrawal-reduction effect will lead to faster onset of withdrawal reduction than expectation of a slow-acting withdrawal effect. Thus the hypothesis of this study is that subjective cravings and withdrawals will begin to reduce faster in the fast-dose group, followed by the slow-dose and no-treatment group.

It is also hypothesised that number of previous attempts to quit will positively correlate with placebo reduction of withdrawal symptoms.

**Consent**

Since it is an expectancy manipulation, in an effort to simulate real-world conditions (where individuals on patches do not doubt that they have bought a genuine product with active pharmacological ingredients) subjects in the two patch conditions will not be told that there is a chance that they will been given placebo patches without their knowledge. Given that the trial is only 24-hours and that the sample will be heavy smokers rather than abstinent ex-smokers (and thus that there is no chance of causing relapse) we would expect minimal harm resulting from this deception.

**Subjects**

Subjects will be recruited from the undergraduate pool and from ads taken out in newspapers and local suburban street press. In order that a marked withdrawal response can be induced upon commencement of abstinence, only heavy, dependent smokers (i.e. those who smoke within 30 min of waking and > 10 medium-to-high dose cigarettes per day) will be admitted to the study. Subjects will be reimbursed for travel expenses and will be provided with patches free of charge. Subjects will be excluded if they: 1) are experiencing severe cardiovascular disease, hypertension, or diabetes; 2) are currently on psychotropic medication; 3) are pregnant or breastfeeding; 4) are suffering from chronic dermatological disorders; 5) have a history of moderate to severe allergies; 6) have been on nicotine replacement therapy of any kind in the 3 months prior to commencement of the study; 7) are regular users of marijuana or other illegal drugs; 8) are currently prescribed or are taking anti-depressants. Carbon Monoxide Meters will be used to verify both extent of dependence (i.e. level of daily use prior to testing) and whether abstinence during test phase has been maintained.

**Procedure**

Once admitted to the study subjects will be asked how many times previous to admission to the study they had attempted to quit smoking. Subjects will be told that the study is a placebo-controlled trial intended to test the precise time of onset of a new fast-acting transdermal nicotine patch. They will be told that they may be allocated to the new fast-acting patch or to a normal slower-acting patch or to no-treatment. If asked about expected time on onset subjects will be told the new patch begins to work within 3-4 hours and the old patch within 6-12 hours of administration. Subjects will then be randomly allocated one of the three conditions and will be supervised administering the patches to the lower back. Upon administration of the patches will be asked to abstain from smoking for 24 hours and will be allowed to leave. Subjects will return the next day and complete the Smoking Withdrawal Questionnaire (Shiffmann & Jarvik, 1976) to assess their symptoms over the previous 24 hours. Subjects will also be asked to rate how long after applying the patch their withdrawal symptoms began to abate.

**Statistical Analyses**

A two-way ANOVA will be performed on the data from the self-report measures of withdrawal symptoms. Treatment Group will be the first independent variable, with three conditions: Fast-Dose, Slow-Dose and No-Dose. Number of previous attempts to come off methadone will be the second independent variable, a two-level classification variable where subjects are classified into two groups: those who are attempting to quit for the first time (the first-attempt group) and those who have attempted to quit one or more times in the past (the one or more attempt group).

Planned Contrasts will be performed on the self-report data both for the main effects of each independent variable and for interactions between independent variables.

**Experiment 2 : Patch-based Nicotine Replacement Reduction Regimen**

The design for Experiment 2 will be as outlined under the heading ‘Proposed Drug Reduction Intervention’ above.As with Experiment 1, the drug will be nicotine and the method of dose reduction will be via transdermal nicotine patches. Exclusion and inclusion criteria, recruitment method, dependent variables and statistical analyses will be the same as in Experiment 1.

**Procedure**

Once allocated to condition subjects will be instructed that they are taking part in a 31-day trial testing the efficacy of different dosing schedules in minimising withdrawal symptoms on a transdermal nicotine-patch replacement therapy intervention. Before giving consent subjects will be told that they may have information about the dosage of their patch withheld during this trial, but that over the course of the trial period they will go from a high-dose patch at the beginning to no patch when the study is completed. They will be asked to return to the university to collect their nicotine patches twice each week where they will also be asked to complete a Withdrawal Rating Form (Shiffman & Jarvik, 1976).

Patches of different strength, including 0-mg placebo patches, will be the same size, shape and colour, i.e. with no inherent indication that the dose has changed. For each condition, save for the blind reduction and delayed reduction condition, patches will be labeled with the actual mg dose. The delayed reduction condition will have half their patches labeled correctly and half incorrectly for each 7-day titration period (see Table 1). Any subjects not randomly assigned to the Blind Reduction Condition will be given the option to complete this reduction regimen free of charge upon completion of the trial. At the end of 28 days, the blind reduction condition will be informed that they have actually been on 0-mg dose patch for a week. The reduction as usual condition will already be aware of this. The no treatment condition will simply discontinue patches. The delayed reduction condition’s patch will say 0-mg accurately for the last 3 days of the study. The reduction as usual and blind reduction conditions will be encouraged to wear the 0-mg labeled patches for the final week for the validity of the study.

For reduction conditions there will be a fixed 7-day titration period. Withdrawal symptom inventories will be completed at the beginning and halfway through each titration period for all conditions.

*Blind Reduction*: Ss actual dose will be reduced at the beginning of each 7-day titration but they will not be given any information about the timing or magnitude of dose reduction. Ss in the Blind Reduction condition will be told that their dose will be reduced but that they will not know when. This is important since this condition represents the particular expectancy conditions that would be present were this regimen to be made available to addicted individuals in a real-world setting, i.e. the participant wishes to enroll in a drug replacement-therapy reduction regimen and thus wishes to reduce their dose gradually, but gives their consent to have the information about when or by how much their dose will be reduced withheld in order to minimise withdrawal symptoms.

*Informed Reduction/Reduction*: Ss dose will be reduced at the beginning of each titration period and Ss will be informed when and by how much.

*Informed Reduction/No Reduction:* Ss will be informed that their doses are being reduced but their actual dose will not be reduced.

*Informed No Reduction/No Reduction:* Ss will be informed that their dose is being maintained at the same level across the entire study and their actual dose will not be reduced.

**Table 1. Reduction Schedule by Condition for Nicotine Patch Reduction Intervention**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Dose | | | |
|  | Blind/No Reduction | False Informed | Informed Reduction | Blind Reduction |
| Day 1 | 21 | 21(21) | 21 | 21 |
| Day 8 | 21 | 21(14) | 14 | 14 |
| Day 15 | 21 | 21(7) | 7 | 7 |
| Day 22 | 21 | 21(0) | 0 | 0 |
| Day 28 | End | End | End | End |

*Note: Numbers refer to mgs of nicotine in each 16-h patch. Numbers in brackets refer to mg indicated on the patch itself.*

**Randomised Dosing**

So that there is no opportunity in the delayed and blind reduction conditions to ascertain, and hence anticipate, withdrawals, actual dose reduction will occur on one day randomly during a ‘window’, on or around the middle of each titration period. Thus, despite each individual titration period being marginally longer or shorter depending on which day within the window the actual dose reduction occurs, duration of titration periods in the delayed and blind reduction conditions will be the same on average across the study as the reduction as usual and no treatment conditions.

**Follow-up**

Follow-up interviews will be sought, at 3, 6 and 12 months from the trial, to determine whether group had any effect on the duration of abstinence.

**Final Paragraph: Demystification of the Substance**

If the main variables that sustain addiction and prompt relapse are psychological rather than physiological, it is possible then that the mechanism by which drug replacement therapies work is by providing the individual with the knowledge that they have ingested the substance they are addicted to. The fact that cravings and psychological withdrawal symptoms persist even on a drug replacement therapy is testament to this. It is likely that addicts engage in a type of mystification or overestimation of the role the substance plays in their addiction, and an underestimation of the psychological factors (learning, motivation, identity).

The subjects in the Hidden/Reduction condition will be told on day 29, the no-patch day, that they have actually been on a placebo patch for 7 days. If it appears on follow-up that this condition abstains from smoking reliably longer, then we would suggest that perhaps, by learning that they have been on 0 mg dose for 7 days, and thus that the relative absence of withdrawals they experienced during this week were not due to the active pharmacodynamic effects of the drug but rather to the expectancy of the absence of withdrawals, they learned that their withdrawals were to a large extent ‘in their head’. It could be that in some sense the knowledge that long-term withdrawal symptoms are mostly ‘in the head’ may be personally empowering, because not only do they realise that the *substance* is not as responsible for their withdrawals as they thought, but that their withdrawals are due mostly to the discontinuation of a habitual routine that is or was cherished and ego syntonic. By showing patients that their addiction is more psychological than physical it may help them to understand that overcoming their addiction is dependent more on establishing new routines, forming new goals, and learning how to find pleasure in other areas, than in their body slowly being weaned off a particular type of molecule.

Stimulus generation and chaining. Tolerance feels similar to withdrawal. Therefore conditioned tolerance response is interpreted as withdrawal, causes anxiety, which is itself a withdrawal symptom, which causes further anxiety (feedback loop), which chains to an avoidance/relapse response. Associative sydtem is agnostic to cause of negative affect, therefore even after chronic withdrawal has passed, a sufficient ‘threshold charge’ of non-drug-related negative affect serves as an interoceptive cue which chains to an avoidance response (i.e. relapse) via hot processing etc.

Stimulus generalization accounts for relapse in tapered dose reduction. 1) causally-ambiguous physical symptoms interpreted/generalized as withdrawals which then chain to response expectancies (culminating in avoidance/relapse response). 2) causally ambiguous affective symptoms also interpreted/generalized as withdrawals which also chain to response expectancies (note: these ambiguous affective symptoms can be the anxiety caused by the expectancy of withdrawals caused by the physical symptoms in 1) or merely just the knowledge that dose of drug has not been ingested and therefore that withdrawals are impending (i.e. this can happen even before any directly withdrawal related negative affect has occurred).

Placebo repsonses come about by two means a) stimulus generalization (i.e. unconsciously and/or consciously conditioned response brought about by stimulus that is similar enough to familiar stimulus to cause a conscious or unconscious expectancy of that familiar response; b) Humans’ ability to decontextualize abstract associations between stimulus and expected response and superimpose these onto novel or ambiguous stimuli (i.e. is unfamiliar but that we nevertheless have sufficient reason to believe will cause a similar response to familiar stimuli) is responsible for placebo effects.

Expectancies sustain drug addiction in that anticipated negative affect and anticipated inability to cope with it, prevent learning that withdrawal a) is not as bad as anticipated b) can be endured and c) will reduce in intensity over time. Panic disorder is a model of how avoidance and expectancy exacerbate and intensify the symptom being avoided.

# Discussion

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1. For example it is traditionally very difficult to implant expectancies concerning effects of alcohol consumption which run contrary to established effects since most participants are very familiar with the effects of alcohol consumption (reference, Rohsenow???) [↑](#footnote-ref-1)
2. Absence and presence of drug should be thought of as S1 and S2 rather than S+ and S–. S+ is a symbol for presence of a particular stimulus. S– is a symbol for absence of S+ as well as *any other* stimuli (Konorsky????) [↑](#footnote-ref-2)