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How could stress lead to major depressive disorder?

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ABSTRACT

Stress is associated with major depressive disorder (MDD), but the underlying mechanism remains elusive. However, some experiences, referred to as stress, may actually lead to resilience. It is thus critical first to define what type of stress may lead to MDD. Long-term potentiation (LTP) and long-term depression (LTD) are both sensitive to stress, but particularly to inescapable and not escapable stress. Thus, these are the psychological aspects of stress which contribute to the development of MDD, but by which mechanisms remains still elusive. Interestingly, the same stress may facilitate LTD and impair LTP in the CA1 region. In addition, repeated efforts are often required for learning under neutral conditions but single- or few learning trials are sufficient for forming stress-related memories. If LTP is crucial for normal learning, a combination of limited LTP and facilitated LTD appears to have higher efficiency for storing stress-related memories. Chronic psychological stress may cause a hyper-link among stress-related memories across the spatiotemporal due to shared quality of inescapability, leading to automatically negative appraisal through memory generalization mechanisms in MDD patients when encountering new distinct events which are perceived to share such similarity with previous experiences.

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Psychological stress vs. stress

The idea that the effects of the physical properties of stress experience should be distinct from the psychological aspects of

E-mail addresses: galrichterlevin@gmail.com (G. Richter-Levin), lxu@vip.163.com (L. Xu). the experience has been put forward by the studies of the impact of uncontrollable versus controllable stress exposure (Seligman and Maier, 1967). The definitions of stress (Selye, 1936; Selye, 1955; Kim and Diamond, 2002) do not often emphasize the difference between physical and psychological aspects of stress despite the neurobiological effects produced by psychological and physical aspects of stress are likely to be much different. A definition of psychological stress should contain the features of inescapability and/or uncontrollability, as well as the diverse responses by individuals due to their own cognition and behavior pattern (such as mindset, learning and memory) etc. The impact of psy-

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Review Article





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chological stress on cognition is suggested to lead to rapid learning of adaptive or maladaptive coping strategies such as in the case of learned helplessness or immobility (Martin et al., 1967). These processes may lead to biased negative emotional processing on memory recall in MDD patients (Beck et al., 1961; Hollon and Kendall, 1980). If this view, which is supported by clinical observation about the causal relationship between stress and MDD (Caspi et al., 2003; Cohen et al., 2007; Mothersill and Donohoe, 2016; Bleys et al., 2018), is correct, the definition of psychological stress should include inescapability and/or uncontrollability. This differentiation between psychological and other forms of stress is further supported by the findings that acute inescapable but not escapable situation of the same stress facilitates LTD (Kim et al., 1996; Xu et al., 1997; Xu et al., 1998) and impairs LTP (Foy et al., 1987; Shors et al., 1990; Kim et al., 1996; Xu et al., 1997; Xu et al., 1998; Kim and Diamond, 2002) in the hippocampal CA1 region. These findings indicate that distinct neural mechanisms underlie psychological stress. While a role for stress-induced LTD in the development of MDD was suggested before (Manji et al., 2001; Duman and Aghajanian, 2012), the difference between psychological stress and stress, and the combination of impaired LTP and facilitated LTD related to MDD has been rarely discussed. In accordance with that, chronic stress models, which are known to induce MDD-related symptoms including the animals' learning that the situation is inescapable or uncontrollable. Furthermore, previous reports have demonstrated that after chronic stress exposure, hippocampal CA3 neurons exhibit loss of dendrite spines and atrophy of dendrites (Magarinos et al., 1996). Functional synaptic plasticity (e.g. LTP and LTD) is suggested to lead to structural synaptic plasticity such as synaptogenesis or 'synaptopruning' respectively (Collingridge et al., 2004), and chronic stress-induced structural changes are likely to attribute to LTD and synaptopruning.

In summary, it is suggested that under acute but mainly chronic psychological stress conditions, the alteration of synaptic plasticity and the formation of stress-related memories are both critical for the development of MDD as is reflected by particular biased learned cognition and behavioral patterns. This view suggests that in order to understand stress-induced MDD we also need to better understand whether chronic psychological stress induces LTD and synaptopruning, and how stress-related memories are stored.

Hans Selve coined the term 'stress' to describe a non-specific response of an organism to stressors that have long been believed to be harmful for health (Selye, 1936; Selye, 1955). However, as was more recently realized, a stressor is not necessary bad or good, but good or bad is determined by the mindset of the individuals' (Crum et al., 2013), suggesting that diverse responses of individuals to psychological stress depend on their formed cognition. Furthermore, the activation of the hypothalamic-pituitary-adrenal (HPA) axis by stress has long been considered to indicate and quantify stress (Kim and Diamond, 2002). However, particularly with respect to MDD, this is likely not an effective or sufficient measurement. A major risk factor for the development of MDD are stressful life events which are suggested to shape biased cognition and behavioral patterns that increase the likelihood to developing MDD in adulthood (Caspi et al., 2003; Cohen et al., 2007). It is likely not accurate to assess psychological stress in the past by measuring the levels of glucocorticoid hormones in the present. Indeed, differences in past events are likely to contribute to individual differences in responding to the same stress in adulthood (Myers and Brewin, 1994; Sandi and Richterlevin, 2009; Crum et al., 2013). The impact of the past on the present may be dependent on a particular retrieval mechanism, termed memory generalization, a phenomenon demonstrated in the famous story of 'Little Albert' who learned was trained to fear a white animal but then generalized his fear, responding to objects or animals with white color (Bower, 1981). Here, memory generalization may have been triggered by the similarity in characteristics related to inescapability and/or uncontrollability. In this way psychological stress and stress-related memories are likely to contribute to the development of MDD. Eventually, cognitive appraisal on the current stress situation (Folkman et al., 1986) and memory generalization (Bower, 1981) would lead to emotional changes that would contribute to the development of neuropsychiatric disorders including MDD.

Evaluating previous effects of psychological stress

Cognitive appraisal has been examined in patients who suffer neuropsychiatric disorders especially MDD. For example, a neutral event or face is often recognized by MDD patients as "sadness", a cognitive appraisal pattern that may be predominant by automatically negative thinking (Beck et al., 1961; Hollon and Kendall, 1980). This is highly consistent with a recent suggestion that a stress is bad because the individual believes the way (Crum et al., 2013), a mindset possibly resulted from cognitive appraisal that is made based on previous stress memories. It is therefore critical to understand how this could occur in MDD patients. There are three processes of a memory, encoding, storage, and retrieval (Atkinson and Shiffrin, 1968). The encoding-retrieval exactly matched conditions lead to specific recall but these of partial matched ones result in generalization recall, according to the theoretical hypothesis "Toward a universal law of generalization for psychological science" (Shepard, 1987). A recent report has demonstrated that rapid form of memory generalization is an active process to build up additional accesses to memory resources that allow fear to be transferred from one memory to another (Zhou et al., 2017). Clinical study has suggested that MDD patients exhibit over generalization of negative memories (Gotlib and Joormann, 2010). Therefore, according the rapid form of memory generalization, similar cues can retrieve negative emotion that links to old stress memories (Zhou et al., 2017; Silva, 2017), possibly leading to automatically negative thinking (Beck et al., 1961). Furthermore, psychological stress memories would have been accumulated to shape the cognitive appraisal pattern in individuals (Bower, 1981; Folkman et al., 1986). If the individuals encounter distinct new events but with similarity to the previous stressful events such as inescapability and/or uncontrollability, memory generalization mechanisms would transfer the negative emotion from the old stress memories to the present so as to manifest automatically negative thinking. Based on this speculation, a behavioral task carefully designed for testing generalization of the old stress memories would be very useful for evaluating the psychological effects of the past up to the present, to detect whether an individual is suffering or going to be suffering from MDD.

Posttraumatic stress disorder (PTSD) vs. MDD

A general unsolved question is why a life-threatening event leads to PTSD or both PTSD and MDD in some, but only MDD in the others. Clinical study suggests that acute response to a trauma cannot distinguish PTSD from MDD, but MDD can be separated by chronic aftermath of the trauma (Odonnell et al., 2004). PTSD but not MDD is associated with certain physiological biomarkers such as hypertension (Kibler et al., 2009). Certain daily pattern of cortisol levels is also associated with PTSD, but not with MDD (Wichmann et al., 2017). It is interesting that memory retrieval is not affected in MDD patients but enhanced in PTSD patients after cortisol administration, suggesting that the most difference between MDD and PTSD may relate to memory retrieval mechanisms (Wingenfeld and Wolf, 2014). Furthermore, over generalization of stress memories in the retrieval is shared by MDD and PTSD (Gotlib and Joormann, 2010; Mahan and Ressler, 2012). Perhaps, accumulation of the life-threatening events may blunt the HPA axis activity, indiDownload English Version:

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