A domain-focused approach for posttraumatic psychopathology – the Intrusive Re-Experiencing Domain (ITRED)

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Abstract
Post-traumatic stress disorder (PTSD) is a debilitating disorder that might ensue following the exposure to traumatic events. Recent advances in neuroscience research has had little effect on advancing diagnosis and treatment of the disorder. Moreover, clinical disagreement on PTSD diagnosis further impedes successful basic-clinical translation, further delaying therapeutic advances. Focusing on core symptom dimensions of a given psychopathology can provide a much needed nidus around which basic and clinical research can coalesce. The recently outlined 'Intrusive Traumatic Re-Experiencing Domain' (ITRED) provides such a nidus, presenting a novel conceptual tool with potential clinical and scientific utility. ITRED argues for a research and clinical focus on the unique symptomology of intrusive and involuntary recollection and re-experiencing the trauma in the here-and-now, aspects that are at the core of traumatic experiences, and which are not shared by other psychopathologies. This, in turn, will inform novel means to understand mechanisms and treatment options. The goal of this study is to explore brain-related correlates of the ITRED domain by examining individual symptom severity and resting-state functional connectivity.

Background and Goal: Posttraumatic stress disorder (PTSD) is a debilitating disorder observed in individuals exposed to traumatic events. It is characterized by intrusive symptoms, avoidance of trauma reminders, negative alterations in cognitions and mood, and heightened arousal (First, Spitzer, Gibbon, & Williams, 1996). Recent advances in neuroscience research has had very little improvements on diagnosis and treatment of the disorder (Hodge et al. 2016; Stein et al. 2007), with clinical disagreement on PTSD diagnosis further impeding the successful basic-clinical translation and contributing to delayed therapeutic advances. Focusing on core symptom dimensions of a given psychopathology can provide a much-needed nidus around which basic and clinical research can coalesce.

For this purpose, a novel focus on the unique PTSD symptom domain of intrusive, involuntary recollection, and re-experiencing traumatic memories has been recently put forward (AJP REF), aiming to focus PTSD research and therapeutics on a unique core feature of the disorder, not shared by other pathologies, and to bridge extant biological and cognitive neuroscience research. This core process, termed 'Intrusive Traumatic Re-Experiencing Domain' (ITRED), provides a conceptual tool with potential clinical and scientific utility (Bar-Haim et al, in press). Specifically, ITRED uses three PTSD criteria listed in the DSM as basis for diagnosis: B1 (recurrent, involuntary, and intrusive distressing memories of the traumatic event), B2 (recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event), and B3 (dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event is recurring).

Importantly, focusing on ITRED might yield an easier diagnostic tool for post-traumatic pathology offering unique therapeutic targets. Thus, further testing the ITRED in a very large sample and in one or more independent cohorts is needed. Furthermore, the neural mechanisms of ITRED vs traditionally diagnosed PTSD using CAPS-5 has not been explored. These large-scale studies have been made possible by the development of research consortia committee such as Psychiatric Genomic Consortium (PGC)-Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA), in which investigators shared their data across the world. These consortiums greatly promote model development on large samples, which can increase statistical power; development of models based on multisite samples, which are more likely to generalize across scanners and commonly encountered variations in study procedures; and tests on independent data sets with different characteristics.

Our overarching goal with this project is to utilize resting state functional MRI (rs-fMRI) and individual CAPS clinical symptoms in classifying patients with PTSD from trauma-exposed healthy controls (TEHC) individuals. Specifically, we aim to explore neural differences using ITRED vs CAPS in a large-scale dataset from ENIGMA PTSD Working Group (PTSD N~=1500; TEHC N~=1500). Finally, we aim to examine its utility in predicting diagnosis, functional impairment, and symptom severity.

Specific Aims: To use rs-fMRI to examine the divergent neural mechanism in PTSD patients from TEHC using ITRED vs CAPS.

Important innovative aspects to this proposal: this is the first study aiming to identify and quantify the ITRED in a large-scale dataset. This study will lay the groundwork to offer new insights into the identification of potential biomarkers for the clinical diagnosis of PTSD.

Preliminary Work: In our preliminary work we used the ITRED in five various large samples of veterans, active duty combat-exposed soldiers, and civilian patients, to examine its clinical utility

in diagnosing posttraumatic pathology. Thus, we compared the diagnosis rates based on traditional DSM-based measures (i.e., CAPS-IV; CAPS-5) and on ITRED (e.g., endorsing at least one of the B1, B2, and B3 symptoms, as described in the DSM). Results showed that: (1) most patients meeting DSM-IV or DSM-5 criteria for PTSD also manifested ITRED symptoms; (2) approximately 10% of trauma-exposed individuals who failed to meet DSM criteria for PTSD did suffer from intrusive memories and re-experiencing symptoms that were identified by ITRED; and (3) only a minuscule percentage of those meeting DSM-IV or DSM-5 criteria for PTSD did not meet the ITRED criteria (Bar-Haim et al, in press). These results show the ITRED to be a conceptual tool with potential clinical and scientific utility.

Methods, Subjects and Settings:
We will analyze neuroimaging and clinical data from ~3000 subjects (~1500 PTSD patients, and ~1500 TEHC subjects). We will exclude participants with 1) history of Axis I psychiatric diagnosis, e.g., psychotic disorder, bipolar disorder, tic disorder, or eating disorder (comorbid current major depressive disorder will be allowed). 2) Depression which is antecedent to PTSD; score of > 25 on the Hamilton Rating Scale for Depression (HAM-D-17-item); significant depression and /or depression related impairment that is judged to warrant pharmacotherapy or combined medication and psychotherapy. 3) For PTSD, history of substance/alcohol dependence within the past six months, and abuse within past two months history. 4) Patients who are receiving effective medication for their PTSD, and/or depression. Antipsychotic, antidepressant, or mood stabilizer medications in the last 4 weeks prior to the study (6 weeks for fluoxetine). Standing daily dosing of benzodiazepine class of medication in the 2 weeks prior to the study (as needed use of benzodiazepines is not an exclusion, but must be clinically judged to tolerate no benzodiazepines for the 72-hour period before each of the fMRI days). Triptan anti-migraine medications. Other medications that may interfere with fear circuitry and fear memory such as blood-brain-barrierpenetrating β-blockers.

Neurocognitive Battery: CAPS individual item scores will be used to assess PTSD symptom. Hamilton Depression Scale (HAMD, 17 item) will be used to assess depressive severityAlso, the SF-36, a 36-item measure of generic health status (Ware, 1996), will be collected across sites to assess functional impairment of patient with PTSD or TEHC.

MRI Data Analysis: A standardized image preprocessing and quality-control pipeline established by the ENIGMA consortium will be used.

Resting state fMRI: First level analyses will also be performed using the ENIGMA resting state pipeline. Mean time series will be extracted from the seed regions based on ROIs defined in Power atlas and correlated with time series of the other regions. To get a normal distribution, fisher's r-to-z transformations will be applied. Seed-based functional connectivity values will be calculated between seed regions within each network and between networks. Second, dual regression analyses will be performed for the different network template ROIs and functional connectivity measures will be calculated.

Second level analysis: For the group analyses, functional connectivity measures within and between networks will be compared between the PTSD diagnosed by DSM and by ITRED and control groups. That is, the three groups will consist of those meeting PTSD diagnosis based only on ITRED (P_ITRED), on CAPS only (P_CAPS), and those which overlap in both ITRED and CAPS (P_Both). Age, sex, depression (yes/no), comorbid anxiety disorder (yes/no), and scanner site will be used as covariates of no interest. For group-level effects to be considered significant

a height-threshold of p<0.001 and a cluster-level false discovery rate (FDR) correction of p<0.05 will be used.

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