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Exploring behavioral pattern separation and risk for emotional disorders

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ABSTRACT

Pattern separation is a facet of memory encoding that facilitates the adaptive integration of old and new experiences. At the computational level, this process reduces overlap between how two entities are represented. Behaviorally, this allows for greater memory resolution while avoiding memory interference; similar entities are perceived as distinct. Poor pattern separation could contribute to psychopathology, especially anxiety, as individuals with high anxiety tend to overgeneralize their perception of threat, or have difficulty distinguishing between currently safe contexts and previously threatening ones. However, there is little empirical work examining this as a contributory mechanism of anxiety in humans. This study examines the relationship between behavioral pattern separation, anxiety, and related symptoms. Participants (N = 111) completed questionnaires assessing anxiety, depression, stress, trait worry, and state affect. They then completed the Mnemonic Similarity Task, a computerized test that serves as a putative behavioral proxy to tax and thus measure hippocampal pattern separation. Behavioral pattern separation performance alone was not predictive of high anxiety, depression, or stress. However, two significant interactions emerged. The interactions between performance and state affect, and between performance and trait worry predicted anxious and depressive symptoms. Only at higher levels of negative affect was performance predictive of symptom severity. Similarly, poor pattern separation and high trait worry together predicted the most severe symptoms. This project provides support for behavioral pattern separation as a plausible factor in anxiety and related psychopathology, particularly in combination with sensitivity to acute distress and known risk factors, such as trait worry.

1. Introduction

Each of us goes through the world continuously encoding new memories. As we do, we automatically compare new experiences to past ones, enabling us to discriminate between safe and potentially dangerous situations (Mattson, 2014). Hippocampal pattern separation is the computational process of encoding details of an environment, object, or event in ways that ultimately allow us to distinguish between similar memories. Behavioral pattern separation is the resultant ability to resolve memory interference, or to discriminate previously encoded stimuli from highly similar stimuli. First established in rodent models, pattern separation is largely subserved by the dentate gyrus-CA3 circuit within the hippocampus, one of two brain regions that generate new neurons across the lifespan, and seemingly depends on such neurogenesis. Young neurons suppress the excitability of the dentate gyrus so that stimuli trigger more selective and thus unique patterns of activation in this region, therefore decreasing the likelihood that two stimuli activate overlapping representations (Kheirbek & Hen, 2014; Sahay et al., 2011). Without this inhibitory action, two cues may be encoded as insufficiently distinct, and consequently interpreted as overly similar.

Impaired pattern separation may be a risk or maintenance factor for emotional disorders, and anxiety in particular (Kheirbek & Hen, 2014). Transdiagnostically, clinical anxiety is conceptualized as involving overgeneralized fear (2014, Lissek et al., 2010; Lissek, 2012). For example, people with panic disorder may learn to fear any situation in which their pulse quickens, whereas those without panic disorder may recognize increased heart rate in non-threatening situations as signifying aerobic exertion or excitement. People with generalized anxiety disorder (GAD) may become distressed by uncertainty in multiple domains of their life, whereas those without GAD may experience high distress in fewer, more selective contexts. Thus, patterns of responding fearfully to benign situations, struggling to dissociate similar perceptions and sensations, and encoding ambiguous cues as more threatening could in part arise from deficient pattern separation as representations of safe and threatening contexts merge (Kheirbek & Hen, 2014; Scharfman & Myers, 2016). This hypothesis is consistent with studies showing structural and functional hippocampal deficits in those at risk for or diagnosed with anxiety and related disorders (DeCarolis & Eisch, 2010).

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However, there is little empirical work in humans examining the relationship between pattern separation and anxiety. Most related human research concerns individuals free of psychopathology who score low on measures of anxiety (Balderston et al., 2015; Lange et al., 2017). Thus, the primary aim of the current project was to test whether behavioral pattern separation predicts anxiety severity and is therefore a promising target in the study of anxiety in humans. To do so, we aimed to recruit a sample varying widely in reported symptoms of anxiety. As overgeneralization and associative learning abnormalities are evident in highly anxious, even subclinical samples (Chan & Lovibond, 1996; Haddad, Pritchett, Lissek, & Lau, 2012) and predict worsening symptoms (Lenaert et al., 2014), we hypothesized that performance on a behavioral pattern separation task would differentiate individuals who scored high and low on these indices of trait anxiety or risk. Positive results would support extant hypotheses that poor pattern separation could precede and contribute to the development of anxiety disorders.

Importantly, it is unclear whether pattern separation should relate *only* to anxiety. For example, some preliminary evidence suggests that behavioral pattern separation is associated with symptoms of depression (Dery et al., 2013; Shelton & Kirwan, 2013). Given high rates of comorbidity among emotional disorders and shared symptoms or features, such as general distress per the tripartite model (Clark & Watson, 1991), we also included measures of depression and stress to consider the specificity of results.

We also measured state negative affect—or how upset versus neutral people felt in the moments preceding a behavioral pattern separation task— given evidence that behavioral pattern separation is not a stable trait and is sensitive to emotional arousal (Balderston et al., 2015; Segal, Stark, Kattan, Stark, & Yassa, 2012). Including this emotional context could be informative as pattern separation performance under neutral conditions (e.g. among participants reporting little or no distress) may fail to distinguish at-risk and clinical individuals from healthy ones (Quinn & Joormann, 2015; Shelton & Kirwan, 2013). Alternatively, at-risk individuals may be those whose resources decline or are insufficient under stress— when they are most needed; if this were the case, we would expect to see a separation in performance between high and low anxious individuals experiencing acute negative affect during the study, but not necessarily between those not experiencing state distress. Additionally, poor pattern separation alone may not directly increase risk for psychopathology. Whereas generalization is largely adaptive and poor pattern separation is agnostic to valence, insufficient pattern separation during encoding may problematically interact with other risk factors, such maladaptive emotional response styles, cognitive biases favoring attention to threat, anxious temperament, or exposure to stressful environments. In this preliminary work, we chose to examine chronic worry, a perseverative, negative response style strongly linked to risk for anxiety and related disorders (Borkovec, Alcaine, & Behar, 2004; Brosschot, Gerin, & Thayer, 2006). For example, if a person is prone to excessive worry, poor pattern separation could result in more frequent worry and subsequently more severe clinical symptoms as ambiguous or uncertain situations are maladaptively coded as threatening. We therefore explored whether worry tendency and behavioral pattern separation performance would interact to exacerbate or predict disorder risk.

Behavioral pattern separation could prove to be a measurable link between basic findings from clinical neuroscience and clinical phenomena, including clinical outcomes. Reliably and immensely sensitive to hippocampal function, cell proliferation, and survival, performance on a behavioral pattern separation task could be a novel, non-invasive, and inexpensive marker of risk and a transdiagnostic target for intervention (Stark, Yassa, Lacy, & Stark, 2013). A positive signal in this foundational study would justify and inform future research to further elucidate these processes, their biological correlates, and their malleability.

2. Method

2.1. Participants

One hundred eleven adults (75 women, M_{age} = 31.36, *SD* = 8.29, age range: 18–50) completed the protocol. The self-reported ethnic and racial composition of the sample was 58.56% Caucasian or white, 17.12% African American or black, 16.22% Asian or Asian American, 0.90% Native American or American Indian, 4.50% multiracial, 1.80% other or unreported, and 6.31% identified as Hispanic or Latino. Participants were recruited through the Harvard University Study Pool and through flyers posted around the Boston area; the sample included students and community members. Harvard University's Committee on the Use of Human Subjects approved the study, and written informed consent was obtained from participants prior to beginning the session. Eligible participants were between the ages of 18 and 50, able to read and sign the consent form, not currently taking any psychiatric medications, without a history of major head trauma, neurologic disorder, or cognitive impairment, and not pregnant.

2.2. Procedure and materials

2.2.1. Baseline measures

Participants completed a battery of self-report questionnaires, which included demographics (age, gender, ethnicity, race, education), symptoms of depression, anxiety, and stress, trait worry, and state affect. Three subscales—depression, anxiety, and stress—can be derived from the Depression Anxiety Stress Scales, 21-item (DASS-21) (Lovibond & Lovibond, 1995). Depression items include sad or low mood, feelings of worthlessness and hopelessness, anhedonia, and psychomotor slowing. Anxiety items capture somatic symptoms (e.g. trembling, sweating, racing heart), situational anxiety, general anxiety, and panic. Stress items include persistent irritability, hyperarousal, fidgeting, tension, heightened startle response, and impatience. The 16-item Penn State Worry Questionnaire (PSWQ) measures severity and chronicity of worry (Meyer, Miller, Metzger, & Borkovec, 1990). High PSWQ scores indicate more habitual and extreme worry. Finally, participants indicated how they were feeling in the moment at the start of the visit by using the valence and arousal items of the Self-Assessment Manikin (SAM; Lang, Greenwald, Bradley, & Hamm, 1993; Suk & Irtel, 2006). This nonverbal, self-report measure requires participants to select the icons of a human-like figure that best correspond to their current levels of negative emotional arousal and valence, respectively. The two items were summed to form a composite state affect score, with higher ratings indicating more distress.

2.2.2. Computer task

The Mnemonic Similarity Task (MST*)* serves as a putative behavioral proxy to tax and thus measure hippocampal pattern separation, with demonstrated ties to the neurobiology of this process (Stark et al., 2013; Yassa, Lacy et al., 2011). The MST included two phases administered via computer. During phase 1 (approximately 5 min), participants were shown a series of 128 visual stimuli (everyday objects) and told to judge whether each is an indoor object or outdoor object by pressing one of two designated buttons on the keyboard. During phase 2 (approximately 8 min), participants viewed a second series of stimuli (everyday objects). Sixty-four were repetitions from phase 1 ("targets"), 64 were novel ("foils"), and 64 were similar but not identical to stimuli from phase 1 ("lures"). Participants were instructed to label each item as old (i.e. repetition), new, or similar and were given a few example trials before beginning. Each image appeared for 2 s with an inter-stimulus interval of 0.5 s. Two scores were derived from accuracy on phase 2 of the MST. First, a behavioral pattern separation score (BPS score or lure discrimination index) was the difference between correct similar ratings given to lures minus incorrect similar ratings given to foils. The latter accounted for any response bias favoring the similar