PhD Thesis

Llew Mills

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

**Table of Contents**

The Role of Expectancies in Drug Withdrawal 4

Expectancies 4

The Placebo Effect 5

Sources of Placebo Effects: Expectancy, Conditioning, Response Shift or Demand Characteristics? 7

Expectancy vs Conditioning: Need there be a debate? 19

Other explanations of placebo effects 22

Response Shift: Demand Characteristics (delusion, contextual responding, impression management) Interoceptive smudging (assimilation), misattribution (symptomatic overlap, attentional shift, windfarms etc.) 23

Sources of Expectancies 26

Verbally-Induced Expectancies 26

Expectancies Acquired from Personal Experience 28

Experimentally-Conditioned Expectancies 29

Chains of Expectancies 30

Drugs of Abuse 31

Drug Withdrawals 31

Expectancy and Withdrawals 33

Evidence for Placebo Withdrawals: Tolerance vs Withdrawal 36

Open/Hidden Designs 42

Caffeine as Model of Processes of Addiction 44

Blah de blah caffeine a good drug for modeling addiction. All experiments in this PhD are on caffeine. Good to use because 44

Chapter 2 44

Experiment 1 44

Chapter 3 44

Experiment 2 44

Chapter 4 44

Treatment of Addiction with Drug Replacement Regimens 45

Hypotheses 46

Experiment 3: Proposed Drug Reduction Intervention 47

Discussion 60

References 61

# The Role of Expectancies in Drug Withdrawal

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 & 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 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, Conditioning, Response Shift or Demand Characteristics?

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 section 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

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; Voudouris et al., 1985), but Kirsch argues that both conditioning procedures and verbal instruction generate expectancies, but that 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 distinguish 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 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 as it stands.

Kirsch suggests that “the occurrence of a subjective experience may be an immediate consequence of its expectation.” (Kirsch, 1999, p179). 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, or how anticipation of pain relief might *directly* relieve pain. He does not identify a neurological, neurochemical or physiological mechanism that may be responsible for the implementation of these direct effects. Kirsch offers evidence for the immediacy hypothesis in findings where placebos have produced physiological changes, such as bronchioconstriction in response to instruction about placebo asthma medication (Butler & Steptoe, 1986) or penile tumescence in response to placebo alcohol (Briddell & Wilson, 1976). However penile tumescence and asthma attacks (Lehrer, Isenberg, & Hochron, 1993) are both physiological conditions 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.

*Problems with Expectancy Model*

1. **Contradiction between animal conditioned effects and human expectancy effects.** As mentioned above placebo effects in humans tend not to be in opposition to unconditioned drug effects whereas animals tend to show conditioned responses that oppose the unconditioned response (i.e. conditioned tolerance; a form of allostatic response). This would suggesteither that humans are incapable of being conditioned *or* that the same drug works on different arms of the nociceptive system in humans vs rodents. Both of these are unlikely given the similarities in human and rodent central nervous systems. Kirsch does not assert either of these positions, instead explaining the 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, 1999, 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. All expectancies mean is that the rodent is able to learn the relations between events and hold beliefs about the predictive value of the CS. Even behaviourists would be unwilling to assert these days that rats learning is *entirely*  unconscious.
2. **Dissociation between physiological markers and subjective symptoms in humans**

If the immediacy hypothesis holds then expectancies should produce changes in physiological markers that match the changes in the concomitant subjective states. Instead many studies show the opposite, a marked dissociation between objective and subjective symptoms.

1. **How does the immediacy hypothesis work?** Kirsch’s immediacy hypothesisis based on the fact that the full range of placebo responses cannot be explained by mediating variables. However this is an assertion that is difficult to prove empirically. He also cites the fact that some studies have shown physiological changes that were brought about by instruction. However these studies either concerned variables that have been shown to be mediated by psychological variables or have failed to be replicated.
2. **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 stipulate what the conditioned response to that response consists of.

## 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.

Classical conditioning can lead to learning which is entirely unconscious and free of expectancy. There are rare examples of placebo effects in the absence of awareness. For example Benedetti et al. (1998) were able to induce a placebo respiratory depression response 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 perception this result would seem to indicate a completely unconsciously mediated placebo response. Such examples are rare however.

Classically conditioned learning can contain elements of both unconscious conditioning and conscious expectancy. 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, Lyons, Bleecker, & McFadden, 1968). 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.

Verbal information on the other hand must *always* result in conscious expectancies. 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 lead 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 (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 responseis 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.

Modern accounts of placebo effects tend not to emphasise the differences between placebo effects caused by conditioning and those brought about by expectancy. Conditioning can sometimes occur independent of expectancy or it can result in the formation of expectancy. In other words it is likely that in most cases conditioning and conscious expectancy mediate placebo effects.

## Other explanations of placebo effects

Four possible explanations for placebo effects.

a) 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.

## Drugs of Abuse

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)***

## 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 2

## 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 3

## Experiment 2

Replication of experiment 1 with more salient prime.

# Chapter 4

## 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

# References

American Psychiatric Association. (2013). Diagnostic ans statistical manual of mental disorders (5th Ed.). Washiington DC: Author.

Ader, R., Cohen, N., & Bovbjerg, D. (1982). Conditioned suppression of humoral immunity in the rat. *Journal of Comparative and Physiological Psychology, 96,* 517-521.

Annis, H. M., & Davis, C. S. (1988). Assessment of expectancies. In D. M. Donovan & G. A. Marlatt (Eds.), *Assessment of addictive behaviors* (pp. 84-111). New York: Guilford Press.

Benedetti, F., Amanzio, M., Baldi, S., Casadio, C., Cavallo, A.,…Mancuso, M. (1998). The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. *Pain, 75,* 313– 319.

Benedetti, F., Carlino, E., & Pollo, A. (2011). Hidden administration of drugs. *Clinical Pharmacology and Therapeutics, 90,* 651-661.

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero….Pollo, A. (2003). Open vs hidden medical treatments: The patient’s knowledge about a therapy affects therapeutic outcome. *Prevention & Treatment, 6,* 1-20.

Benfari, R. C., & Eaker, E. (1984). Cigarette smoking outcomes at four years of follow-up, psychosocial factors, and reactions to group intervention. *Journal of Clinical Psychology, 40,* 1089-1097.

Best, J.A. (1975). Tailoring smoking withdrawal procedures to personality and motivational differences. *Journal of Consulting and Clinical Psychology, 43,* 1-8.

Bolles, R.C. (1972). Reinforcement, expectancy, and learning. *Psychological Revue, 79,* 394-409.

Butler, C., & Steptoe, A. (1986). Placebo responses: An experimental study of psychophysiological processes in asthmatic volunteers. *British Journal of Clinical Psychology, 25,* 173-183.

Colagiuri, B., McGuinness, K., Boakes, R.A., & Butow, P.N. (2012). Warning about side-effects can increase their occurrence: An experimental model using placebo treatment for sleep difficulty. *Journal of Psychopharmacology, 26,* 1540-1547.

Cronkite, R. C., & Moos, R. H. (1980). Determinants of the post-treatment functioning of alcoholic patients: A conceptual framework. *Journal of Consulting and Clinical Psychology, 48,* 305-316.

Dar, R., Stronguin, F., & Etter, J. (2005). Assigned versus placebo effects in nicotine replacement therapy for smoking reduction in swiss smokers. *Journal of Consulting and Clinical Psychology, 73,* 350-353.

Dekker, E., & Groen, J. (1959). Reproducible psychogenic effects of asthma. *Journal of Psychosomatic Research, 1,* 58-67.

Elal-Lawrence, G., Slade, P.D., & Dewey, M.E. (1987). Treatment and follow-up variables discriminating abstainers, controlled drinkers and relapsers. *Journal of Studies on Alcohol, 48,* 39-46.

Fillmore, M. T., Carscadden, J. L., & Vogel-Sprott, M (1998). Alcohol, cognitive impairment, and expectancies. *Journal of Studies on Alcohol, 59*, 174–179.

Fillmore, M., & Vogel-Sprott, M. (1992). Expected effects of caffeine on motor performance predicts the type of response to placebo. *Psychopharmacology, 106,* 209-214.

Flaten, M. A. (1998). Information about drug effects modifies arousal: An investigation of the placebo response. *Nordic Journal of Psychiatry, 52,* 147–151.

Gottlieb, A.M., Killen, J.D., Marlatt, G.A., & Taylor, C.B. (1987). Psychological and pharmacological Influences in cigarette smoking withdrawal: Effects of nicotine gum and expectancy on smoking withdrawal symptoms and relapse. *Journal of Consulting and Clinical Psychology, 55,* 606-608.

Hall, S.M., Rugg, D., Tunstall, C., & Jones, R.T. (1984). Preventing relapse to cigarette smoking. *Journal of Consulting and Clinical Psychology, 52,* 372-382.

Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine, 344,* 1594–1602.

Hughes, J.R., Higgins, S.T., & Bickel, W.K. (1994). Nicotine Withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction, 89,* 1461-1470.

Hughes, J.R. (1992a) Tobacco withdrawal in self- quitters. *Journal of Consulting and Clinical Psychology, 60,* 689-697

Hughes, J.R. & Hatsukami, D.K. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry, 43,* 289-294.

Juliano, L.M., & Brandon, T.H. (2002). Effects of nicotine dose, instructional set, and outcome expectancies of the subjective effects of smoking in the presence of a stressor. *Journal of Abnormal Psychology, 111,* 88-97.

Kenny, P.J., Chen, S.A., Kitamura, O., Markou, A., & Koob, G.F. (2006). Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. *The Journal of Neuroscience, 26,* 5894-5900.

Killen, J.D., & Fortmann, S.P. (1997) Craving is associated with smoking relapse: findings from three prospective studies. *Experimental and Clinical Psychopharmacology 5*, 137–142.

Kirk, J. M., Doty, P., & deWit, H. (1998). Effects of expectancies on subjective responses to oral delta-9 tetrahydrocannabinol. *Pharmacology, Biochemistry, & Behavior, 59*, 287–293.

Kirsch, I., & Weixel, L.J. (1988). Double-blind vs deceptive administration of a placebo. *Behavioural Neuroscience, 102,* 319-323.

Krueger, D. W.(1981). Stressful life events and the return to heroin use. *Journal of Human Stress, 7,* 3-8.

Lotshaw, S. C., Bradley, J. R., & Brooks, L. R. (1996). Illustrating caffeine’s pharmacological and expectancy effects utilizing a balanced placebo design. *Journal of Drug Education, 26*, 13–24.

Luparello, T.J., Lyons, H.A., Bleecker, E.R., & McFadden, E.R. Jr. (1968). Influences of airway reactivity in asthmatic subjects. *Psychosomatic Medicine, 31,* 819-825.

Miller, W. R. (1985). Motivation for treatment: A review with special emphasis on alcoholism. *Psychological Bulletin, 98,* 84-107.

Mitchell, S. H., Laurent, C. L., & deWit, H. (1996). Interaction of expectancy and the pharmacological effects of d-amphetamine: Subjective effects and self-administration. *Psychopharmacology, 125*, 371–378.

Mitchell, C.J., De Houwer, J., & Lovibond, P.F. (2009). The propositional nature of human associative learning. *Behavioural and Brain Sciences, 32,* 183-246.

Mothersill, K. J., McDowell, I., & Rosser, W. (1988). Subject characteristics and long term post-program smoking cessation. *Addictive Behaviors, 13,* 29-36.

Patten, C.A., & Martin, J.E. (1996) Does nicotine withdrawal affect smoking cessation? Clinical and theoretical issues. *Annals of Behavioural Medicine 18*, 190–200.

Piasecki, T.M., Niaura, R., Shadel, W.G., Abrams, D., Goldstein, M., Fiore MC,…Baker, T.B. (2000). Smoking withdrawal dynamics in unaided quitters. *Journal of Abnormal Psychology,* *109,* 74–86.

Pollo, A., Torro, E., Lopiano, L., Rizzone, M., Lanotte, M., Cavanna, A….Benedetti, F. (2002). Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *Cognitive Neuroscience and Neuropsychology, 13,* 1383-1386.

Rescorla, R.A. (1987). A Pavlovian analysis of goal-directed behaviour. *American Psychologist, 42,* 119-129.

Rescorla, R.A. (1988). Pavlovian Conditioning: It’s not what you think it is. *American Psychologist, 43,* 151-160.

Rosen, T.J., & Shipley, R.H. (1983). A stage analysis of self-initiated smoking reductions. *Addictive Behaviors, 8,* 263-272.

Rosenberg, H. (1983). Relapsed versus non-relapsed alcohol abusers: Coping skills, life events, and social support. *Addictive Behaviors, 8,* 183-186.

Russell, M.A. (1988). *Nicotine replacement: role of blood nicotine levels, their rate of change, and nicotine tolerance*. In O. F. Pomerleau & C. S. Pomerleau (Eds.), Nicotine replacement: A critical evaluation (pp. 63-94). New York: Alan R. Liss.

Schenk, S., & Partridge, B. (1997). Sensitization and tolerance in Psychostimulant self-administration. *Pharmacology Biochemistry and Behaviour, 57,* 543-550.

Sdao-Jarvie, K., & Vogel-Sprott, M. (1991). Response expectancies affect the acquisition and display of behavioural tolerance to alcohol. *Alcohol, 8,* 491-498.

Shapiro, A.K., Chassan, J., Morris, L.A., & Frick, R. (1974). Placebo induced side effects. *Journal of Operational Psychiatry, 6,* 43–46.

Shiffman, S., Engberg, J., Paty, J.A., Perz, W., Gnys, M., Kassel, J.D.,…Hickcox, M. (1997a). A day at a time: predicting smoking lapse from daily urge. *Journal of Abnormal Psychology 106*, 104–116.

Shiffman, S., Ferguson, S.G., Gwaltney, C.J., Balabanis, M.H., & Shadel, W.G. (2006). Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology, 184,* 637-644.

Shiffman, S.M, & Jarvik, M.E. (1976) Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology,* *50*, 35–39

Siegel, S., Classical conditioning, drug tolerance and drug dependence. In: Y. Israel, F.B. Glaser, H. Kalant, R.E. Popham, W. Schmidt and R.G. Smart (Eds.), *Research Advances in Alcohol and Drug Problems,* (Vol. 7), Plenum Press, New York, 1983.

Siegel, S., Baptista, M.A.R., Kim, J.A., McDonald, R.V., & Weise-Kelly, L. (2000). Pavlovian Psychopharmacology, The associative basis of tolerance. *Experimental and Clinical Psychopharmocology, 8,* 276-293.

Solomon, R.L., & Corbit, J.D. (1974). An opponent-process theory of motivation: I. Temporal Dynamics of affect. *Psychological Review, 81,* 119-145.

Stapleton, J.A., Michael, A.H., Russell, C.F., Wiseman, S.M., Gustavsson, G., Sawe, U…..Wiseman, D. (1995). Dose effects and predictors or outcome in a randomized trial or transdermal nicotine patches in general practice. *Addiction, 90,* 31-42.

Stewart-Williams, S., & Podd, J. (2004). The Placebo Effect: Dissolving the expectancy versus conditioning debate. *Psychological Bulletin, 130,* 324-340.

Valliant, G.E. (1988). What can long-term follow-up teach us about relapse and prevention of relapse in addiction? *British Journal of Addiction, 83,* 1147-1157.

West, R.J., Hajek, P., & Belcher, M. (1989). Severity of Withdrawal Symptoms as a predictor of outcome of an attempt to quit smoking. *Psychological Medicine, 19,* 981-985.

West, R. J., & Schneider, N. (1987). Craving for cigarettes. *Journal of Addiction, 82,* 407-415.

Wickramasekera, I. (1980). A conditioned response model of the placebo effect: predictions from the model. In: L. White, B. Tursky and G. Schwartz (Eds.), *Placebo: Theory, Research and Mechanisms*, Guilford Press, New York, 1985.

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *The Journal of Neuroscience, 19*(1), 484-494. Retrieved from <http://www.jneurosci.org/content/19/1/484.full.pdf>

Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: a role for non-specific activation of endogenous opioids. *PAIN, 90*(3), 205-215. doi:10.1016/S0304-3959(00)00486-3

Amin, N., Foa, E. B., & Coles, M. E. (1998). Negative interpretation bias in social phobia. *Behaviour Research and Therapy, 36*(10), 945-957. doi:10.1016/S0005-7967(98)00060-6

Asch, S. E. (1946). Forming impressions of personality. *The Journal of Abnormal and Social Psychology, 41*(3), 258.

Aslaksen, P. M., Zwarg, M. L., Eilertsen, H.-I. H., Gorecka, M. M., & Bjørkedal, E. (2015). Opposite effects of the same drug: reversal of topical analgesia by nocebo information. *PAIN, 156*(1), 39-46. doi:10.1016/j.pain.0000000000000004

Atlas, L. Y., Whittington, R. A., Lindquist, M. A., Wielgosz, J., Sonty, N., & Wager, T. D. (2012). Dissociable influences of opiates and expectations on pain. *The Journal of Neuroscience, 32*(23), 8053-8064.

Benedetti, F. (1996). The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *PAIN, 64*(3), 535-543.

Benedetti, F., Amanzio, M., Rosato, R., & Blanchard, C. (2011). Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. *Nature Medicine, 17*(10), 1228-1230.

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment, 6*(1), 1a.

Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. *Science Translational Medicine, 3*(70), 70ra14. doi:10.1126/scitranslmed.3001244

Boissel, J., Philippon, A., Gauthier, E., Schbath, J., & Destors, J. (1986). Time course of long-term placebo therapy effects in angina pectoris. *European heart journal, 7*(12), 1030-1036.

Bolles, R. C. (1972). Reinforcement, expectancy, and learning. *Psychological review, 79*(5), 394.

Briddell, D. W., & Wilson, G. T. (1976). Effects of alcohol and expectancy set on male sexual arousal. *Journal of Abnormal Psychology, 85*(2), 225.

Butler, C., & Steptoe, A. (1986). Placebo responses: an experimental study of psychophysiological processes in asthmatic volunteers. *British Journal of Clinical Psychology, 25*(3), 173-183.

Clark, D. M., & McManus, F. (2002). Information processing in social phobia. *Biological Psychiatry, 51*(1), 92-100. doi:10.1016/S0006-3223(01)01296-3

Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. *Social phobia: Diagnosis, assessment, and treatment, 41*(68), 00022-00023.

Colagiuri, B., McGuinness, K., Boakes, R. A., & Butow, P. N. (2012). Warning about side effects can increase their occurrence: an experimental model using placebo treatment for sleep difficulty. *Journal of psychopharmacology (Oxford, England), 26*(12), 1540-1547. doi:10.1177/0269881112458730

Collins, K., & Tatum, A. (1925). A conditioned salivary reflex established by chronic morphine poisoning. *American Journal of Physiology--Legacy Content, 74*(1), 14-15.

Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M., & Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *PAIN®, 151*(2), 430-439.

Crisler, G. (1928). The effect of withdrawal of water on the salivary conditioned reflex induced by morphine. *American Journal of Physiology--Legacy Content, 85*(2), 324-331.

Crowell, C. R., Hinson, R. E., & Siegel, S. (1981). The role of conditional drug responses in tolerance to the hypothermic effects of ethanol. *Psychopharmacology, 73*(1), 51-54.

Daly, J. A., Vangelisti, A. L., & Lawrence, S. G. (1989). Self-focused attention and public speaking anxiety. *Personality and Individual Differences, 10*(8), 903-913. doi:10.1016/0191-8869(89)90025-1

Dawson, M. E. (1970). Cognition and conditioning: effects of masking the CS-UCS contingency on human GSR classical conditioning. *Journal of Experimental Psychology, 85*(3), 389.

Dawson, M. E., & Biferno, M. A. (1973). Concurrent measurement of awareness and electrodermal classical conditioning. *Journal of Experimental Psychology, 101*(1), 55.

Dekker, E., & Groen, J. (1956). Reproducible psychogenic attacks of asthma: a laboratory study. *Journal of psychosomatic research, 1*(1), 58-67.

Dekker, E., Pelser, H., & Groen, J. (1957). Conditioning as a cause of asthmatic attacks: a laboratory study. *Journal of psychosomatic research, 2*(2), 97-108.

DiMaggio, P. (1997). Culture and cognition. *Annual review of sociology*, 263-287.

Dodge, K. A., & Crick, N. R. (1990). Social Information-Processing Bases of Aggressive Behavior in Children. *Personality and Social Psychology Bulletin, 16*(1), 8-22. doi:10.1177/0146167290161002

Eikelboom, R., & Stewart, J. (1979). Conditioned temperature effects using morphine as the unconditioned stimulus. *Psychopharmacology, 61*(1), 31-38.

Eikelboom, R., & Stewart, J. (1981). Temporal and environmental cues in conditioned hypothermia and hyperthermia associated with morphine. *Psychopharmacology, 72*(2), 147-153.

Eikelboom, R., & Stewart, J. (1982). Conditioning of drug-induced physiological responses. *Psychological review, 89*(5), 507.

Evans, F. J. (1974). The placebo response in pain reduction. *Adv Neurol, 4*, 289-296.

Fillmore, M., & Vogel-Sprott, M. (1992). Expected effect of caffeine on motor performance predicts the type of response to placebo. *Psychopharmacology, 106*(2), 209-214. Retrieved from [http://download.springer.com/static/pdf/487/art%3A10.1007%2FBF02801974.pdf?auth66=1426558477\_ea1d9489fa9d8c3ce09de1771ebaab6d&ext=.pdf](http://download.springer.com/static/pdf/487/art%253A10.1007%252FBF02801974.pdf?auth66=1426558477_ea1d9489fa9d8c3ce09de1771ebaab6d&ext=.pdf)

Flaten, M. A., Simonsen, T., & Olsen, H. (1999). Drug-related information generates placebo and nocebo responses that modify the drug response. *Psychosomatic medicine, 61*(2), 250-255. doi:10.1097/00006842-199903000-00018

Frankenhaeuser, M., Järpe, G., Svan, H., & Wrangsjö, B. (1963). Psychophysiological reactions to two different placebo treatments. *Scandinavian Journal of Psychology, 4*(1), 245-250.

Frankenhaeuser, M., Post, B., Hagdahl, R., & Wrangsjoe, B. (1964). Effects of a depressant drug as modified by experimentally-induced expectation. *Perceptual and motor skills, 18*(2), 513-522.

Hope, D. A., & Heimberg, R. G. (1988). Public and private self-consciousness and social phobia. *Journal of personality assessment, 52*(4), 626-639. doi:10.1207/s15327752jpa5204\_3

Hull, J. G., & Bond, C. F. (1986). Social and behavioral consequences of alcohol consumption and expectancy: a meta-analysis. *Psychological Bulletin, 99*(3), 347.

Ikemi, Y., & Nakagawa, S. (1962). A psychosomatic study of contagious dermatitis. *Kyushu Journal of Medical Science, 13*, 335-350.

Kimble, C. E., & Zehr, H. D. (1982). Self-Consciousness, Information Load, Self-Presentation, and Memory in a Social Situation. *Journal of Social Psychology, 118*(1), 39-46. doi:10.1080/00224545.1982.9924416

Kirsch, I. (1999). Specifying Nonspecifics: Psychological. *The placebo effect: An interdisciplinary exploration, 8*, 166.

Kirsch, I., & Weixel, L. J. (1988). Double-blind versus deceptive administration of a placebo. *Behavioral Neuroscience, 102*(2), 319-323. doi:10.1037/0735-7044.102.2.319

Klopfer, B. (1957). Psychological variables in human cancer. *Journal of Projective Techniques, 21*(4), 331-340.

Korol, B., Sletten, I., & Brown, M. (1966). Conditioned physiological adaptation to anticholinergic drugs. *American Journal of Physiology--Legacy Content, 211*(4), 911-914.

Lang, W., Brown, M., Gershon, S., & Korol, B. (1966). Classical and physiologic adaptive conditioned responses to anticholinergic drugs in conscious dogs. *International journal of neuropharmacology, 5*(4), 311-315.

Lê, A. D., Poulos, C. X., & Cappell, H. (1979). Conditioned tolerance to the hypothermic effect of ethyl alcohol. *Science, 206*(4422), 1109-1110.

Lehrer, P. M., Isenberg, S., & Hochron, S. M. (1993). Asthma and emotion: a review. *Journal of Asthma, 30*(1), 5-21.

Longo, D. L., Duffey, P. L., Kopp, W. C., Heyes, M. P., Alvord, W. G., Sharfman, W. H., . . . Rosenstein, D. L. (1999). Conditioned Immune Response to Interferon-γ in Humans. *Clinical Immunology, 90*(2), 173-181. doi:10.1006/clim.1998.4637

Luparello, T., Lyons, H. A., Bleecker, E. R., & McFadden, E. R. (1968). Influences of suggestion on airway reactivity in asthmatic subjects. *Psychosomatic medicine, 30*(6), 819-825.

Mansell, W., Clark, D. M., Ehlers, A., & Chen, Y.-P. (1999). Social Anxiety and Attention away from Emotional Faces. *Cognition & Emotion, 13*(6), 673-690. doi:10.1080/026999399379032

Marlatt, G. A., & Rohsenow, D. J. (1980). Cognitive processes in alcohol use: Expectancy and the balanced placebo design. *Advances in substance abuse: Behavioral and biological research, 1*, 159-199.

McFillin, R. K., Cahn, S. C., Burks, V. S., Levine, M. P., Loney, S. L., & Levine, R. L. (2012). Social information-processing and coping in adolescent females diagnosed with an eating disorder: Toward a greater understanding of control. *Eating disorders, 20*(1), 42-59.

Mellings, T. M. B., & Alden, L. E. (2000). Cognitive processes in social anxiety: the effects of self-focus, rumination and anticipatory processing. *Behaviour Research and Therapy, 38*(3), 243-257. doi:10.1016/S0005-7967(99)00040-6

Mitchell, C. J., De Houwer, J., & Lovibond, P. F. (2009). The propositional nature of human associative learning. *Behavioral and Brain Sciences, 32*(02), 183-198.

Montgomery, G., & Kirsch, I. (1996). Mechanisms of placebo pain reduction: an empirical investigation. *Psychological Science, 7*(3), 174-176. Retrieved from <http://pss.sagepub.com/content/7/3/174.full.pdf>

Montgomery, G. H., & Bovbjerg, D. H. (2001). Specific response expectancies predict anticipatory nausea during chemotherapy for breast cancer. *Journal of Consulting and Clinical Psychology, 69*(5), 831. Retrieved from <http://graphics.tx.ovid.com/ovftpdfs/FPDDNCDCMFNDMJ00/fs046/ovft/live/gv023/00004730/00004730-200110000-00010.pdf>

Montgomery, G. H., & Bovbjerg, D. H. (2004). Presurgery Distress and Specific Response Expectancies Predict Postsurgery Outcomes in Surgery Patients Confronting Breast Cancer. *Health Psychology, 23*(4), 381-387. doi:10.1037/0278-6133.23.4.381

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *PAIN, 72*(1–2), 107-113. doi:<http://dx.doi.org/10.1016/S0304-3959(97)00016-X>

Morrot, G., Brochet, F., & Dubourdieu, D. (2001). The Color of Odors. *Brain and Language, 79*(2), 309-320. doi:10.1006/brln.2001.2493

Neukirch, N., & Colagiuri, B. (2015). The placebo effect, sleep difficulty, and side effects: a balanced placebo model. *Journal of Behavioral Medicine, 38*(2), 273-283. doi:10.1007/s10865-014-9590-5

Pangborn, R. M., Berg, H. W., & Hansen, B. (1963). The influence of color on discrimination of sweetness in dry table-wine. *The American Journal of Psychology*, 492-495.

Pangborn, R. M., & Hansen, B. (1963). The influence of color on discrimination of sweetness and sourness in pear-nectar. *The American Journal of Psychology*, 315-317.

Parton, D. A., & Denike, L. D. (1966). Performance hypotheses of children and response to social reinforcement. *Journal of Personality and Social Psychology, 4*(4), 444.

Pavlov, I. P. (1927). Conditioned reﬂexes. *An Investigation of the physiological activity of the cerebral cortex*.

Penick, S. B., & Fisher, S. (1965). Drug-set interaction: psychological and physiological effects of epinephrine under differential expectations. *Psychosomatic medicine, 27*(2), 177-182.

Penick, S. B., & Hinkle, L., E. (1964). The effect of expectation on response to phenmetrazine. *Psychosomatic medicine, 26*(4), 369-373.

Pollo, A., Torre, E., Lopiano, L., Rizzone, M., Lanotte, M., Cavanna, A., . . . Benedetti, F. (2002). Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. *Neuroreport, 13*(11), 1383-1386. Retrieved from <http://graphics.tx.ovid.com/ovftpdfs/FPDDNCDCEEBGJD00/fs036/ovft/live/gv019/00001756/00001756-200208070-00006.pdf>

Rescorla, R. A. (1968). PROBABILITY OF SHOCK IN THE PRESENCE AND ABSENCE OF CS IN FEAR CONDITIONING. *Journal of Comparative and Physiological Psychology, 66*(1), 1-5. doi:10.1037/h0025984

Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *American psychologist, 43*(3), 151. Retrieved from <http://graphics.tx.ovid.com/ovftpdfs/FPDDNCJCMDBPFJ00/fs046/ovft/live/gv023/00000487/00000487-198803000-00002.pdf>

Rescorla, R. A., & Solomon, R. L. (1967). Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning. *Psychological review, 74*(3), 151.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical conditioning II: Current research and theory, 2*, 64-99.

Roscoe, J. A., Hickok, J. T., & Morrow, G. R. (2000). Patient expectations as predictor of chemotherapy-induced nausea. *Annals of Behavioral Medicine, 22*(2), 121-126. Retrieved from [http://download.springer.com/static/pdf/555/art%3A10.1007%2FBF02895775.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775&token2=exp=1456460127~acl=%2Fstatic%2Fpdf%2F555%2Fart%3A10.1007%2FBF02895775.pdf%3ForiginUrl%3Dhttp%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775\*~hmac=5cb0eaa11b321ce95bbc8dad4a4b313d7299dfc7bf86d4fd2f61857442ccd9ea](http://download.springer.com/static/pdf/555/art%253A10.1007%252FBF02895775.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775&token2=exp=1456460127~acl=%2Fstatic%2Fpdf%2F555%2Fart%25253A10.1007%25252FBF02895775.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Farticle%252F10.1007%252FBF02895775*~hmac=5cb0eaa11b321ce95bbc8dad4a4b313d7299dfc7bf86d4fd2f61857442ccd9ea)

[http://download.springer.com/static/pdf/555/art%3A10.1007%2FBF02895775.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775&token2=exp=1456460138~acl=%2Fstatic%2Fpdf%2F555%2Fart%3A10.1007%2FBF02895775.pdf%3ForiginUrl%3Dhttp%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775\*~hmac=df85807ce4472d89a918443041eed86d4e4631061b0519a82d943a12e1ebd16a](http://download.springer.com/static/pdf/555/art%253A10.1007%252FBF02895775.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02895775&token2=exp=1456460138~acl=%2Fstatic%2Fpdf%2F555%2Fart%25253A10.1007%25252FBF02895775.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Farticle%252F10.1007%252FBF02895775*~hmac=df85807ce4472d89a918443041eed86d4e4631061b0519a82d943a12e1ebd16a)

Rush, M., Pearson, L., & Lang, W. (1970). Conditional autonomic responses induced in dogs by atropine and morphine. *European journal of pharmacology, 11*(1), 22-28.

Shapiro, A. K., Chassan, J., Morris, L. A., & Frick, R. (1974). Placebo-induced side effects. *Journal of Operational Psychiatry*.

Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Physiological Psychology, 89*(5), 498.

Siegel, S. (1983). Classical conditioning, drug tolerance, and drug dependence *Research advances in alcohol and drug problems* (pp. 207-246): Springer.

Stewart-Williams, S., & Podd, J. (2004). The Placebo Effect: Dissolving the Expectancy Versus Conditioning Debate. *Psychological Bulletin, 130*(2), 324-340. doi:10.1037/0033-2909.130.2.324

Stopa, L., & Clark, D. M. (2000). Social phobia and interpretation of social events. *Behaviour Research and Therapy, 38*(3), 273-283. doi:10.1016/S0005-7967(99)00043-1

Suetsugi, M., Mizuki, Y., Yamamoto, K., Uchida, S., & Watanabe, Y. (2007). The effect of placebo administration on the first-night effect in healthy young volunteers. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(4), 839-847. Retrieved from <http://ac.els-cdn.com/S0278584607000516/1-s2.0-S0278584607000516-main.pdf?_tid=ae70f8d6-db85-11e5-bad9-00000aacb35d&acdnat=1456380470_3fd1bd29ae07170aa4afea7e7c3cf198>

Traut, E. F., & Passarelli, E. W. (1957). Placebos in the treatment of rheumatoid arthritis and other rheumatic conditions. *Annals of the rheumatic diseases, 16*(1), 18.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1985). Conditioned placebo responses. *Journal of Personality and Social Psychology, 48*(1), 47. Retrieved from <http://graphics.tx.ovid.com/ovftpdfs/FPDDNCJCEEAHLE00/fs047/ovft/live/gv024/00005205/00005205-198501000-00004.pdf>

Wickramasekera, I. (1980). A conditioned response model of the placebo effect - Predictions from the model. *Biofeedback and Self-Regulation, 5*(1), 5-18. doi:10.1007/BF00999060

Yeung, S. T. A., Colagiuri, B., Lovibond, P. F., & Colloca, L. (2014). Partial reinforcement, extinction, and placebo analgesia. *PAIN®, 155*(6), 1110-1117.

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)