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A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders

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ABSTRACT

Over the past decades, behaviour and cognitive psychology have produced fruitful and mutually converging theories from which hypotheses could be derived on the nature and origin of fear and anxiety disorders. Notwithstanding the emergence of effective treatments, there are still many questions that remain to be answered. Here, I will argue that the burgeoning field of behavioural neuroscience may advance our understanding of fear, anxiety disorders and its treatments. Decades of fear-conditioning research across species have begun to elucidate the neurobiological mechanisms underlying associative fear learning and memory. The fear-conditioning paradigm provides a well-controlled and fine-grained research platform to examine these processes. Although the traditional fear conditioning paradigm was originally designed to unveil general principles of fear (un)learning, it is well-suited to understand the transition from normal fear to pathological fear and the mechanisms of change. This paper presents 1) a selection of fear conditioning studies on the generalization and persistence of associative fear memory as intermediate phenotypes of fear and anxiety disorders, and 2) insights from neuroscience on the malleability of fear memory with the potential to provide a long-term cure for anxiety and related disorders.

Our brains are programmed to learn. For most animals their brains are largely encoded by their genes, whereas human beings have more behaviour that is learned and relatively less is programmed right from the beginning (Roberts, 2014). Although fear is innately programmed, and is well conserved across species, we still have to learn about the potential dangers in life, and even more important about the predictors of danger. Given that associative fear memory lies at the root of fear and anxiety disorders, there has been considerable interest in understanding neurobiological mechanisms that mediate long-term storage and retrieval of fear memories, as well as the mechanisms underlying the weakening of these memories. The quintessential model to study associative fear memory is Pavlovian fear conditioning (Barlow, 2002; LeDoux, 2000; Mineka & Zinbarg, 2006; Phelps & LeDoux, 2005). A clear advantage of this paradigm is that it is well-suited for research across species (e.g., rats, crabs, primates and humans) to probe the neural, cellular and molecular mechanisms underlying associative fear learning and memory. However, the problem in anxiety disorders is not the fear memory itself – programmed throughout evolution to be rapidly acquired – but the persistence and the broader generalization of fear to familiar and novel stimuli and contexts in the absence of actual danger. In this review I will discuss how insights from behavioural neuroscience on fear conditioning may contribute to a better understanding of the transition from normal to abnormal fear. Furthermore, I will argue that insights into the plasticity of fear memory might eventually advance treatments for pathological anxiety. In the past century, the behavioural and cognitive theories were of great value for the development of effective interventions for fear and anxiety disorders. Yet new insights from the behavioural neuroscience may eventually enrich the field.

Experimental research on fear and anxiety disorders

The empirical science of fear and anxiety disorders harks back to the introduction of behaviourism in the fifties. The idea that stimuli could control behaviour strongly advanced the science of fear and anxiety because it enabled to deduce hypotheses that could be critically tested by observations. Thus, instead of being dependent

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on participants' introspective capabilities, reliable and accurate methods of behavioural assessment became the standard. One of the highlights was evidently the development of behaviour therapy, which was grounded on the notion that if fear learning lies at the heart of anxiety disorders, it should also be possible to unlearn fear. Over the years, numerous variants of behaviour therapy for fear and anxiety disorders have been evolved and tested. Of these therapies exposure to the threatening cue is still considered one of the most effective ingredients of successful treatment (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014).

A shortcoming of the early behavioural paradigm was that it eschewed the mental processes. This opened avenues for the cognitive revolution and the information-processing paradigm in the late seventies. Stimulus–response associations were no longer a central topic of interest in clinical psychology and were replaced by processes of attention, memory, interpretation, attribution and representation (Williams, Watts, MacLeod, & Mathews, 1988). The cognitive theory on psychopathology postulated that disorder specific memory representations influence lower level cognitive processes resulting in processing biases for concern-related information. From the eighties onwards, the information processing paradigm has dominated the field with (1) Beck (1967) and Ellis (1958) as the founding fathers of cognitive therapy; (2) the seminal work of Lang (1977, 1979) followed by the highly influential work of Edna Foa and Michael Kozak on fear representation (1986); and (3) the development of experimental procedures by Mathews and MacLeod (1985) that enabled to objectively test the information processing biases. In the eighties and nineties, behaviour theory was supposed to be virtually irrelevant for our understanding of anxiety disorders and the development of better treatments, but the paradigm never really lost ground in the neuroscience of fear memory.

Currently, cognitive behavioural treatment (CBT) for anxiety and related disorders dominates clinical practice with a combination of intervention techniques inferred from both the behavioural and cognitive theory (Hofmann & Smits, 2008). It evolved from a long tradition of experimental research aimed to unveil disorder-specific processes underlying the aetiology and maintenance of that particular disorder. Parallel to this disorder-specific model, transdiagnostic cognitive and behavioural processes (i.e., information processing biases, ruminations) have been recognized as potential factors to target in treatment (Hallion & Ruscio, 2011; Harvey, Watkins, Mansell, & Shafran, 2004). Even though CBT is considered to be the most effective treatment for anxiety and related disorders, it is still far from optimal (Craske et al., 2014; Hofmann & Smits, 2008). There are many patients who fail to benefit from CBT, or fail to maintain their gains. The current information-processing theories do not satisfactorily explain why treatment sometimes fails. In fact, there is relatively little knowledge about the underlying mechanisms of change. And as stated nicely by McNally (2007): "Theoretical agnosticism about mediating mechanisms is acceptable only when treatment works with flawless fidelity".

During the last two decades, the behaviour and cognitive theories have merged into what is referred to as the behavioural neuroscience of fear learning and memory. Instead of unpacking the artificial categorization of DSM disorders, it seeks general principles of fear learning and memory, which may finally turn into maladaptive behaviour (see also the Research Domain Criteria initiative of the National Institute of Mental Health). In addition to the behavioural and cognitive processes of fear learning and memory, also molecular, cellular and neural processes are incorporated. In this review, I will argue that a neuroscientific approach may improve our understanding of 1) the transition from normal fear into abnormal fear, and 2) the mechanisms of change in the treatment of pathological anxiety. Understanding the mechanisms of change is crucial to delineate the necessary, optimal and boundary conditions for effective treatments. Here I present only a small selection of insights and observations from the huge body of Pavlovian fear conditioning research with a slight predominance of work from my own lab. The aim of the present paper is to illustrate the heuristic validity of behavioural neuroscience for understanding fear and anxiety disorders.

Associative fear learning and memory

Pavlovian fear conditioning serves a well-controlled experimental model to study associative fear learning and memory across a wide range of organisms (LeDoux, 1996; Rescorla & Holland, 1982). In a prototypical fear conditioning study, an innocuous and biologically neutral conditioned stimulus (CS), e.g., a tone or picture, acquires the capacity to elicit fear responses after the pairing with an intrinsically noxious or harmful unconditioned stimulus (US), e.g., electric stimulus. If the CS becomes a reliable predictor of the US, the CS will elicit species-typical conditioned behavioural responses (e.g., freezing in rats and potentiated startle reflex in humans).

Environmental cues indicating the unambiguous presence of an immediate threat give rise to intense fearful defensive behaviours ('fight or flight'), experimentally modelled by cue conditioning. Whereas more diffuse, distal or unpredictable threat cues produce sustained anxiety-like behaviour that is basically modelled by context conditioning (Phillips & LeDoux, 1992). Both the relatively short-lived situation-specific fearful responding and the more sustained anxiety are observed in the anxiety and related disorders such as PTSD (DSM-5) (American Psychiatric Association, 2013) and therefore relevant to be studied in translational research.

Decades of research in rodent models have provided tremendous insight into the neurobiology of fear and anxiety and the circumstances under which different defensive responses are recruited (Blanchard & Blanchard, 1998; Fanselow, 1994). Fear conditioning studies have consistently demonstrated that the amygdala is critically involved in the formation, consolidation and retrieval of associative fear memory (Davis, 1997; LeDoux, 1996, 2000). Neuroimaging research in humans corroborates the central role of the amygdala in associative fear learning (Büchel, Morris, Dolan, & Friston, 1998; Morris & Dolan, 2004), though a much broader network of brain areas is also critically involved (including the anterior cingulate cortex, hippocampus, insula, and vmPFC) (Mechias, Etkin, & Kalisch, 2010; Sehlmeyer et al., 2009; Visser, Scholte, & Kindt, 2011; Visser, Scholte, Beemsterboer, & Kindt, 2013; van Well, Visser, Scholte, & Kindt, 2012). Insights in the brain areas that are involved in fear learning and memory instigated further research on the molecular and cellular processes in those areas with a specific focus on the basolateral nucleus of the amygdala (Lamprecht & LeDoux, 2004).

An inherent restriction of memory research however, including fear conditioning, is that fear memory is not directly observable but can only be inferred from the degree to which conditioned responding during learning overlaps with the behaviour at later retention tests. Whereas the expression of fear during learning is certainly related to long-term memory, much of what we learn does not eventually transform into long-term memory. The dissociation between learning and memory has been most convincingly illustrated by studies in which pharmacological manipulations, administered immediately after learning, induced full amnesia at long-term, while leaving short-term memory intact (e.g., Miserendino, Sananes, Melia, & Davis, 1990; Schafe & LeDoux, 2000). Post-learning processes (i.e., off-line learning) account for this dissociation, as they induce the structural changes underlying the stabilization of a memory trace after its acquisition (i.e.,