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Impact of Common Mental Health Disorders on Cognition: Depression and Posttraumatic Stress Disorder in Forensic Neuropsychology Context

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Abstract
The assessment and diagnosis of posttraumatic stress disorder (PTSD) and depression in forensic evaluations may lack an acknowledgement of the neurocognitive impact of these disorders and how they interact with other causative factors, such as traumatic brain injury (TBI), pain or fatigue. Both PTSD and depression have a complex, growing and consolidating neuroscientific and neuropsychological evidence base, and both can affect neuropsychological test results. In forensic neuropsychological assessments, they are often considered to be confounding factors in evaluating TBI and neurodegenerative disorders but not a source of cognitive impairment in their own right. Yet, an accurate neuropsychological assessment of both cognition and affect is vital to causality determination, prognosis and treatment planning. To complicate matters, selective brain injuries, contingent on the location of injury, can produce symptoms of depression that also affect the neurocognitive profile. Therefore, behavior can overlap not only due to overlapping or comorbid diagnoses, but also due to similar neuroanatomical correlates of both conditions. This paper focuses on reviewing and integrating the available empirical evidence from neuroscience and neuropsychology regarding the cognitive impact of PTSD and depression. Our critical review will emphasize the implications of the more recent evidence for forensic assessment determinations regarding causality, diagnosis, and the impact on function, prognosis and treatment. Hence, electronic search engines, PubMed, PsycINFO, and Google Scholar (up to January 2018) were screened and reviewed both for the neuroscience and neuropsychological literature related to depression and PTSD.

Keywords Depression · PTSD · Neuropsychology · Neuroimaging · Cognition · Forensic · Assessment · Medicolegal

Introduction

Depressive disorders and posttraumatic stress disorder (PTSD) are commonly diagnosed, exclusively or co-occurring, in forensic neuropsychological assessments. However, the ease with which assessors diagnose these disorders is not always paralleled by recognition of the nature of cognitive impact of these disorders and how they interact with other causative factors, such as traumatic brain injury (TBI) or fatigue.

The importance of understanding the impact of common mental health disorders on cognition is paramount in forensic neuropsychology, where the results of disentangling multiple determinants of cognitive impairment often become a subject of courtroom dispute. There are a number of problems with existing causative scenarios implicit in forensic neuropsychology reports that may include the following: (1) under-estimation: although mental disorders are appropriately diagnosed, their cognitive impact is minimized; (2) over-attribution: mental disorders, though present, are incorrectly identified as a primary source of cognitive impairment whilst other possible causes are minimized. For example, the often disputed possible protracted effects of mild traumatic brain injury (mTBI) are minimized without appropriate consideration given the mTBI severity and the time sequence between the mTBI, depression, PTSD, and other factors; (3) misunderstanding of the significance and chronicity of cognitive impairments arising from mental disorders which can be associated with implicit or explicit dismissal of long-term effects; (4) misattribution: cognitive difficulties associated with depression and PTSD may be erroneously attributed to other causes such as single remote mTBI; and (5) multifactorial causality: cognitive difficulties arising from mental disorders interact with cognitive vulnerabilities related to other factors, such as history of mTBI(s), fatigue, pain, and/or the effects of medications.

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Mental health disorders are frequently encountered in forensic assessments, particularly depression and PTSD, which also have relatively high prevalence rates in the general population (Kessler & Bromet, 2013; Kilpatrick et al., 2013). One estimate has suggested that 61% of patients with TBI also present with depression (Rapoport, 2012; Singh, Mason, Lecky, & Dawson, 2018). This finding has several crucial ramifications for assessments. Assessors should be aware of several important issues with presentations of depression and PTSD, including the symptomatic and neuroanatomical overlap, issues related to effort and motivation, fatigue and other medical comorbidities, and the potential for additive neurocognitive deficits.

Depression

The diagnosis of depression consists of a list of heterogeneous symptoms, including anhedonia/abulia, eating behavior change, fatigue, helplessness, hopelessness, sadness, sleep impairment, suicidal ideation, weight change, and cognitive symptoms including concentration difficulty and psychomotor functioning change, as per the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for Major Depressive Disorder (MDD) (American Psychiatric Association, 2013). Importantly, the presentation of depression can vary from individual to individual. As there is the potential for overlapping endorsement of symptoms among different clinical conditions within the DSM-5, diagnostic accuracy can fluctuate. However, an accurate assessment of cognition and affect is vital to causality determination, prognosis, and treatment planning. To complicate matters, some brain injuries, depending on the location of injury, can present with symptoms of depression that can also impact the neurocognitive profile. As such, assessors may note a degree of symptom overlap not only due to overlapping diagnostic criteria but also due to the similar neuroanatomical correlates of both conditions (McAllister, 2011).

The assessment of depression can be further complicated by the hugely varying clinical presentations. Depression has been recognized to manifest differently across ages (Alexopoulos, Katz, Reynolds 3rd, & Ross, 2001; Sepehry et al., 2017; Steuer, Bank, Olsen, & Jarvik, 1980; Thomas & O'Brien, 2008; Whittle et al., 2014), and within several related mental health disorders, such as bipolar disorder. Depression has also been linked to various neuropsychiatric conditions, such as acromegaly, aphasia, dementias, Parkinson's disease, diabetes, fatigue, human immunodeficiency virus (HIV), hypothyroidism, hypopituitarism, migraines, motor neuron disease, narcolepsy, hydrocephalus, PTSD, sarcoidosis, stroke, and subarachnoid hemorrhage (David, Fleminger, Kopelman, Lovestone, & Mellers, 2009).

Considering the relationship between depression and effort on performance validity testing is also highly pertinent. In one study, no significant neurocognitive differences could be identified between depressed and non-depressed healthy controls if motivation and effort were taken into consideration (Rohling, Green, Allen 3rd, & Iverson, 2002). However, this study was limited by the lack of recognition that the group of individuals with depression might have consisted of individuals with minimal or fewer cognitive symptoms (including concentration difficulty or psychomotor changes) compared to the control group when making cross-sectional comparisons, despite controlling for the severity of depression. This limitation affected group balancing within the study and renders interpretation of the results, and particularly the determination of performance validity at the level of forensic neuropsychology, more complex.

Overall, the literature on performance validity in depression, PTSD, and anxiety is mixed, and three lines of thinking are evident: (1) other independent groups have replicated Rohling and colleagues' findings (Considine et al., 2011; Rees, Tombaugh, & Boulay, 2001), (2) documentation of a positive relationship between depression/anxiety and performance validity testing exists (Erdodi et al., 2017; Erdődi et al., 2017; Keiski, Shore, & Hamilton, 2007), and yet, (3) a complex relationship among multiple factors, including depression/PTSD, cognitive functioning, and performance validity, has also received some empirical support (Clark, Amick, Fortier, Milberg, & McGlinchey, 2014; Greiffenstein & Baker, 2008; Suhr, Tranel, Wefel, & Barrash, 1997).

Moreover, effort and motivation can be significantly correlated with fatigue (Boksem, Meijman, & Lorist, 2006; DeLuca, 2005; Hockey & Cambridge, 2013), and this issue is evident in individuals with depression. Fatigue is reported to be present in 46% of TBI patients (Kreutzer, Seel, & Gourley, 2001). As such, neuropsychological assessment of depression should take into consideration the effects of both fatigue and effort/motivation, which can produce differing neurocognitive profiles. Notably, depression-related factors may act as additive symptoms in TBI presentations, i.e., compound their existing severity, or may constitute a distinct presentation, over and above the TBI clinical profile. Thus, in the context of a forensic neuropsychological assessment of TBI with depression, further in-depth examination of other relevant correlates to increase performance and symptom validity is warranted.

PTSD

According to the DSM-5, the clinical features of PTSD include memory impairment with intrusive and involuntary memories of traumatic events, or inability to remember an important aspect of the traumatic event, typically due to dissociative amnesia sleep impairment with nightmares; affect dysregulation associated with intense distress, anxiety on reminders of the traumatic event, persistent negative emotional state, and

hyperarousal of autonomic nervous system (American Psychiatric Association, 2013). Neuropsychological aspects of these symptoms and their neuroscientific underpinnings have been studied in the context of PTSD alone and its common comorbidities. The issue of symptom overlap among diagnostic criteria for many different mental health disorders remains pertinent from research, clinical, and forensic perspectives. Comorbidity is a significant issue in presentations of PTSD, depression, and TBI, a common diagnostic triad in forensic evaluations. Nearly 50% of PTSD patients present with depression (Angelakis & Nixon, 2015; Flory & Yehuda, 2015; Kaufman & Charney, 2000), with statistics showing 69% prevalence in some studies (Elhai, Grubaugh, Kashdan, & Frueh, 2008). Several authors have pointed to the symptom overlap between depression and post-concussive symptoms (Busch & Alpern, 1998; Rosenthal, Christensen, & Ross, 1998), a common finding of post-motor vehicle accidents (O'Donnell, Creamer, & Pattison, 2004). Furthermore, under the heading of Mild Neurocognitive Disorders Due to Traumatic Brain Injury in the DSM-5, neurocognitive changes such as attention, executive function, learning and memory, perceptual-motor difficulties, and posttraumatic amnesia are possible (American Psychiatric Association, 2013). Importantly, all of these are symptoms that could also emerge from depression or PTSD, individually, or comorbidly. Other areas of overlap and concern include when depression presents as pseudodementia (Kang, Zhao, You, Sarkhel, & Prakash, 2014; McNeil, 1999; Tripathi & Mehrotra, 2015), or cognitive symptoms of depression mimicking those of mild cognitive impairment (MCI) (Feinberg & Goodman, 1984; Ganguli, 2009; Wells, 1979). Thus, it is often difficult for practitioners to reliably determine if specific symptoms or symptom profiles are due to effects of the TBI, the emotional disturbance that is present in depression or PTSD, or a combination of both.

Depression also shares many common symptoms with PTSD. Depression may manifest as a symptom of PTSD, or vice versa, or either of the conditions can emerge as a reaction to a different diagnosis. As such, either directly or indirectly, depression could affect a neurocognitive profile in an additive way (Murrey & Starzinski, 2007). However, experts have also posited that PTSD with depression can represent a distinct trauma-related phenotype (Blanchard, Buckley, Hickling, & Taylor, 1998; Flory & Yehuda, 2015). This presentation has been associated with higher level of distress (Campbell et al., 2007), neurocognitive impairment (Nijdam, Gersons, & Olff, 2013; Olff, Polak, Witteveen, & Denys, 2014), and a greater risk of suicide than one condition alone (Ramsawh et al., 2014), resulting in worsening of prognosis.

Current Research Review: Objectives and Method

The remainder of this paper will focus on reviewing and integrating the available empirical evidence regarding depression and PTSD and will consider issues related to the differing presentations of both disorders (Alexopoulos, Katz, Reynolds 3rd, & Ross, 2001; Sepehry et al., 2017; Steuer, Bank, Olsen, & Jarvik, 1980; Thomas & O'Brien, 2008), together with their impact on cognition. Medicolegal practice recommendations will be proposed on the basis of this critical review, as informed by existing research and clinical expertise.

To this end, electronic search engines including PubMed, PsycINFO, and Google Scholar (up to January 2018) have been screened both for the neuroscientific and neuropsychological literature related to depression and PTSD independently, and on the overlap, and subsequently appraised to the best of our knowledge. It is important to note that, in a given meta-analysis, the results of data aggregates with three or more studies are considered reliable, and all others are subject to scrutiny due to low sample size and possible publication bias. Thus, only results with more than three studies will be reported within the current paper. Several meta-analyses and systematic reviews over the past decade have examined the neurocognitive profile of individuals diagnosed with MDD, or PTSD versus healthy controls, other controls, or individuals experiencing trauma but not developing PTSD. The reviewed studies have presented the neurocognitive profiles of PTSD and depression as accounted for in forensic psychological and neuropsychological assessments. Of note, the term depression within the scope of this review has been interchangeably used with major depressive disorder or major depressive episode, and to depressive symptoms, consistent with its use in the underlying literature to which we are referring.

PTSD

Neuroscience

The neurobiology of PTSD has been thoroughly studied from multiple perspectives, including the behavioral presentation (i.e., symptoms), and the neuroanatomical correlates and alterations that occur in the neurotransmitter systems (Bremner, 2006; Sherin & Nemeroff, 2011). To understand the implications of PTSD on neurobiology, it is important to consider some of the key clinical features of PTSD, including memory disruption that involves the inability to remember an important aspect of the traumatic event secondary to dissociative amnesia; concentration problems; sleep disturbance with nightmares; affect dysregulation or anxiety on reminders of the traumatic event; or persistent negative emotional state, as well as diminished interest and participation in significant activities (DSM-5). Each of these behavioral and cognitive symptoms has been thoroughly studied and can be linked to abnormal brain region functioning. For example, memory impairment and anxiety have been related to the hippocampus

and associated networks and can influence the amygdala and limbic system functions (Chen & Etkin, 2013). More specifically, declarative memory deficits in adult patients with PTSD have been correlated with impairment of stress-sensitive regions of the hippocampus (Samuelson, 2011). Other brain regions that help regulate normal functioning of these areas, such as the cerebral cortex, hypothalamus, and pituitary gland, have also been linked to the stress response/fight-or-flight response.

Neuroimaging studies of PTSD have investigated these brain regions in the context of PTSD alone, in the context of comorbidities, and taking into consideration the presence of varying degrees of other forms of psychopathology. For PTSD alone, as compared to the control group, cross-sectional and postmortem evidence has shown smaller volumes of the hippocampus, amygdala, orbitofrontal cortex, and anterior cingulate (Bremner, 2006). Other studies have reported change in the neuronal activation of the amygdala and prefrontal cortex (Malejko, Abler, Plener, & Straub, 2017), and the amygdala and ventral anterior cingulate (Bryant et al., 2008). The involvement of the amygdala as a way of assessing the response to psychotherapy has been noted on the PTSD severity spectrum (Cisler et al., 2015; Shou et al., 2017). However, some of the research findings have been scrutinized more recently, particularly that of hippocampal atrophy, which had been previously presented as a robust finding in a neuroimaging meta-analysis (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005). Researchers are currently considering whether this atrophy may be driven by a genetic predisposition, rather than by PTSD alone (Gilbertson et al., 2002; Moore & Puri, 2012).

In the context of chronic PTSD, neuroanatomical changes (either permanent or ephemeral) and alterations in neurotransmitters (including serotonin, dopamine, norepinephrine, and GABA), as well as hormones (such as cortisol), have been reported to mediate behavioral changes. Chronic PTSD is a condition that may involve chronic stress, or prolonged abuse or maltreatment, and the neuroanatomical and neurochemical correlates are examined differently relative to a more acute presentation via longitudinal neuroimaging studies. Current evidence suggests that although the capacity for neuroplasticity exists, the effect of PTSD on neurobiology can be long term (Bremner, Elzinga, Schmahl, & Vermetten, 2008), particularly on the hippocampus and amygdala (Koenigs & Grafman, 2009; Nutt & Malizia, 2004; Shin, Rauch, & Pitman, 2006). However, these changes may be reversible with pharmacotherapy (Bremner, Elzinga, Schmahl, & Vermetten, 2008), and they appear to be dependent on the length of time between the trauma and the occasion of neuroimaging. Evidence has suggested that in the acute phase (i.e., between one week to six months' post-trauma), there is no substantial change in hippocampal volume (Bonne et al., 2001). However, the literature on this topic is limited and controversial and would benefit from further scrutiny via a neuroimaging meta-analysis.

More recently, researchers have proposed that chronic symptoms of PTSD may be predicted by hyperactivity of the amygdala, and poor recovery can be identified by a failure to maintain ventral anterior cingulate cortex activation in response to fearful stimuli (Stevens et al., 2017). Additionally, brain microstructural changes, such as lower fractional anisotropy and higher mean diffusivity, have been reported in neuroimaging studies, particularly for patients with both TBI and chronic PTSD (Li et al., 2016). Further evidence has emerged from cross-sectional studies on maltreated youth compared to maltreated youth with PTSD, suggesting that there is a brain volume loss difference between the two groups in the ventral medial prefrontal cortex (Morey, Haswell, Hooper, & De, 2016). Moreover, a recent animal study has suggested that chronic PTSD may alter neuroplasticity in the hippocampal region (Tse et al., 2014).

In sum, based on the current state of research in this area, it remains uncertain whether neuroanatomical changes and associated neurocognitive deficits in individuals diagnosed with chronic PTSD are ephemeral (fleeting) or placid (steady). Nonetheless, it is important to remain abreast of the emerging research on the neuroanatomical and neurofunctional correlates of PTSD to inform and continue advancing data interpretive practices in the forensic clinical neuropsychological assessment.

Neuropsychology

The evidence regarding the neuropsychological impact of PTSD is consolidating. Three meta-analyses (Schuitevoerder et al., 2013; Scott et al., 2015; Woon, Farrer, Braman, Mabey, & Hedges, 2017), one review (Brenner, 2011), and one book chapter (Vasterling, Grande, Graefe, & Alvarez, 2010) have reported on the neurocognitive profiles of the individuals with PTSD of various age groups and symptom severity. Additionally, examination of neuropsychological data from Holocaust survivors has demonstrated substantial impairment in learning, free and cued recall, and recognition memory compared to controls (Golier, Harvey, Legge, & Yehuda, 2006). It should be noted that the connection between memory impairment and PTSD in Holocaust survivors is confounded by the extreme and prolonged physical violence, starvation, and disease; as such, generalizations of the evidence obtained from this population should be made with caution.

Starting with the book chapter (Vasterling, Grande, Graefe, & Alvarez, 2010), the authors stipulated that the neuropsychological impact of PTSD is associated with deficits in executive function aspects of attention, sustained attention, learning, and memory. They noted that verbally mediated tasks, including IQ and anterograde memory tasks, were less sensitive for this purpose among individuals with PTSD compared to controls.

A research review (Brenner, 2011), which examined neuropsychological and neuroimaging findings in TBI and PTSD,

highlighted several neurocognitive domains where either subtle or significant impairment was experienced in individuals with PTSD, including verbal memory (and learning), executive functioning (especially response inhibition) and attention regulation. This review posited that attentional bias and alteration in cognitive control mechanisms could influence the memories being retrieved.

Specific to older adults (60+), one meta-analysis (Schuitevoerder et al., 2013) examined the neurocognitive profile of individuals with PTSD (PTSD+) in comparison to older healthy adults (HC), and older adults experiencing trauma but no PTSD (PTSD-). The analysis included 11 studies ($n = 654$ participants of both male and female, with primary trauma types including Holocaust, combat, and prisoner of war). A series of relevant neurocognitive domains were reported, including all cognitive domains, timed and untimed tests, global cognitive functioning, premorbid intelligence, processing speed, attention and working memory, learning, memory, language, visuospatial abilities, executive functioning, and fine motor skills. The magnitude of impairments for PTSD+ versus HC by standardized measure of effect size (EF: Hedges' g) ranged between − 0.28 and − 1.49, notably from small to a very large difference (where PTSD+ individuals did the worst across domains), without including language tests. Similarly, the magnitude of impairments for PTSD+ versus PTSD- ranged between −0.34 and − 1.17, markedly from a small to a very large difference, where PTSD+ did worst across domains, excluding fine motor skills and global cognitive functioning tests. There were no measures provided for language, fine motor skills, and global cognitive functioning tests; hence, these were excluded from further analyses.

This meta-analysis has indicated that in comparison to PTSD-, PTSD+ presented with the largest deficit in processing speed and the lowest deficit in language functions. In comparison to HC, PTSD+ showed the largest deficit in executive functioning and the lowest deficit in attention and working memory. Visuospatial abilities deficits were observed in both comparison groups with similar magnitudes (EF − 0.61). An important limitation to this study is that the significant values were not specified, so it is difficult to determine the level of statistical significance across cognitive domains. The authors reported the worst performance across all measures for PTSD+ in contrast to other groups. Moreover, this study showed higher global cognitive impairment in combat veterans than in the Holocaust survivors (ES − 0.91 vs. − 0.66, respectively) (see Table 1 for the group comparisons).

A subsequent meta-analysis (Scott et al., 2015) incorporated 60 studies ($n = 4108$, PTSD $n = 1779$, PTSD mean age 44.02), including male and female, and examined neurocognitive functioning differences between PTSD+ and two types of control groups (PTSD- and HC). The authors aggregated test scores from paper-and-pencil and computerized neurocognitive tests for a range of cognitive functions (see Table 1 in (Scott et al., 2015)). It included various primary trauma types, including military, interpersonal, state persecution/terror, and mixed or unknown. Across 60 included studies, the study reported neurocognitive deficits in PTSD+ relative to controls ranging from − 0.29 to − 0.62, notably small to medium effect size estimates, where the verbal learning showed the largest deficit. Other domains were identified with medium magnitude effect size including speed of information processing (EF − 0.59), attention and working memory (EF − 0.50), verbal memory (EF − 0.46), executive functions (EF − 0.45), and language (EF − 0.43). The smallest effect sizes were for visuospatial functioning (EF − 0.38), visual learning (EF − 0.32), and visual memory (EF − 0.29). The authors found no significant differences between trauma types, or control group types, or PTSD severity on the magnitude of deficits. However, the severity of PTSD was significantly associated with the severity of deficit in verbal learning, but not with regard to attention/working memory, or speed of information processing. A clinical variable that was found to significantly affect the results was whether individuals were seeking treatment or not, where treatment seekers tended to have higher cognitive deficits in magnitude.

A more recent meta-analysis (Woon, Farrer, Braman, Mabey, & Hedges, 2017) used 14 studies (total $n = 848$, PTSD $n = 368$, PTSD mean age 43.4), and examined the relationship between symptom severity and executive function, found differences when comparing the measure to assess PTSD, with possible implications for the subset of PTSD being experienced. The authors compared PTSD+ to two control groups (PTDS− and HC) and reported that PTSD+ individuals assessed via a Clinician-Administered PTSD Scale (CAPS) performed worse on executive function tests than individuals assessed by the Mississippi Scale for combat-related PTSD. This meta-analysis reported significant effect sizes in the range of small to medium magnitude (0.39 to 0.46), showing the severity of executive dysfunction on a range of executive function measures.

In sum, there is robust evidence from meta-analyses that executive functioning, memory, learning, speed of information processing, and attention tend to be impaired in patients diagnosed with PTSD, especially chronic PTSD, and possibly for combat-related PTSD. Visual-spatial processing, visual memory, and visual learning are likely less affected than language-mediated domains. Thus, the overall cognitive impact of PTSD on function is significant and neuropsychological assessment may be warranted not only for individuals with PTSD comorbid with brain injury but also for those with a sole diagnosis of PTSD. However, major research confounds need to be accounted for, including significant variability in samples, measurement instruments that assessed the nature and etiology of PTSD, and the use of DSM-IV-TR versus DSM-5 diagnostic criteria that may potentially

Table 1 Cognitive differences between individuals with PTSD versus two other control groups (Schuitevoerder et al., 2013)

Domains	Comparison sample	Effect size *g*	Comparison sample	Effect size *g*
All cognitive domains	PTSD+ vs. PTSD-	− 0.58	PTSD+ vs. HC	− 0.72
Timed tests	PTSD+ vs. PTSD-	− 0.52	PTSD+ vs. HC	− 0.63
Untimed tests	PTSD+ vs. PTSD-	− 0.66	PTSD+ vs. HC	− 0.74
Global cognitive functioning	PTSD+ vs. PTSD-	NA	PTSD+ vs. HC	− 1.01
Premorbid intelligence	PTSD+ vs. PTSD-	− 0.71	PTSD+ vs. HC	− 0.98
Processing speed	PTSD+ vs. PTSD-	− 1.17	PTSD+ vs. HC	− 0.87
Attention and working memory	PTSD+ vs. PTSD-	− 0.67	PTSD+ vs. HC	− 0.28
Learning	PTSD+ vs. PTSD-	− 0.4	PTSD+ vs. HC	− 0.72
Memory	PTSD+ vs. PTSD-	− 0.97	PTSD+ vs. HC	− 0.73
Language	PTSD+ vs. PTSD-	− 0.34	PTSD+ vs. HC	NA
Visuospatial abilities	PTSD+ vs. PTSD-	− 0.61	PTSD+ vs. HC	− 0.61
Executive functioning	PTSD+ vs. PTSD-	− 0.8	PTSD+ vs. HC	− 1.49
Fine motor skills	PTSD+ vs. PTSD-	NA	PTSD+ vs. HC	− 0.47

NA, no measurement provided; *(−)*, negative sign refers to deficit in neurocognitive test performance in PTSD versus the control group

PTSD+: individuals that sustained a traumatic event that did lead to PTSD, and PTSD-: individuals that sustained a traumatic event but did not develop PTSD. *HC*, healthy control group

Please note, Table 1 has been shortened from the original article

influence interpretation of this data. These factors warrant a degree of caution pertaining to knowledge transfer to practice when assessing for PTSD.

Depression

Neuroscience

Depression as a disorder of the representation and regulation of mood and emotion (Davidson, Pizzagalli, Nitschke, & Putnam, 2002), with a heterogeneous list of symptoms (e.g., apathy, sadness, fatigue, sleep impairment, eating behavior change, and suicidal ideation), has been extensively studied from a neurobiology perspective (Cowen, Sharp, & Lau, 2013; López-Muñoz & Álamo GonzÁlez, 2012). A comprehensive review of the neuroscience of depression is beyond the scope of this paper. We have therefore selected key anatomical and neurochemical correlates of depression that have a particular bearing on the neuropsychological aspects of depression.

Evidence from neuroimaging studies has illustrated the neuroanatomical correlates of depression, including the frontal lobes (prefrontal cortex), anterior cingulate, amygdala, hippocampus, and thalamus. Other regions such as basal ganglia, brain stem, and limbic regions are thought to be involved (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Drevets, 1998; Pandya, Altinay, Malone Jr., & Anand, 2012). Furthermore, other changes have been emphasized in this literature, including brain network alteration (Chen et al., 2017), cortical and subcortical abnormalities (such as atrophy and thinning) (Lebedeva et al., 2018; Pravata et al., 2017; Zhao et al., 2017), and white and gray matter changes (de Groot et al., 2000; Nobuhara et al., 2006; Taylor et al., 2011; Vasic, Walter, Hose, & Wolf, 2008). Depression tends to alter brain metabolism and regional blood flow, affecting glucose levels (Abi Zeid Daou, Boyd, Donahue, Albert, & Taylor, 2017; Drevets, 1998; Kimbrell et al., 2002; Skibinska et al., 2018). It has also been suggested that cranial nerves may be affected by depression (Gillig & Sanders, 2010).

The neurotransmitters correlated (positively or negatively) with depression include dopamine, norepinephrine, and serotonin (Nutt, 2008), and, less frequently, acetylcholine (Higley & Picciotto, 2014; Janowsky, El-Yousef, & Davis, 1974; Philip, Carpenter, Tyrka, & Price, 2010). GABA has also been indicated in some studies (Anisman, Merali, & Poulte, 2012; Luscher, Shen, & Sahir, 2011). Other neurochemicals correlating with depression include hormones, such as thyroid hormone (Kirkegaard & Faber, 1998), and sex hormones (Studd & Panay, 2004; Young & Korszun, 2010). Moreover, changes in the neuroinflammatory response have been identified in depression (Kop & Gottdiener, 2005). Of note, recent evidence has indicated an altered microbiome in patients with major depression (Chen et al., 2018), suggesting that an alteration in the metabolic/digestive pathway may be involved in depression. Similar evidence has demonstrated the relationship between depression and cardiovascular disease and other functions (Grippo, Moffitt, & Johnson, 2002; Musselman, Evans, & Nemeroff, 1998; Rechlin, Weis, Spitzer, & Kaschka, 1994). Causality in all of these relationships remains speculative and may be bidirectional.

The neurocognitive deficits (e.g., memory, executive functions, attention, and processing speed) in individuals suffering

from depression may emerge from the multitude and interplay of bodily systems with the brain (Austin, Mitchell, & Goodwin, 2001; Jaeger, Berns, Uzelac, & Davis-Conway, 2006; Porter, Gallagher, Thompson, & Young, 2003). These deficits have also been associated with a range of alterations in the body, including imbalances in neurotransmitters, hormonal level changes, gross anatomical changes, cerebrovascular system changes with resulting lack of proper oxygen delivery or glucose absorption, liver function and glucose metabolism, and alteration in function of the digestive organs, and immune system.

Given the reciprocal relationship between depression and functioning in the body, such as alterations in appetite and fatigue (Golden, Lazo, Carnethon, et al., 2008; Schafer et al., 1991), it is important to note that any substantial changes in physical functions (or the brain) could lead to neurocognitive deficits associated with depression. In other words, depression could influence brain function, or brain alterations could lead to depression. At present, it is considered more likely that the relationship between these variables is complex and multidirectional.

Neuropsychology

The neurocognitive profile of individuals with depression has been extensively studied. Here, key findings can be drawn from two reviews (Austin, Mitchell, & Goodwin, 2001; Porter, Robinson, Malhi, & Gallagher, 2015) and four meta-analyses (Henry & Crawford, 2005a; Rock, Roiser, Riedel, & Blackwell, 2014; Snyder, 2013; Zakzanis, Leach, & Kaplan, 1998). Notably, the meta-analyses included in the current review variably commented on the specific neuropsychological tests/versions which showed impaired findings. Where these are not listed below, the specific tests were not indicated.

A review by Austin, Mitchell, and Goodwin (Austin, Mitchell, & Goodwin, 2001) examined the literature between 1966 and 1998 and reported several neurocognitive deficits in depression, including episodic memory, explicit verbal (recall, immediate, and delayed) memory and visual memory. The authors also noted language and executive function deficits, with impaired performance on tests of verbal fluency, attentional set-shifting (Trail Making Test: Part B; and digit symbol substitution), motor speed, working memory (Digits Backwards), perseverative error (Wisconsin Card Sorting Test (WCST)), planning (Tower of London [TOL]), spatial working memory, and simple and choice reaction time.

The most recent review, by Porter, Robinson, Malhi, and Gallagher (Porter, Robinson, Malhi, & Gallagher, 2015), examined neurocognitive deficits in depression versus other mood disorders and highlighted five meta-analyses showing the neurocognitive profiles of individuals with depression. One of the five meta-analyses compared depression to Alzheimer's disease (Christensen, Griffiths, Mackinnon, & Jacomb, 1997), which is not relevant for the purposes of this paper. The remaining four meta-analyses are discussed further in greater detail.

Firstly, the meta-analysis by Zakzanis, Leach, and Kaplan (Zakzanis, Leach, & Kaplan, 1998) examined the nature and pattern of neurocognitive function in MDD and included 22 studies (total $n = 1521$, depression $n = 726$, depression mean age 55, including both males and females). The authors aggregated test results from one or more number of studies per scale and concluded on various magnitudes of deficits, ranging from minimal to large effect sizes. These included results from tests of the Mini-Mental State Examination (MMSE), Wechsler Adult Intelligence Scale-Revised (WAIS-R) subscales [Arithmetic, Comprehension and Digit Symbol, Block Design, Performance IQ, Full Scale IQ, Verbal IQ, Vocabulary; Digit Span Forward and Backward, Information], Trail Making Test, Wechsler Memory Scale-Revised (WMS-R) subscales [Visual Reproduction I, and Logical Memory], Stroop Word Reading, Rey-Osterrieth Complex Figure: Delayed Reproduction, Rey-Osterrieth Complex Figure Copy, California Verbal Learning Test (CVLT): List A Trial 5, Controlled Oral Word Association Test (COWAT), Boston Naming Test, WCST: perseveration, and Paced Auditory Serial Addition Test. The cognitive deficits across these tests, with exception of Stroop Word Reading, Trail Making Test, and WAIS-R: Verbal IQ, ranged from − 0.18 to − 1.03. For Stroop Word Reading, Trail Making Test, and WAIS-R: Verbal IQ, the effect sizes were positive, indicating that individuals with depression outperformed the non-depressed on these three tests. The authors highlighted the effect of effort in encoding information and inefficiency of retrieving poorly encoded information from declarative memory. This portrayal is consistent with the body of literature in this area, with various neurocognitive deficits ranging from memory and executive function to attention in individuals diagnosed with MDD of varying severity.

A second meta-analysis of 42 studies emerging from the years 1982 to 2002 examined the effect of depression on verbal fluency (Henry & Crawford, 2005b). It reported statistically significant ($P < 0.05$) and moderate in magnitude effect size estimates for both semantic and phonemic fluency (effect size $r = 0.44$ and 0.30, respectively). Additionally, non-fluency measures of executive, episodic, and declarative memory showed significant effects, including premorbid IQ, Verbal IQ, Trail Making Test: Part A, Digit Symbol, Boston Naming Test, Verbal Learning, delayed recall, WCST: Category Completed, WCST: Perseverative Errors, and Stroop Interference. For these measures, the effect sizes (mean untransformed correlation coefficients) ranged from as low as 0.05 on the Boston Naming Test to as high as 0.42 on Verbal IQ. Measures of episodic memory, delayed recall ($r = 0.40$), and Verbal Learning from the Selective Reminder Test ($r = 0.35$) fell within the moderate effect-size range. Thus, this

study has illustrated a link among deficits in verbal fluency, episodic memory, and verbal intelligence, and depression.

Thirdly, Snyder (Snyder, 2013) examined 131 studies assessing broad neuropsychological measures of executive function (i.e., verbal working memory, visuospatial working memory, planning, verbal fluency, speed of information processing and vocabulary). This large meta-analysis and systematic review reported weighted mean effect size (Cohen's *d*) for executive function deficits in individuals with MDD compared to healthy controls ranging from 0.32 to 0.97, small to large in magnitude, respectively. With regard to response suppression/inhibition, the Hayling Brixton Test demonstrated the highest deficit ($d = 0.97$); within shifting, Trail Making Test: Part B had the largest with a medium effect size ($d = 0.59$); within updating, according to the authors the *n*-back test indicated the largest effect, with a medium effect size ($d = 0.63$); within verbal working memory, digit span backward showed the largest effect with a medium effect size ($d = 0.55$); within visuospatial working memory, spatial span backward had the largest effect with a medium effect size ($d = 0.72$); and within verbal fluency, semantic verbal fluency demonstrated the largest effect size with a medium effect size ($d = 0.70$). Within comparison measures (psychomotor speed, digit symbol substitution, and vocabulary), the largest effect was in digit symbol substitution with a medium effect size ($d = 0.55$), and planning was reported to have a single small effect size at 0.38. All effect sizes were statistically significant at alpha < 0.05.

Importantly, this meta-analysis examined the effect of specific moderating factors including age, medication, symptom severity, and comorbidity and suggested that the significant effects could not be attributed to slower processing speed (Snyder, 2013). Given the power limitation of this study (one variable per ten included studies), the author performed limited meta-regression analyses to examine for the effect of selected moderating factors, and it was noted that symptom severity and psychotropic medication tended to affect some tests. Of note, post hoc evaluation and discussion of other moderating factors were omitted.

Lastly, the most recent meta-analysis examined 24 studies (including males and females, of various age groups) and reported mild to moderate effect sizes for cognitive deficits in executive function, memory, and attention in depressed patients compared to healthy controls ($d = -0.34$ to -0.65) (Rock, Roiser, Riedel, & Blackwell, 2014). However, these effects were only significant for executive and attention functions, and cognitive deficit symptoms tended to persist in remitted depression. This study reported on individuals with depression as diagnosed by various versions of the DSM, with added cutoff scores from depression scales. The "depressed" groups included patients who were either taking medications or were drug naïve. Of note, this study only included computerized neuropsychological tests (i.e., CANTAB) (see Table 2 for the list of tests and results).

Table 2 Neurocognitive domain as per CANTAB for depression versus healthy controls (Rock, Roiser, Riedel, & Blackwell, 2014)

Domains	Comparison sample	Effect size *d*
OTS/SOC	Dep vs. HC	− 0.43
SWM	Dep vs. HC	− 0.54
IED	Dep vs. HC	− 0.44
SSP	Dep vs. HC	− 0.34
DMS	Dep vs. HC	− 0.46
PAL	Dep vs. HC	− 0.50
PRM	Dep vs. HC	− 0.46
SRM	Dep vs. HC	− 0.41
RVP	Dep vs. HC	− 0.65
RTI	Dep vs. HC	− 0.07

CANTAB, Cambridge Neuropsychological Test Automated Battery; *DMS*, Delayed Matching to Sample; *IED*, Intra-Extra Dimensional Set Shift; *OTS/SOC*, (One Touch) Stockings of Cambridge; *PAL*, Paired Associates Learning; *PRM*, Pattern Recognition Memory; *RVP*, Rapid Visual Information Processing; *RTI*, Reaction Time; *SWM*, Spatial Working Memory; *SSP*, Spatial Span; *SRM*, Spatial Recognition Memory

Dep, depression; *HC*, healthy control group

Please note, Table 2 has been shortened from the original article

In sum, extensive meta-analyses and systematic reviews on the cognitive impact of depression have provided robust evidence of executive dysfunction and attention deficits, in addition to a myriad of other cognitive impairments. The importance of effort with regard to the encoding of information and the difficulties of retrieving poorly encoded information from memory need to be carefully considered in our understanding of the neuropsychology of depression.

PTSD and Depression: Shared Cognitive Vulnerabilities and Neuroanatomy

Upon review of the existing neuroanatomical correlates and neuropsychological evidence, significant shared cognitive vulnerabilities between PTSD and depression are clear, including attention, executive, learning, memory (working, verbal, visual), language, response inhibition, processing speed, and visuospatial abilities. Shared neuroanatomical correlates likely involve the amygdala, anterior cingulate, hippocampus, and prefrontal cortex. These overlaps are consistent with those reports that consider PTSD and depression to be almost indistinguishable (Angelakis & Nixon, 2015; O'Donnell, Creamer, & Pattison, 2004). As a note of caution, studies of the neuropsychological and neuroanatomical correlates of the combined conditions are scarce and we have found no specific meta-analysis on this topic. Moreover, it appears that almost all other evidence related to PTSD and comorbid depression (or vice versa) emerges from studies that either primarily investigated PTSD and secondarily, among multiple moderating

factors and conditions, examined for depression (either as symptoms or as diagnosis), rather than establishing both disorders as equal and comorbid conditions. The same is true for studies that investigated primarily depression and secondarily PTSD.

Additionally, the existing literature examining clusters of neurocognitive functions has provided equivocal findings. One study suggested that depression may mediate the relationship between executive function deficit and PTSD (Olff, Polak, Witteveen, & Denys, 2014), while others underscored the severity of verbal memory (learning and retrieval) dysfunction (Nijdam, Gersons, & Olff, 2013). Figure 1 illustrates the overlap between PTSD and depression from a neuroanatomical perspective. Please note, this figure, as a summary of the studies included within the current review, is by no means exhaustive.

Additionally, maladaptive coping has been considered as a possible mediating factor between depression and PTSD. This is a relatively unexplored field of research, but may shed light on some presentations. For example, to date, limited data has suggested that women with a history of both PTSD and depression tend to have increased difficulties coping with antenatal mental health disorders (Choi et al., 2015). However, the evidence in this area is mixed, as other studies did not find such a relationship (Ullman, Peter-Hagene, & Relyea, 2014). This lack of consistency may be related to both sample and methodology issues. Sensitivity is required when conducting assessments of patients with both PTSD and depression, as maladaptive coping may be linked to sociocultural or socioeconomic disadvantage.

The comparability of the neuropsychological profile of individuals with PTSD to that of depression, and that of TBI, is an ongoing issue. Ample data exists to support the profiles of patients with each of the conditions singly (Bryant, 2011; Pineau, Marchand, & Guay, 2014). However, few neuropsychological studies have examined the profiles in a head-to-head comparison (Vasterling et al., 2012). This data needs to be carefully examined for comparability across the literature, as TBI type, PTSD types, and depression severity all vary across cross-sectional studies. Future neuropsychological meta-analyses are warranted, particularly those comparing all three conditions at once and taking into account the effect of moderating factors such as severity of depression, types of PTSD and TBI, age, and how depression and PTSD are manifested across the lifespan. Given the scope of the current review, further elaboration on the neuropsychological profile of each condition has been omitted, and selected references are provided for direction to readers (Vasterling et al., 2012). It would also be advisable to measure anxiety during neuropsychological assessment as a potential confounding factor in future studies.

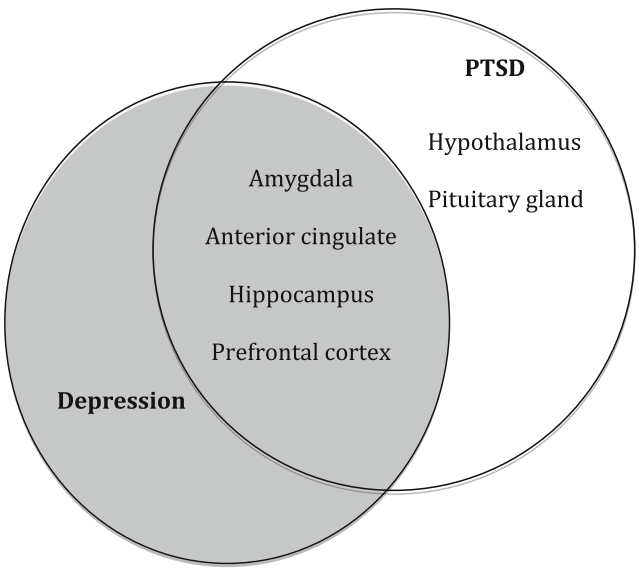

Fig. 1 Diagram showing the neuroanatomical overlap between PTSD and depression

Depression-PTSD and TBI

Within the existing literature, evidence strongly supports the emergence of disruptive psychological disorders, such as PTSD with depression in the aftermath of TBI sequelae (Khoury & Benavides, 2017). Examples of this nature may include post-war or following a motor vehicle accident, just to name a few. The additive effect of PTSD and depression on neurocognitive and psychological functioning has also been strongly indicated (Combs et al., 2015).

Future Research Directions

Additional research is needed regarding the long-term course of neuropsychological problems in depression and PTSD and their persistence after treatment. The issue of maladaptive coping that may accompany cognitive impairments in depression and PTSD has also not been investigated. Likewise, the role of common medical and mental health comorbidities of depression and PTSD has not been adequately studied and the cognitive impact of differences among various subtypes of depression and PTSD is not well understood. Nevertheless, the existing meta-analyses and systematic analyses can assist the forensic neuropsychologist's search for the unique cognitive imprint of depression and PTSD as compared to other conditions, such as TBI, in addition to thorough qualitative and quantitative case analyses. Since the recent change from a categorical to dimensional approach within DSM, future studies comparing data from DSM-5 to an earlier version of the manual are justified for depression, PTSD, combined or singly, with TBI.

Discussion and Conclusions: Implications for Medicolegal Practice

From a forensic neuropsychology perspective, the cognitive impact of acquired brain injury, commonly determined in assessments, needs to be carefully disentangled from the effects of depression and PTSD, alone and together. From a forensic perspective, this exercise is challenging as the causality opinion needs to rely on the integration of case-specific evidence, which may be inadequate, and on existing research, which has gaps and non-convergent findings that are associated with "boundary of science" scenarios. To complicate matters, other variables need to be considered, including the impact of age and how depression and PTSD are manifested across the lifespan. Furthermore, a variety of presentations of depression and PTSD should be examined, including severity, type, persistence, comorbidity, functional impact, responsiveness to treatment, and trajectory.

Although neuropsychological evaluations have traditionally focused on TBI and neurodegenerative disorders, robust evidence of the significant cognitive impact of depression and PTSD, either independently or comorbidly, suggests that routine examinations constitute a future field for expansion in forensic neuropsychology, even in the absence of acquired brain injuries. In the meantime, separating the effects of depression and PTSD from brain injury is a common exercise in medicolegal cases.

Given the nature of the evidence regarding the cognitive impact of PTSD and depression, neuropsychologists can compare and contrast their assessment results with existing published neuropsychological profiles (together with the specific tests from which they were derived) for PTSD, depression, and other potential causal factors. In the context of relevant case data, especially those regarding clinical trajectories, the temporal patterns involved and comorbidities may be analyzed. It is important to consider both PTSD and depression as significant and potentially markedly disabling conditions, from both cognitive and functional perspectives. This is particularly crucial in the context of their long-term effects, rather than just considering the transient assessment confounds and unwanted "noise" in investigation of a primary brain injury condition.

The reciprocal relationship between the brain and depression also needs to be appropriately recognized in forensic causality determination. Given the accumulating research on the cognitive impact of depression and PTSD and their scientific findings, the specialty gap between clinical psychology and neuropsychology is becoming narrower than ever before. This process is likely unstoppable and in keeping with an emerging overarching cognitive neuroscience approach that integrates etiology, brain mechanisms, the impact of experience on brain development, a specification of the disruption of neuropsychological processes, and the delineation of the symptoms at the surface level of the psychopathological condition (Pennington, 2002; Pennington, 2014).

Notably, several limitations exist in our review and the underlying literature. Firstly, we have not reported on meta-analytic results whereby less than three studies were used to report on an aggregate. Therefore, there may exist evidence of other neurocognitive deficits that we did not report on within this review. Secondly, meta-analytic studies pertaining to depression and PTSD that were conducted for clinical rather than forensic purposes do not control for feigned or exaggerated symptoms, which could have affected their results. These symptom validity factors tend to be difficult to capture in larger scale mental health research and may or may not have been controlled for by the underlying individual studies. Thirdly, there are no meta-analyses that were explicitly designed to examine the neurocognitive profile of individuals with a history of single-episode trauma(s) versus multiple traumas (e.g., one-time rape, or motor vehicle accident), or versus repeated exposure to similar traumas (e.g., ongoing domestic violence, or extended combat experience). Additionally, no meta-analyses have considered, as well as on the relationship to the perpetrator (stranger vs. attachment figure) as a potential mediator of the emotional impact of the traumatic event. One can hypothesize that this shortcoming of the current literature is associated with difficulties in accessing research participants, particularly those with complex, repeated trauma of a specific type.

The current review of evidence on the neuropsychological impact of depression and PTSD provides ample grounds for discussion of the emerging best clinical practices of causality determination, and particularly in cases where disentangling the cognitive effects of brain injury from depression and PTSD is a challenge. In this vein, with the limitations of the literature as they are, we would like to propose the following medicolegal practice recommendations:

(1) Conceptualize the impact of depression and PTSD (alone or together) on cognition as of potentially equal clinical significance as compared to acquired brain injury that warrants separately focused investigation using existing research evidence as a guide. Notably, the cognitive effects of these disorders are likely to have a greater cumulative impact relative to the ABIs in milder injuries (for example, uncomplicated single mTBI), as compared to more severe ABI (such as severe TBI).
(2) Consider age, comorbidity, chronicity, severity, coping and functional impact factors, treatment outcomes, and other individual differences that can mediate relationships between common mental disorders and cognition and complicate causality and prognostic determinations.
(3) While carefully reviewing case history, consider exploring temporal (time-based) factors of relevance, such as trajectory of recovery from injury or illness, presence of

cognitive impairment prior to onset of depression or PTSD, and evidence of cognitive improvement following treatment and recovery from these conditions;

(4) During the testing, consider monitoring the examinee's behavior for symptom interference arising from depression and anxiety and explore use of instruments that can help capture situational effects of emotional distress and/or various scales that assess subjective comfort levels during the testing. When examinees become excessively emotionally aroused during the assessment, consider taking a break, suggest a form of relaxation or distraction that can situationally decrease the hyperarousal, or reconvene at another time. Also, keep in mind that it is important to minimize any possible adverse emotional effects of the trauma-focused part of the interview on subsequent testing;

(5) Although low motivation and fatigue are inherent symptoms of depressive disorders and the results of research on the relationship between depression and effort in testing are not consistent, the use of PVTs continues to be recommended. The inclusion of PVTs it is now an expected standard aspect of any neuropsychological assessment and the measurement research in this area is growing rapidly. Nevertheless, caution needs to be exercised when interpreting individual test scores on PVTs. A well-balanced multimethod assessment of effort, combined with recognition of psychosocial and clinical contextual factors at play, constitutes an optimal approach to the measurement of complex motivational constructs such as performance and symptom validity. Sole reliance on performance validity testing is not recommended.

(6) Rely on the multimethod approach for establishing causality, diagnosis, and functional impact, especially using independent sets of collateral data to assist with disentangling of multiple determinants and identifying converging patterns of evidence; the same test score can be affected by multiple causative factors and corroborating emerging quantitative evidence with qualitative clinical data (e.g., observation of cognitive difficulties by family members, coworkers, and supervisors; suddenly increased reliance on compensatory strategies and task accommodations; effortful performance in testing; all in the temporal context) can help with the differentiation of various cognitive impacts[1];

(7) In cases of multifactorial causality, such as involving TBI, PTSD, and/or depression, consider re-assessment following appropriate treatment for a given mental health condition to monitor changes in cognitive functioning;

(8) In prognostication, consult research on the long-term effects of PTSD and depression; do not assume that "just depression and PTSD" are inconsequential from a neuropsychological perspective.

[1] It is important to note that sources of collateral information (e.g., family members) are not always independent sources of information. However, their information is helpful if also consistent with observations of other collateral sources, such as peers and employers. We would emphasize that none of the collateral data via interviews is truly objective. Collateral interview methodology is poorly described in the assessment literature and, in our opinion, warrants a separate paper. The addition of standardized instruments with validity scales for collateral informants (such as in the BRIEF-A) may improve the quality of the data obtained in this area.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent No informed consent was needed for this review paper.

Animal Rights No animal studies were carried out by the authors for this article.

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