"Aversive stimulus pairings are an unnecessary and insufficient cause of pathological anxiety"

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Why do only some people develop psychopathology and others do not? This is a fundamental question in mental health research, with implications for etiological theories (what *causes* the disease) and clinical theories of psychopathology (what *cures* the disease). Laboratory-based individual differences research can be an important tool in this light: Comparisons of patients and healthy volunteers in experimental protocols have the potential to reveal specific characteristics of the patient sample, and hence shape etiological theories and clinical strategies. Unfortunately, patient recruitment in this type of experiments is often difficult and slow, which has resulted in many underpowered studies with inconsistent results.

In this issue, Abend et al. report the results of a study on fear learning in a relatively large sample of anxiety patients and healthy volunteers. They used a Pavlovian conditioning procedure to examine the development of fear reactions to an innocuous stimulus (conditional stimulus, CS) that is systematically followed by an aversive stimulus (unconditional stimulus, US). To their surprise, and in contrast with some previous observations in smaller samples, patient versus volunteer comparisons did *not* reveal differences in fear conditioning per se, but only generally increased fearful responding to any stimulus in the protocol.

In this commentary, we consider implications of this null result for the Pavlovian conditioning account of pathological anxiety. In essence, this account holds that anxiety symptoms are conditioning effects, which means that they result from experienced pairings of stimuli (CS—US; for an elaborate discussion see De Houwer, in press). We start by tracing the historical roots, early criticisms, and later developments of this account.

Exactly 100 years ago, John B. Watson and Rosalie Rayner (1920) demonstrated in a toddler known as Little Albert that phobia-like symptoms can result from aversive

conditioning experiences. By pairing a white rat with a loud clanging noise over and over again, Little Albert gradually started reacting fearfully to the sight of the white rat (he cried, crawled away…). Because these fearful reactions also generalized to other stimuli, Watson and Rainer proposed that most of our fears, including phobic fears, are derived from such stimulus pairings. This resulted in the bold hypothesis (1) that strong conditioning experiences *always* lead to an anxiety disorder (sufficient cause) and (2) that *all* anxiety patients have had a strong conditioning experience in their past (necessary cause).

In the 1960s, accumulating evidence in rodents indicated that strong conditioning experiences (CS—US pairings) do not always lead to fear development, thereby challenging the sufficient cause hypothesis. As first observed by Leon Kamin (1967), *surrounding stimuli* play a major role in the CS—US conditioning process. If an aversive foot shock (US) is already reliably signaled by a surrounding stimulus (e.g., a light), pairings of a target stimulus (e.g., a tone) with the light and shock will generate little fear to the tone (CS). Thus, CS—US pairings do not always lead to conditioned fear of the CS. Many moderators have been identified since, including stimulus characteristics (intensity, modality, evolutionary relevance etc.), response characteristics (subjective ratings, physiological reactions, neural recordings, behavioral actions, etc.), participant characteristics (species, age, personality, etc.), prior experiences (US habituation, latent inhibition, chronic stress) and so on (for an extensive overview, see De Houwer and Hughes, 2020).

Clinical observations also challenged the hypothesis that CS—US pairings are a necessary and sufficient cause of anxiety disorders. As first documented by Jack Rachman (1977), many anxiety patients have no recollection of an aversive conditioning experience, and many people suffer aversive conditioning experiences but do not develop pathological anxiety. These failures led to a depreciation of the conditioning model in cognitive-

behavioral therapy during the 1980s and 1990s. More recently, the model regained interest alongside the increased emphasis on individual differences research in psychopathology since 2000. Susan Mineka and Richard Zinbarg (2006) proposed a stress-diathesis framework for understanding the development of pathological anxiety. In this framework, it is assumed that many moderating factors on the level of the individual (genetic constituency, temperament, learning history, etc.) determine whether an aversive conditioning experience will lead to an anxiety disorder. Furthermore, novel demonstrations in humans revealed that fear development can also proceed via vicarious and verbal learning experiences, without direct CS—US pairings. It thus became clear that CS—US pairings are an insufficient (dependent on moderating factors) and unnecessary (among alternative pathways) cause of pathological anxiety. For a more in-depth discussion of criteria for necessary and sufficient causes in the context of fear conditioning and pathological anxiety, we refer the reader to De Houwer (2020).

So, given that CS—US pairings are an insufficient and unnecessary cause of pathological anxiety, how should we interpret the absence of fear learning differences between anxiety patients and healthy volunteers reported by Abend et al. (this issue)?

First, it is precisely *because* so many candidate-moderators exist (individual traits, stimulus contexts and modalities, response characteristics, etc.) that conditioning experiences can underlie real-life development of pathological anxiety in patients, while at the same time fear learning differences do not show up in a specific CS—US conditioning procedure. For example, Abend et al. used *mild* and *disorder-irrelevant stimuli* (neutral picture as CS, loud scream as US) in order to examine fear learning across various anxiety disorders and healthy volunteers in a standardized way. Although this is a defendable choice, it leaves open the possibility that patients would show fear learning differences when CS—

US pairings comprise stimuli and situations of their concern. Actually, if Abend et al. had observed generic fear learning differences, then the challenge would be to explain *why* a given patient develops one anxiety disorder and not the other.

Relatedly, the choice of fear responses in the CS—US conditioning task is also critical; individual differences may only show up with certain types of responses. For example, most anxiety disorders are characterized by elevated and persistent avoidance of feared situations, which is commonly believed to maintain the increased levels of fear (by precluding corrective experiences of safety). Avoidance is an operant class of behaviors that can be integrated in the CS—US pairings procedure by designating a voluntary action that prevents US occurrence. It is possible that elevated levels of fear in anxiety patient result from differences in avoidance, rather than fear learning differences per se (pittig et al., 2018). Patient studies that characterize individual differences in avoidance learning are scarce, but urgently needed.

As noted above, fear development can also result from vicarious and verbal learning in the absence of direct CS—US experiences. Whether these alternative pathways rely on similar or different learning processes is currently under investigation. Furthermore, it is not clear yet whether individual difference factors moderate CS—US, vicarious, and verbal learning in similar ways. To the extent that these pathways diverge, an absence of individual differences to CS—US pairings as in Abend et al. (this issue) does not imply an absence of fear learning differences per se.

Another point is that, according to the diathesis-stress perspective (Mineka & Zinbarg, 2006), putative vulnerability factors are distributed over the entire population and will only lead to the disorder in those individuals that additionally have been exposed to a relevant conditioning experience. This implies that at least some individuals will possess the

vulnerability factor without having the disorder. Consequently, it is perfectly possible that aberrant fear learning occurs in a healthy volunteers group as well, which would make it more difficult to find significant differences against an anxiety group. Thus, if individual differences in fear learning are considered as a pre-existing vulnerability factor (which seems to be the basic assumption in many individual difference studies in this domain), it is not immediately clear how to select an appropriate healthy control group.

Finally, individual differences research is inherently correlational. This means that there could always be a multitude of variables that differ between patient and control groups and influence experimental results, but are not necessarily relevant to the disorder. For example, it is good to keep in mind that participants in a Pavlovian fear conditioning experiment are not like a specimen sample in a petri dish, but social individuals for whom participating in an experiment is a social experience. Even if we use objective measures like skin conductance or BOLD responses, the overall experimental context has a social nature that can influence their responses. For example, general expectations about psychological experiments and trust in the experimenter may influence how participants respond in a task. Elevated fear reactions to *any* stimulus, as observed by Abend et al. (this issue), could therefore reflect a level of distrust in the experimenter and an a priori expectancy to be hassled. Although this might or might not be relevant to the disorder, it would have nothing to do with hardwired biological deficits in conditioning processes as such.

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