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REVIEW

The Role of the Amygdala and the Ventromedial Prefrontal Cortex in Emotional Regulation: Implications for Post-traumatic Stress Disorder

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Abstract
The importance of the amygdala as a salience detector and in emotional learning is now well accepted. The mechanisms that regulate and inhibit the amygdala, however, are less well understood. This review provides evidence from imaging and lesion studies to support the role of the ventromedial prefrontal cortex (vmPFC) as a moderator and inhibitor of the amygdala. The *dual inhibition* model centres on the broadly defined ventromedial prefrontal cortex (vmPFC) and the distinct role of two of its subcomponents, the rostral anterior cingulate cortex and orbitofrontal cortex. The *dual inhibition model* posits that these two regions, along with their associated inhibitory pathways, must interact for adequate inhibitory control of the amygdala and emotional regulation. Following a description of the model's experimental support, it is then proposed as a neuropsychological mechanism for post-traumatic stress disorder (PTSD). *Flashbacks,* as a defining feature of PTSD, are described in terms of a subcortical orienting network. Finally, there is a discussion of how a neuropsychological understanding of post-traumatic stress disorder (PTSD) might inform a clinician's approach to treatment and how the dual inhibition model might have a more general application to understanding emotional dysregulation.

Keywords Ventromedial prefrontal cortex · Post traumatic stress disorder · PTSD · Amygdala · Emotion · Emotional regulation · Treatment · Emotional dysregulation · Anxiety · Neuropsychology · Affective neuroscience · Brain

Introduction

This review paper seeks to extend previous broader reviews (Koenigs & Grafman, 2009; Hiser & Koenigs, 2018; Roy, Shohamy, & Wager, 2012; Schneider & Koenigs, 2017) by focusing on the role of the vmPFC in emotion regulation as a neuropsychological mechanism for post-traumatic stress disorder. Although we acknowledge that a multi-component network of structures serves emotional regulation and this network may be undermined in a number of ways (Grupe & Nitschke, 2013; Etkin, Buchel, & Gross, 2015), our recent lesion research provides evidence that the vmPFC plays a central and controlling role.

In this review, following a broad description of the functional roles of the amygdala and the vmPFC, the *dual inhibition model* is described with supporting evidence from animal studies. We then demonstrate the application of this model with the specific, albeit complex example of post-traumatic stress disorder (PTSD). Following a discussion of the neuroimaging literature, we present evidence for the controlling role of the vmPFC in the dissociative a sub-type of PTSD. We follow this by description of the enigmatic phenomenon of the *flashback.* The final section of this review discusses therapeutic implications of an improved understanding of this disorder.

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The Functional Relationships Between the Brain Areas Under Discussion

The Amygdala

The amygdala is an anterior medial temporal lobe structure consisting of a collection of multiple sub-nuclei. This phylogenetically old structure is present in all vertebrates, and as such, is assumed to make an evolutionary contribution to self-preservation (Adolphs, 2013). Indeed, the amygdala influences the constellation of sympathetic autonomic preparations for *flight, fight or freeze* (Mobbs, Hagan, Dalgleish, Silston, & Prévost, 2015).

The early field studies by Klüver and Bucy (1939) and experimental studies by Weiskrantz (1956) highlighted the crucial role of the amygdala in threat detection by first finding that bilateral amygdala lesions to the adult macaque result in increased tameness. However, the involvement of the amygdala as an emotional evaluator is limited compared with cortical regions such as the orbitofrontal cortex (Morrison & Salzman, 2010).

Bilateral lesions to the amygdala also result in a reduced ability to detect fearful and other negative facial expressions, as well as a difficulty in detecting subtler threatening facial features such as untrustworthiness and jealousy (Adolphs, Baron-Cohen, & Tranel, 2002; Santos, Almeida, Oliveiros, & Castelo-Branco, 2016). Within the auditory modality, patients with amygdala damage also have difficulty recognising dramatic music intended to evoke fear (Gosselin et al., 2005).

Human lesion studies support the function of the amygdala in threat detection. Aside from one retrospective study showing a reduction in anxiety related disorders in Vietnam veterans with amygdala lesions (Koenigs et al., 2008), most human lesion studies have focused on patients with a rare genetic disorder, Urbach Wiethe disease, and thus these studies tend to have small samples. Tranel and Hyman (1990) report a patient with Urbach Wiethe that showed poor social judgement, with a history of selecting a series of unreliable and disreputable partners. There is also evidence of reduced feelings of fear in a patient with the same disorder (Feinstein, Adolphs, Damasio, & Tranel, 2011).

While the process of threat detection primarily involves the amygdala, as will be argued the periaquaductal grey area. There is activity that is sustained following the phasic activity of the amygdala (Silverstein & Ingvar, 2015). There is a close relationship between the amygdala, vmPFC, the anterior insula (AI), and dorsomedial anterior cingulate, which is sometimes referred to as part of the salience network (Seeley et al., 2007). In studies were there is continued anticipatory anxiety over time there is often an initial phasic amygdala activity, which is then replaced by activity in the AI and other areas within the bed nucleus of the stria terminalis (BNST; the extended amygdala) (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011; Brinkmann et al., 2017; Münsterkötter et al., 2015; Straube, Mentzel, & Miltner, 2007). The BNST is found to be active during threat monitoring and with its connections to the hypothalamus and septal area, these areas are also predictably, related to feelings of anxiety (Somerville, Whalen, & Kelley, 2010).

It is difficult to determine the degree of adaptation that individuals may have achieved when they have sustained bilateral amygdala lesions in the early stages of their life (Becker et al., 2012). Such an understanding necessitates an examination of animal studies, which have greater experimental control than observational case studies in humans. For example, Moadab, Bliss-Moreau, Bauman, and Amaral (2017) reported that adult monkeys who had sustained amygdala lesions in infancy demonstrated reduced signs of abnormal social emotional response compared to monkeys with lesions in adulthood. Nevertheless, some of these macaques with lesions at infancy did exhibit increased social caution (Moadab et al., 2017). Therefore it appears that by adulthood, there may be some adaptation to amygdala lesions acquired in infancy, however some aberrant behaviours remain.

It has also been found that macaque monkeys' with bilateral amygdalectomy were preferred as cage companions by macaques without brain lesions (Amaral, 2003). Thus the function of the amygdala is also relevant to social functioning, and this concept has been addressed by other field studies in macaques (Kling & Brothers, 1992). Finally, Costa and colleagues found that the amygdala also reflects the arousal level of imagined pleasurable situations (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010). Broadly, amygdala activations are correlated with activity in both the medial PFC and the nucleus accumbens, whose activations are also correlated with each other when responses are pleasurable or rewarding (Pujara & Koenigs, 2014). When asked to imagine aversive images, the amygdala is active, but ceases to correlate with the medial PFC and nucleus accumbens, suggesting some degree of independence in threat detection (Baxter & Murray, 2002; Bonnet et al., 2015; Janak & Tye, 2015).

The Ventromedial Prefrontal Cortex

The amygdala is clearly important in a role of novel threat recognition, but some authors question its sophistication and see the vmPFC playing a more complex and central role (Blair, 2016; Rolls, 2005). An animal might conceivably be driven to needless and eventually exhausting false-alarms of

threat if they did not possess the modifying influences of other neuropsychological mechanisms. Most pertinently, the ventromedial prefrontal cortex (vmPFC) is seen as having a modifying influence on the amygdala.

The term ventromedial prefrontal cortex (vmPFC) requires some clarification. It is sometimes used to denote areas excluding the rostral anterior cingulate (rACC) and/or the orbitofrontal cortex (mOFC). However, following Damasio and Anderson (1993), and consistent with our previously published lesion work (Jenkins et al., 2014, 2018; Hornak et al., 2003 and Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015), we define the vmPFC as including the medial structures of the OFC and rACC (see Fig. 1). In terms of Brodmann areas (BAs), these regions include the rACC, BAs 25, lower 24, 32 and the medial aspects of the orbitofrontal

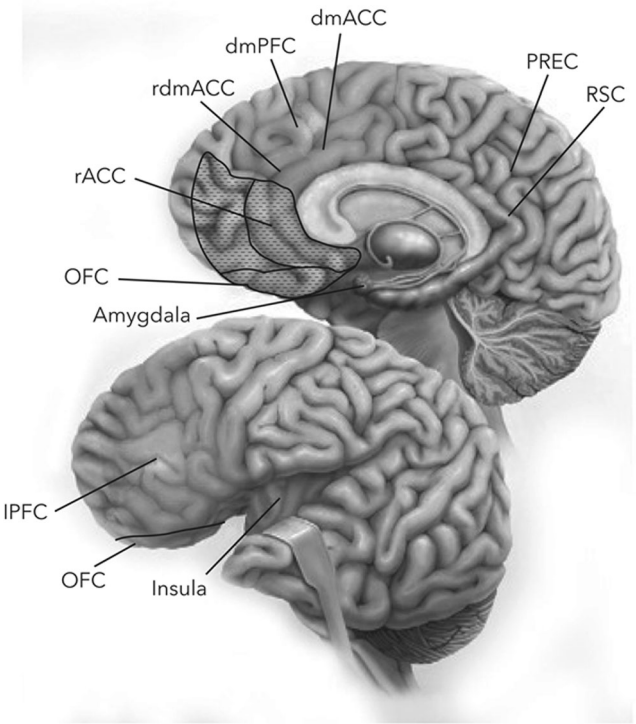


Fig. 1 Shows the areas implicated in the implicit emotional regulation under discussion. The shaded vmPFC area includes the rostral anterior cingulate cortex (rACC) and adjacent medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC, both medial and lateral). Also shown are the areas of the amygdala and the insula (the anterior aspect is most implicated), the rostral dorsal anterior cingulate (rdACC), the dorsomedial prefrontal cortex (dmPFC), dorsomedial anterior cingulate (dmACC). Posterior and medial to the structures are the precuneus (PREC) and retrosplenial cortex (RSC). Dorsal to the central area of the lateral prefrontal cortex (LPFC) is referred to as the dorsolateral PFC (more superior) with ventral to this area referred to as the ventrolateral PFC. These last lateral areas are more active in studies of explicit (instructive) emotional regulation, where there is cognitive control

cortex BAs 10, 11 and 12. This contrasts with the distinction sometimes used between the vmPFC and the rostral ventral areas of the ACC (e.g. Schneider & Koenigs, 2017).

In their seminal work, Damasio and Anderson (1993) use the term vmPFC to describe lesions in patients who sometimes exhibited socially inappropriate behaviour in daily life. This usually occurred after neurosurgical damage of this area following brain tumour removal. While there are a number of possible neuropsychological explanations for this behaviour (Andrewes, 2016, pp. 537-541), we argue that the social deficits following vmPFC damage are related to the importance of this area for providing the conceptual perspectives of self. Socially appropriate behaviour is dependent on monitoring one's own behaviour as it occurs. A number of neuroimaging studies have now shown activation of the vmPFC when processing self-relevant information within autobiographical memory (Bergström, Vogelsang, Benoit, & Simons, 2015; D'Argembeau, 2013; Denny, Kober, Wager, & Ochsner, 2012; Kurczek et al., 2015; Wagner, Haxby, & Heatherton, 2012). It is of interest that these patients are only able to judge their own socially inappropriate behaviour when it is described to them (Hornak, Rolls, & Wade, 1996) or when they are able to view their own videoed behaviour (Beer, John, Scabini, & Knight, 2006). In other words, when an objective view of the self is *provided* for them, in such a case they only have access to semantic knowledge of social mores without additionally having to monitor ongoing conceptual knowledge concerning self.

Within the broad vmPFC area, functional sub-areas have been identified. For example, the medial orbitofrontal cortex (mOFC) is associated with reward evaluation and reinforcement expectation (Mishkin, 1964; Hornak et al., 2004; Wallis, 2007). More anteriorly, the rACC and the medial perigenual PFC have been linked to the understanding of social events, autobiographical memory (Maguire, 2014), and the reflection on self and the mentation of others. This includes mentalization (conscious introspection) concerning personal relationships (Amodio & Frith, 2006), and monitoring of self and others (Wittman et al., 2016). These areas are also implicated in empathy (Lev-Ran, Shamay-Tsoory, Zangen, & Levkovitz, 2012) and theory of mind (Jenkins et al., 2014; Shamay-Tsoory & Aharon-Peretz, 2007) and in particular, affective theory of mind (Sebastian et al., 2012). Unlike the amygdala, the vmPFC is involved in the analysis of personally relevant information *over time*. This is revealed in impaired performance on gambling tasks that require learning through

experience (Bechara, Damasio, Damasio, & Lee, 1999) and reversal learning paradigms (Hornak et al., 2004).

The mOFC and the rACC are closely and richly interconnected ventromedially and with the anterior insula (AI), especially at area BA 14 (Ongür & Price, 2000), and these areas also have robust and separate neural pathways with the amygdala and hippocampus. The mOFC and the rACC pathways with the amygdala are reciprocal, and these pathways are important when considering their functional role. However, the *inhibitory* projections are most robust from the rACC to the amygdala when compared to the OFC, while the majority of connections between the amygdala and the posterior mOFC are projecting from the amygdala to the posterior medial PFC (pm OPC) (see Fig. 2; Ghashghaei, Hilgetag, & Barbas, 2007; Likhtik, Pelletier, Paz, & Paré, 2005; Ongür & Price, 2000; Timbie & Barbas, 2014). All three of these areas (OFC, rACC and amygdala) have input from tertiary levels of sensation. There are also connections with the anterior insula that are associated with interoception, and possibly empathy for those same sensations in others e.g. pain (Gu, Hof, Friston, & Fan, 2013), although this last proposal is not without controversy. There are also connections between the vmPFC with the hypothalamus that are important for visceral reactivity and part of the defence response, with effector connections to the periaqueductal grey area. There are also pathways from these three areas vmPFC, Insula and amygdala to the hippocampus that are important for retrieving emotional memory associations. The acquisition of new emotional memories involves efferent pathways from the vmPFC and the amygdala to the hippocampus and the anterior temporal cortex (Price & Drevets, 2010). Non-human studies show connections of the hippocampus with more ventral aspects of the vmPFC influencing extinction and more dorsal vmPFC for strengthening of memories (Ye, Kapeller-Libermann, Travaglia, Inda, & Alberini, 2017; Sotres-Bayon & Quirk, 2010). Studies with nonhuman animals also provide evidence that the vmPFC acts to inhibit the amygdala (Delgado, Olsson, & Phelps, 2006; Quirk & Beer, 2006). Evidence for the vmPFC modulation of the amygdala, comes from studies highlighting the importance of the vmPFC in the extinction of fear, in both delayed and emotional learning (Åhs, Kragel, Zielinski, Brady, & LaBar, 2015; Milad & Quirk, 2002; Milad, Rauch, Pitman, & Quirk, 2006; Milad et al., 2008; Milad et al., 2009, ; Winkelmann et al., 2016). These findings are also reflected in certain aspects of the human literature on emotional regulation (Etkin, Egner, & Kalisch, 2011; Ochsner & Gross, 2005; Phillips, Ladouceur, & Drevets, 2008). However, as will be argued, the combined evidence of two human lesion studies have only recently supported these animal and neuroimaging models (Jenkins et al., 2018; Motzkin et al., 2015).

The vmPFC should be conceived broadly as a *social modulator that supports the understanding of social interactions and decisions concerning self over time.* This accent on social interaction was demonstrated in a recent primate study which showed that selected electrodes implanted in the vmPFC only become active during social interaction (Mao et al., 2017). Studies that use stimuli that are *not* consistently related to self are less likely to show involvement of the vmPFC, although there are additional explanations as to why this might be the case (see Buhle et al., 2014 p. 2986). For this reason, fearful faces, trauma narratives and films that induce a feeling of personal relevance are often used in studies interested in the function of vmPFC, and are most successfully used in experimental work that will be described in the area of post-traumatic stress disorder.

In the case of our own study (Box 1), we used film clips that showed social interactions and allowed viewer identification with the characters. Here, we refer to *implicit emotional regulation*, which is more reliably associated with vmPFC activation, rather than *explicit emotional regulation,* that may result from active cognitive reappraisal instructions in which lateral PFC structures are more involved (Buhle et al., 2014). Implicit emotional regulation implies an emotional modulation that is more often present when an individual passively responds according to knowledge of the feared stimulus in the past and present (Etkin et al., 2015).

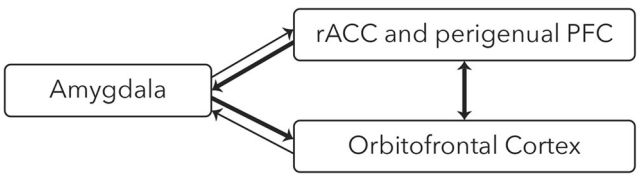
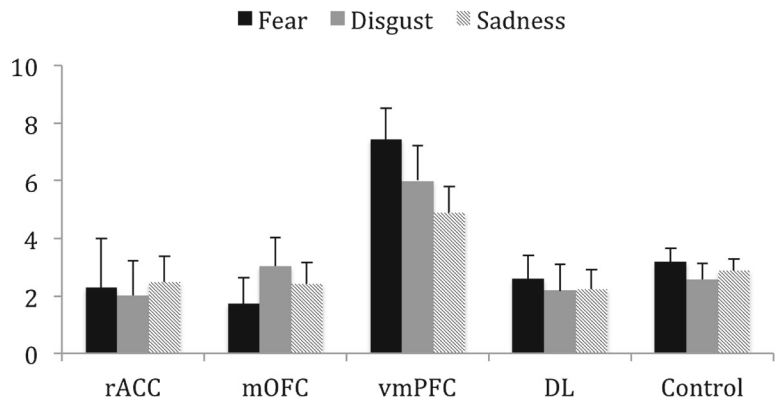


Fig. 2 A schematic representation pathways connecting the amygdala and the ventromedial prefrontal cortex (vmPFC). Robustness of connection is demonstrated by line thickness. The most robust inhibiting pathway is efferent from the rACC and perigenual PFC to the amygdala. A minor inhibitory pathway is also shown from the orbitofrontal cortex to the amygdala. PFC= prefrontal cortex, rACC= rostral anterior cingulate cortex

Box 1: Excessive Emotional Reactivity to film clips in patients following neurosurgery to the vmPFC

Table shows correlations between composite negative self–report (adjusted for neutral self –report) with percentage of damaged Brodmann area.

	BA 10	BA11	BA 9	BA 24	BA 32
Negative Rating	.37 NS	-.33 NS	.64 p <.05	.65 p <.05	.72 p <.01



The above graph shows the average self-ratings for the Fear, Disgust and Sadness films respectively for the groups with rostral anterior cingulate (rACC), medial orbitofrontal cortex (mOFC), ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (DL) lesions and the Control group. See Jenkins et al. (2018) for details of the groups and methods. This analysis using a composite average negative score minus neutral ratings found a group effect $F(4, 48) = 3.28$, $p = .02$, $g^2=.22$ and comparisons vmPFC > mOFC , $t(10)= 2.26$, $p= .047$, vmPFC > Control , $t(29)= 2.79$, $p< .01$.

A dual inhibition model (Jenkins et al., 2018) provides that the interconnected nature of the rostral anterior cingulate (rACC) with the medial orbitofrontal cortex (OFC) means there may still be an inhibiting influence on the amygdala even when one area (or connection) is lesioned in isolation. Therefore, while the rACC has the main potential for influence on the amygdala, there remains an efferent inhibiting pathway from the orbitofrontal cortex (mOFC) on the amygdala.

Lesion Studies and Excessive Emotional Reactivity

Hornak and colleagues (Hornak et al., 2003) reported on patients following neurosurgical lesions to the vmPFC which included areas of the affective cingulate cortex (Bush, Luu, & Posner, 2000), being rACC (BA 24/42) and BA 9, in other words the rostral medial area of the PFC. Many of those patients with BA9/rACC lesions reported marked emotional changes, and some described such profound effects on their daily life that they felt as though they had become different people since their surgery. In many cases the patients' described how these changes had an adverse effect on their relationships with their family and/or friends. Overall changes included increases in the intensity and frequency of different emotions. Increases in emotional intensity occurred approximately twice as often as decreases in intensity in patients with medial BA9/rACC lesions. Most commonly, there were increases in sadness, anger and happiness. Many of these patients described themselves as having become far more 'emotional' than before their surgery, becoming far more easily upset, and being more likely to cry (Hornak et al., 2003).

Despite these reports of excessive changes in emotional dysregulation following brain damage and tumour removal (Hornak et al., 2003), the lack of self–knowledge, described

above, is likely to be the reason for a reduction of diagnosis of anxiety disorders such as depression and PTSD. For example, Koenigs and colleagues have reported that Vietnam veterans with vmPFC damage have a reduced incidence of depression and post-traumatic stress disorder, compared to veterans without vmPFC damage (Koenigs & Grafman, 2009; Koenigs et al., 2008). We agree with the interpretation of Koenigs and Grafman that "…. PTSD is characterized by the experience of distress and anxiety associated with past autobiographical events. Thus a loss of self-insight or self-reflection would diminish the core symptoms of the disorder." (Koenigs & Grafman, 2009, p.6; see also Philippi & Koenigs, 2014). Also the emotional change following damage to the vmPFC can be described as being diffusely reactive rather than focused. There is therefore a difference between the effect of gross damage to the vmPFC and a weakly influential vmPFC that will be discussed in the next section.

Our own research (see Box 1) supports Hornak and colleagues' (Hornak et al., 2003) work using a psychophysiological experimental approach. In our study, patients with neurosurgical vmPFC lesions were presented standardised film clips (Jenkins & Andrewes, 2012). We measured the subjective emotional response and heart rate variability to negative, positive and neutral film clips (Jenkins et al., 2018). The results of this study lead to a dual inhibition model that found the that while the rACC contributes mostly to the inhibition of amygdala reactivity, a double disconnection between the amygdala with both the mOFC and rACC was required prior to complete disinhibition of the amygdala (see Box 1). It is of interest that Hornak and colleagues also found no emotional changes in a bilaterally lesioned OFC group without rACC lesions, although there were signs of reduced empathy in this group (Hornak et al., 2003).

The view that hyper emotional reactivity is specifically the result of disinhibition of the amygdala is lent support by Motzkin and colleagues (Motzkin et al., 2015). In their study, patients with bilateral damage to the vmPFC showed increased amygdala activity compared to controls when exposed to emotionally probing stimuli. A similar demonstration of the inhibitive role of the medial prefrontal cortex on the amygdala has also been found in non-human studies (Delgado, Nearing, Ledoux, & Phelps, 2008; Delgado et al., 2016; Quirk, Likhtik, Pelletier, & Pare, 2003). Our own results in humans suggest excessive and dysregulated emotional reactivity in groups with more discrete lesions that indicate the importance of the rACC in this role (see Box 1). If excessive emotional reactivity is associated with poor control over amygdala arousal and reported emotional reactivity, then this evidence may contribute to a further understanding of existing imaging studies of persons with psychiatric disorders without brain damage.

The Case of Post-Traumatic Stress Disorder (PTSD)

A Description of PTSD

The following case reveals many of the features typical of post-traumatic stress disorder (PTSD). *The client's history included a traumatic event, which occurred while he was a manager at an all-night vendor store. A man disguised in a balaclava had entered the shop holding a gun and demanded the client lie on the floor, telling him that if he got up, he would be shot. The assailant then poured kerosene over the floor of the shop and set the fuel alight. The client witnessed "a wall of fire coming towards him" and at the very last second he stood up to avoid the flames, at the same time fearing that he would be shot. The assailant had by this time disappeared. The client claimed that when the police arrived they were suspicious of him and treated him roughly. Just after the event, he experienced nightmares that were involving, or related to, the event. Since the event, small things had reminded him of his experience (e.g. strip lighting in a shop), and would set off a replaying of the event in his mind, accompanied by extreme anxiety. Later at another workplace he had to be physically restrained when he showed uncontrolled anger and violence after a work mate, as a prank, set fire to the newspaper he was reading.*

This vignette shows the core symptoms of PTSD, that include an extreme sensitivity to the associated context of the traumatic event and the consequent avoidance of the situations that are likely to remind the patient of the event. The patient may react to reminders with hyperarousal, but there may also reports of emotional numbing and dissociation. The patient is irritable, jumpy, or constantly hypervigilant. Also, there are *flashbacks* which involve re-experiencing of the event, that seem very real to the patient. The complete history reveals some instances of irritability and aggression with elements of depression (DSM 5 diagnostic criteria, American Psychiatric Association, 2013). A patient is only classified as suffering PTSD after reporting symptoms for a month. Prior to this they are classified as suffering an *acute stress disorder*.

Around 50% of people are exposed to a traumatic event in their lifetime, but only a minority of persons (around 20%) will go on to show symptoms of PTSD (Breslau, 1998; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). Therefore, persons with PTSD are often deemed to have some form of predisposed vulnerability. Such vulnerability is also found in a greater percentage of persons with sub-threshold PTSD who show symptoms following symptom provocation (Stark et al., 2015). In the following section there is a discussion of the brain functional relationships according to neuroimaging meta analyses.

Neuroimaging and PTSD

The amygdala with the anterior insula (AI) and the anterior cingulate (ACC) are part of a putative *salience network.* A *salience network* has been described as processing information of a threatening personal relevance (Seeley et al., 2007). Seeley also describes an *executive control network* that includes lateral PFC areas that are important for cognitive control of emotions. Perhaps surprisingly, these lateral areas have only sparse *direct* connections with the central emotional processing network that involves the vmPFC (Ghashghaei et al., 2007). Therefore, it is necessary to consider a further network that influences emotional reactivity that involves the vmPFC. Here we refer to this network as part of an *emotional modulating network,* arguing that the emotional modulating network is especially relevant in a passive implicit response to threat, rather than an explicit strategic effort to appraise and cognitively control emotional reactivity (see Buhle et al., 2014).

Several meta-analyses of studies have provided a relatively consistent neuroimaging profile of PTSD persons following the exposure to feared material in the scanner (Etkin & Wager, 2007; Hayes, Hayes, & Mikedis, 2012; Kühn & Gallinat, 2013; Patel, Spreng, Shin, & Girard, 2012). This profile, although based on studies that frequently contain small samples, they nevertheless consistently show a hyperactive salience network and an underactive vmPFC (see Fig. 3).

A model of PTSD that has gained support from imaging studies proposes that the vmPFC is weakly influential in modulating and inhibiting the amygdala and anterior insula (AI). It will be further argued that this leads to emotional dysregulation and the disinhibited fear response of PTSD. Further support for this model of disinhibition comes from structural neuroimaging analyses. For example, reduced volume of the rACC within the vmPFC may predict greater intensity of PTSD symptoms (Bryant et al., 2008; Baldaçara et al., 2014; Cha, Weiner, & Neylan, 2013; Clausen et al., 2017; Sadeh et al., 2015; Offringa et al., 2013). In addition, some of these studies showed a reduced connectivity between the amygdala and vmPFC (Stevens et al., 2013; Thome et al., 2017), and a meta-analysis has revealed that PTSD patients have reduced integrity of the white matter pathway between the amygdala and vmPFC (Jenkins et al., 2016). Amygdala over activity is associated with an exaggerated fear response. PTSD symptom ratings show a positive relationship with the activity in the insula and a negative relationship with the activity in the anterior cingulate and medial PFC (Hughes & Shin, 2011; Ke et al., 2015; Zhang et al., 2016). Therefore as described schematically in Fig. 4 and proposed by others based on neuroimaging results (Goldin, McRae, Ramel, & Gross, 2008; Milad et al., 2006; Rauch, Shin, & Phelps, 2006; Shin, Rauch, & Pitman, 2006). There is evidence, therefore, for PTSD being associated with a weakly inhibiting vmPFC and a high arousal of the amygdala both from the above reviewed lesion and the neuroimaging evidence.

In summary, we have reviewed our own lesion work that supports a model of excessive emotional reactivity and a hyperactive amygdala. Based on neuroimaging results, the model was also found to apply to the disorder of PTSD (e.g. Rauch et al., 2006). The advantage of lesion research is that sometimes it may be easier to imply cause and effect. The dual inhibition model describes how a lack of influence on the amygdala by the rACC leads to emotional dysregulation. Although because of the close relationship between the rACC and the OFC a double disconnection from these structures is required for a substantive lack of amygdala modulation.

A Neuropsychological Model of PTSD

We argue that the dual inhibition model can be applied to the case of PTSD, whereby there is a weak inhibition of the amygdala. In this section this evidence will be combined with a more comprehensive analysis of the dysfunctional neurocircuitry attributed to PTSD in support of the more elaborate model provided in Fig. 4.

There are now a number of studies exploring the neuroimaging profile of anxious and healthy controls, comparing a response to extreme imminent danger with control conditions of safety. Typically, safety conditions are associated with increased vmPFC and hippocampal activity that we argue allows protection against habitual and reflexive emotional reactivity. Williams and colleagues (Williams, Kemp, & Felmingham, 2006) provide evidence that the process of stimulus provocation and subsequent vmPFC reactivity may be studied in two phases. Williams and colleagues (Williams et al., 2006) rapidly presented fearful faces to PTSD patients and measured fMRI at an immediate and delayed interval. Healthy controls showed initial activity in the right amygdala with anterior insula and reduced activity in the rACC a delayed profile was associated with lowered left amygdala activity and an increase in activity within the left rACC. The PTSD group, however, showed the high amygdala and insula lowered rACC activity in response to fearful faces, but did not show the pattern of amygdala and rACC interaction shown in the controls (Williams et al., 2006). In other words, Williams and colleagues described the initial activity within the amygdala, which is acting as a fear detector, and activity in the anterior insula (AI) as phase 1. This attentional focus on the threat is sometimes referred to as *high jacking* the brain (Pineles, Shipherd, Mostoufi, Abramovitz, & Yovell, 2009). However, this attentional focus to threat may be reduced in healthy individuals in a second phase, in which the vmPFC inhibits the amygdala hyperactivity (Williams et al., 2006).

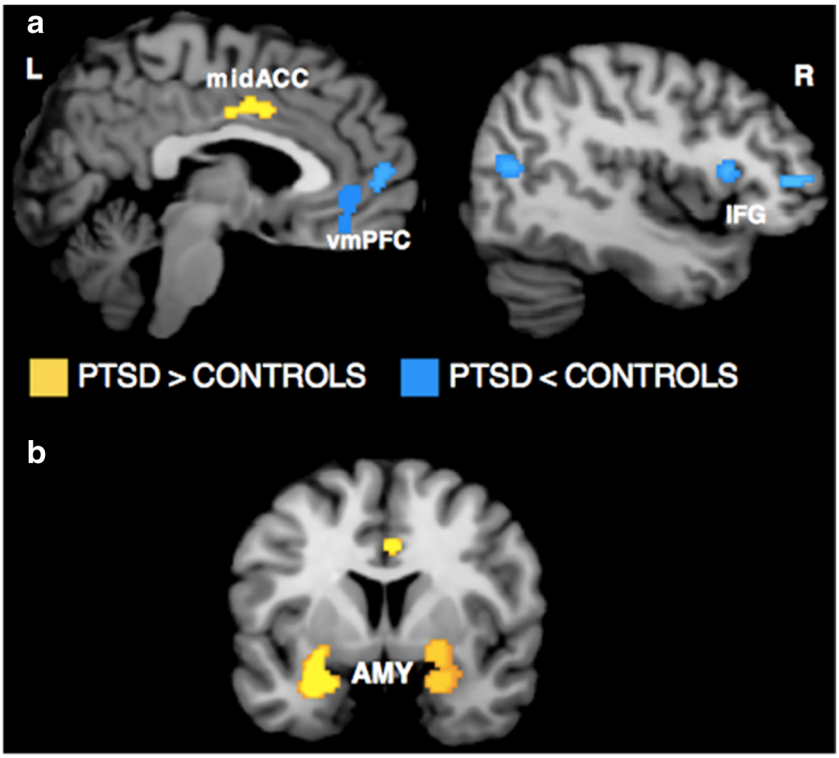


Fig. 3 Shows a meta-analysis of PTSD imaging studies with reduced activation in blue and increased activation in yellow. Areas of increased activity include the amygdala, dorsal ACC (midACC) and posteriorly the precuneus/retrosplenial cortex. Under activity is shown in the vmPFC area. With permission from Elsevier press Hayes et al., (2012)

This vmPFC reactivity is also revealed in persons who are resilient to PTSD despite a trait of high anxiety. While a trait of high anxiety is associated with excessive amygdala reactivity (Etkin et al., 2004), PTSD is not inevitable in these individuals. For example, Lin and colleagues identified army personnel with a high propensity for anxiety and found those who showed an accompanying high vmPFC reactivity during stimulus provocation were resilient and tended not to develop PTSD following combat (Lin et al., 2015). This is in keeping with arguments made here concerning the protective, modulating role of vmPFC and more specifically the rACC.

A further feature of the model is the relationship between the hippocampus (HC) and PTSD vulnerability. PTSD patients show a reduced volume of the hippocampi and this is

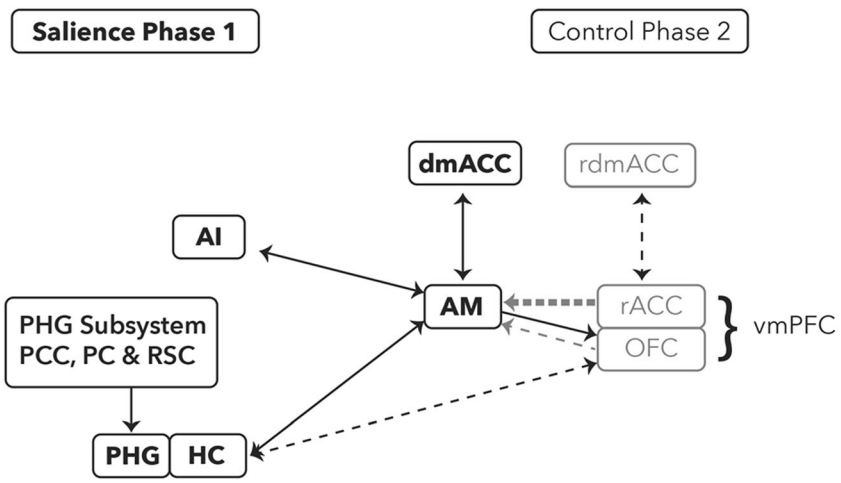


Fig. 4 A simplified framework for understanding the PTSD response. Phase 1 involves a "brain capture" in which the amygdala reacts with the insula and hippocampus in a salience response to imminent danger. The sub-circuit of the parahippocmpal subsystem involves the parahippocampal gyrus (PHG), the precuneus (PC) and the retrosplenial cortex (RSC). This last hub is often reduced in activity during symptom provocation. Following Phase 1, Phase 2 would normally then be immediately initiated thereby allowing the modulation of the amygdala by the rostral anterior cingulate within the vmPFC. However, this phase is weakly initiated by the PTSD patient, leaving a dominant salience phase with its associated sympathetic autonomic visceral arousal initiated by the amygdala. Thalamic involvement such as that provided by the paraventricular nucleus would allow the appropriate arousal levels with its connections to all the labelled areas (Price and Drevets , 2010, p.200)

associated with PTSD severity (Admon et al., 2009; Admon et al., 2013, b; Nelson & Tumpap, 2016; reviewed by O'Doherty et al., 2017). Nonhuman studies show evidence of a reduction in HC volume and neurogenesis as a response to chronic stress (Fa et al., 2014). A review by Admon, Milad, and Hendler (2013) argues for a prominent influential position of the HC within a model of PTSD. The amygdala has robust connectivity with the HC and this relationship has had a long-acknowledged role in the acquirement of conditioned fear (LaBar, LeDoux, Spencer, & Phelps, 1995; Milad et al., 2006; Phelps, Delgado, Nearing, & LeDoux, 2004; van Well, Visser, Scolte, & Kindt, 2012). The process of extinction, associated with the ventral vmPFC, provides a counter to this conditioning, and a relief from conditioned fear. The reduced connectivity found between the vmPFC and the amygdala is also found between the vmPFC and the HC, and both are related to PTSD severity (Kalisch et al., 2006; Phelps et al., 2004; Wicking et al., 2016). The under activity of the vmPFC found in PTSD patients is also associated with reduced ability to benefit from extinction learning, in which an alternate response is learned to replace the old unwanted fear response (Kalisch et al., 2006; Phelps et al., 2004; Wicking et al., 2016). Therefore, in PTSD a conditioned fear response persists outside of the context of the trauma.

A further contribution of this relationship between the vmPFC and the HC lies in the role of the interaction between these two areas in the retrieval of autobiographical memory (Maguire, 2014). An accurate autobiographical recall allows a rational perspective of our past history and is likely to be protective against the distorted, fearful memories that are often associated with PTSD (Nelson & Tumpap, 2016).

Two aspects of the Fig. 3 neuroimaging profile remain to be addressed. The first is the over activity in dorsomedial areas that is associated with readiness for impending action that might be required for "fight or flight." Nonhuman primate research shows direct connections between the amygdala and the dorsomedial PFC and dorsal ACC areas shown as active in Fig. 3 (Bates & Goldman-Rakic, 1993). As part of the salience network, the dorsomedial area is often shown to be active and coupled with the amygdala when there is hypervigilance and an anticipation of uncertain threat (Geng et al., 2018; Robinson, Charney, Overstreet, Vytal, & Grillon, 2012; Vytal, Overstreet, Charney, Robinson, & Grillon, 2014; Ye et al., 2017).

A final aspect of the model is the tendency for reduced activity in the area of the precuneus during stimulus provocation (See Fig. 3). The precuneus is a hub with connections to other brain areas, and has a number of functional roles, including imagery (Cavanna & Trimble, 2008) and consciousness of self as an agent (Freton et al., 2014). As part of the default mode network, the precuneus is active during reflective mind-wandering (Raichle et al., 2001). The implication of the reduced role of the precuneus in the presence of an imminent threat is possibly associated with a focus on threat at the expense of self-reflection. Finally, as argued above, the anterior insula, as part of the salience network, is often active during stimulus provocation and may contribute to conscious feelings of sustained anxiety and the feelings of fear associated interoception (Straube et al., 2007).

In summary, at the centre of this model (Fig. 4) is the importance of the vmPFC. As we have shown here more specifically, of particular importance is the rACC as an inhibitor of amygdala arousal and interaction with the HC. As indicated, when compared to healthy individuals, PTSD patients go through a more extended period of high amygdala arousal in which an underactive vmPFC fails to compensate for anxiety and fear in its described role as an inhibitor. Also, reduced connections between the vmPFC and the HC result in a failure to extinguish learned fear and provide a rational memory perspective of past trauma. However, and despite the agreement between the lesion and neuroimaging literature, a sub-set of PTSD patients may cope in different ways when faced with a reminder of trauma. Patients with dissociative PTSD may actually appear to show less emotion than expected and an *excess* of vmPFC activity.

The Case of Dissociative PTSD: The Exception that Proves the Rule?

While a basic model for PTSD implies a dysregulated emotional system and an underactive vmPFC, the few imaging studies available of the dissociative sub-type of PTSD appear to counter this model. Dissociative PTSD (PTSD+D), occurs in around 10 to 30% of patients with PTSD (Lanius et al., 2002; Stein et al., 2013; Wolf et al., 2012). Such patients typically report that they feel as if they are unreal or depersonalised. These patients complain of changes in awareness of memory, self and the environment. There are increased reports of emotional numbing and psychogenic amnesia (Bremner, 1999; Lanius, Bluhm, Lanius, & Pain, 2006).

Patients with PTSD+D are also deemed to have more severe and chronic symptoms compared to other PTSD patents (Bremner, 1999; Bremner & Brett, 1997; Wolf et al., 2012). They are more likely to have a history of chronic physical and or sexual abuse, which may have continued from childhood into adulthood (Lanius et al., 2006; Wolf et al., 2012). Importantly, some of these patients have reported that the dissociative response has been used throughout their lives in order to escape overwhelming experiences. This process has been described as a learned helplessness in situations in which the child cannot escape a stressful situation. They therefore learn to dissociate as a way of coping (Lanius, Bluhm, & Frewen, 2011). In keeping with this behaviour, these patients often exhibit passive or submissive defensive responses accompanied by autonomic blunting. Patients with PTSD+D generally show less hyperarousal to emotional provocation as measured by self-report, heart rate and skin conductance

compared to non-dissociative PTSD (Felmingham et al., 2008; Lanius et al., 2002). Therefore, there is the understanding that such patients have a strategy of detachment when faced with a traumatic event.

Nevertheless, while these patients appear to be less effected, PTSD+D patients report a high incidence of re-experiencing the traumatic event and these experiences have a close relationship with the severity of symptoms (Wolf et al., 2012). Felmingham and colleagues (Felmingham et al., 2008) found that PTSD+D patents had a reduced response to *consciously* presented fearful faces, they responded with *hyper-arousal* in a non-conscious presented condition (*masked* fearful faces). This is in keeping with a theory of fear detection proposed by LeDoux (2000). LeDoux proposed that there was a *low road* and a *high road* in emotional processing. The *high road* supports more complete emotional processing and involves the amygdala, ACC, anterior insula, OFC, and other areas important for visceral output such as the periaqueductal grey area. In terms of the present argument, this slower *high road* (around 350 msec) would allow the time and neural resource for dissociation or detachment to take place. However, the quicker processing associated with the *low road* (around 50-100 msec) involves the fast magnocellular pathway and the sub-cortical areas of the superior colliculus and the pulvinar of the thalamus, prior to reaching the amygdala (Almeida, Soares, & Castelo-Branco, 2015; Carlsson et al., 2004; Silverstein & Ingvar, 2015; Koller, Rafal, Platt, & Mitchell, 2018; Tamietto, Pullens, deGelder, Weiskrantz, & Goebel, 2012). In this way it is argued that the PTSD+D patients when presented a subliminal exposure to feared material are unable to use "top-down" prefrontal inhibition and protective control that they would normally be used to inhibit amygdala and anterior insula arousal (see also Box 2 for an explanation of *flashbacks*).

The very areas that are underactive in PTSD (the rACC and rostral medial PFC) show over-activity for PTSD+D individuals (Lanius et al., 2001; Lanius et al., 2002; Felmingham et al., 2008). In a study that elicited traumatic imagery via audio scripts, amygdala activity was lower for PTSD+D patients compared to non-dissociative PTSD patients, and not different to controls. The authors interpreted this as an indication of *increased* inhibition of the amygdala by the rACC in PTSD+D. This is in keeping with the view that the vmPFC is involved in self-relevance processing, and is crucially involved in the modulation and control of the amygdala.

The reduction of activity in the amygdala and anterior insula in PTSD+D is also accompanied by reduced activity in the rostral dorso-medial anterior cingulate (rdmACC) (Lanius et al., 2002). This may be a sign of reduced concern over self and well known others, as this area is associated with mentalization and thought concerning self and others (Amodio & Frith, 2006; Wittman et al., 2016). Healthy individuals show more activation in this area when they report more daily self-introspection. PTSD+D patients have reduced activity in this area, which is related to degree of emotional numbing. These persons also have a higher degree of alexithymia, i.e. a difficulty in identifying and labelling their own emotions (Frewen, Pain, Dozois, & Lanius, 2006; Frewen et al., 2010; Lanius et al., 2011).

The reduction of insula activity found in PTSD+D patients is also of interest. Reported high anxiety supported by skin conductance measures, is correlated with peak activity in the left insula (Britton, Phan, Taylor, Fig, & Liberzon, 2005). The anterior insula and rACC often show conjoint activity in fMRI studies (Medford & Critchley, 2010; Gu et al., 2013; Engström, Karlsson, Landtblom, & Craig, 2015). Both of these structures have layers of the von Economo cells that are found in humans and other social animals and are assumed to serve functions of self-awareness (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001).

There is also increased medial/hippocampal and middle/superior temporal and ventral rACC activity associated with PTSD+D that may be seen as part of the conscious dissociation process (Lanius et al., 2002; Felmingham et al., 2008). The argument for the increased temporal lobe involvement is based on evidence that temporal lobe seizure activity is associated with impaired consciousness, which is diagnostic of temporal lobe epilepsy (Lanius et al., 2006). Stimulation of this area by Penfield (1957), especially in the vicinity of the hippocampus, resulted in patients evoking an alternative reality, which, from his anecdotal evidence, were based on the stimulated past memories of the patient. A dissociative strategy may, but not always, include a focus on alternative internally generated thoughts that provide a distraction from the traumatic event (Lanius et al., 2011). This is in keeping with the involvement of the superior temporal lobe BA38, which is a memory base for semantic/conceptual emotional memories (Patterson, Nestor, & Rogers, 2007; Andrewes, 2016. pp. 323-328).

The increased rACC activity found with PTSD+D compared to non-dissociative has been recently modelled by Harricharan and colleagues (Harricharan et al., 2016) and also Nicholson and colleagues (Nicholson et al., 2017), who have extended the posited neural network to include the periaqueductal grey area (PAG). Rodent research has found that when the PAG is lesioned, this influences fear reaction through the amygdala (Johansen, Tarpley, LeDoux, & Blair, 2010; Watson, Cerminara, Lumb, & Apps, 2016), while other studies have found interactions between the PAG and the amygdala during fear conditioning (Kim et al., 2013). The Harricharan and Nicholson studies used large numbers of PTSD patients and PTSD+D patients compared with healthy controls, asking them to let their mind wonder while in the scanner. In keeping with our argument, these researchers argued that the PTSD+D patients utilized top-down inhibition

by the vmPFC on the amygdala and PAG respectively and a further a top-down influence from the amygdala to the PAG. Because this was during the resting state, it was assumed to be state of readiness for a defensive response and an indication of an ongoing hypervigilance in the PTSD+D patients. Hypervigilance is also assumed to be present in the "resting state" in the non-dissociative PTSD patients but here the model of their activity is one of bottom-up with the PAG influencing the amygdala and both the PAG and amygdala influencing the vmPFC (Nicholson, Friston, et al., 2017).

In summary, limited research has investigated PTSD+D, but there is enough evidence to suggest that this sub-type (American Psychiatric Association, 2013) should be acknowledged and researched separately. It is possible to conclude from the extant evidence that while PTSD is associated with *under* activity of the vmPFC and a reduced influence on structures within the salience network, PTSD+D patients with a frequent history of inescapable abuse in childhood is associated with overactivity of the vmPFC and excessive control. This profile of bottom-up and top-down, respectively, confirm the importance of the vmPFC and more specifically the rACC as a modulator of emotion. It is hypothesised that the distracted thoughts away from self (associated with reduced activity in the rdmACC) and focusing on an alternative reality (associated with increased hippocampal and cortical middle temporal lobe activity) may contribute to this process.

Flashbacks Memories

A Key Feature of PTSD

Flashbacks no doubt have their origins in the evolutionary pressures placed on our ancestors. The ability to rehearse future threats for survival would have been a life-saving advantage. As an aberrant, habitual and involuntary re-living of trauma in the modern world, the process remains one of the most stressful features that are distinctive to this disorder. In their review of pathological intrusive memory, Brewin and colleagues (Brewin, Gregory, Lipton, & Burgess, 2010) argue that flashbacks are central to PTSD and distinguish it from the intrusive memories suffered by other psychiatric disorders (Brewin et al., 2010). Brewin defines important terms that are often used too loosely. Intrusive memories are a broad category of involuntary repetitive memories that are usually referred to as negative and are associated with pathology, e.g. ruminations associated with depression. Involuntary autobiographical memories may be positive or negative but not necessarily involve repetitive recollection. *Flashbacks*, in contrast, involve the overwhelming stressful reliving of the negative traumatic event, as if the patient were re-experiencing the event (Brewin 2015; Brewin et al., 2010; Hellawell & Brewin, 2002). Flashbacks are described as sensory images (usually visual) of the traumatic scene referred to as "hot spots" that may take the person by surprise and "swamp" them with a vivid and overwhelming experience that is out of the patient's control (Whalley et al., 2013). They are also accompanied by negative emotions of fear but there may also be shame and guilt depending on the context of trauma and what the feelings of the patient were at the time of the event. The frequency of flashbacks with increased severity of PTSD and they decrease in frequency following therapeutic intervention (Brewin et al., 2010; Hackmann, Ehlers, Speckens, & Clark, 2004).

Neuropsychological Modelling of Flashbacks

Many of the features of healthy autobiographical memory retrieval involving controlled search that is associated with dorsolateral PFC activity and reflection on self as an agent associated with precuneus activity (Cabeza & St Jacques, 2007; Svoboda, McKinnon, & Levine, 2006) appear to be reduced during *flashbacks*. Based primarily on two studies (Osuch et al., 2001; Whalley et al., 2013), Brewin and colleagues model flashbacks based on the dominance of the dorsal sensory network over a ventral contextual network (Brewin et al., 2010; Brewin, 2014). Brewin's contextual representation is based on Corbetta and Shulman's ventral network that is described as a multisensory feature detector. In contrast, the dorsal sensory network is seen as being part of a search and detection network (Corbetta & Shulman, 2011; Corbetta, Miezin, & Shulman, 2002; see also Pessoa, Kastner, & Ungerleider, 2002). Brewin and colleagues describe the Sensory representation network (S-Reps) as follows: "S-Reps capture the entire visual field, are egocentric (rely on the person's own viewpoint), are automatically activated by related cues, and are relatively inflexible." (Brewin et al., 2010, p222; Brewin, 2014, p.88). In contrast, Contextual-Representation network (C-Reps) involve a conscious, contextualised encoding and retrieval of autobiographical memory. This network is described as being processed ventrally from the visual cortex to the inferior temporal cortex and the medial temporal lobe e.g. hippocampus "C-Reps are selective, correspond to the focus of conscious attention, are allocentric, and can be strategically or automatically retrieved." (Ibid).

Both these ventral and dorsal representations may be networked to emotionally salient areas, e.g. the amygdala and the anterior insula, when there is emotional content in a provocation paradigm. Both these networks may also involve the precuneus for egocentric based imagery that also allows interaction between the two networks (Cavanna & Trimble, 2008; Freton et al., 2014). The S-Reps dorsal network activates in a bottom-up manner being driven by sensory input while the C-Reps may act as a top-down process. It is understood that *both* these networks are activated in healthy participants when they recollect autobiographical memories

emotional or otherwise. *Flashbacks*, in contrast, are described as an imbalance between these two parallel networks whereby the S-Reps, the dorsal pathway, becomes dominant and the effect of the contextual-Reps network is reduced (Brewin, 2014; Brewin et al., 2010; Whalley et al., 2013).

In support of this model, the reduction of the contextual network predicts a reduction of reported flashback detail. Flashbacks are described as containing not only less contextual detail (a gist of the event), but are also as being judged fractionated and disorganised by independent judges. The patients, however, generally do not concur with this assessment of their reports (Brewin, 2015). There is evidence that context for autobiographical memory is made up of two contributory components: the contextual detail of the autobiographical memory e.g. the background details and timing of the event, is provided by the hippocampi, which are underactive during PTSD flashbacks, while vmPFC proportionally supplies memories that are self-related (Kurczek et al., 2015; Maguire, 2014).

Capturing a *flashback* following emotional provocation is usually achieved by presenting a personalised traumatic event that is, following an interview, tailored to the individual. Often in research the individual participants are asked to describe their flashback triggers so that this material can be used later in the experiment. As testament to the difficulties of this research only two neuroimaging group studies having a small number of patients have managed to capture flashbacks. The Brewin group using fMRI (Whalley et al., 2013) broadly supported their model by finding increased activation in dorsal sensory visual areas and motor areas described by their S-Rep network. They also found decreased activity in areas that can be described as part of a C-Rep pathway, including ventral visual areas and the medial temporal area, the hippocampus and parahippocampal area. Osuch and colleagues using positron emission tomography (PET) (2001) examined 8 PTSD patients found that subjective flashback intensity was positively correlated with increased left inferior frontal cortex, bilateral insula, brain stem, cerebellum and right putamen activity. Blood flow correlated directly with flashback intensity in the brainstem, lingual of the cerebellum, bilateral insula, right putamen and left hippocampal and parahippocampal areas, somatosensory and cerebellar regions. Inverse correlations with flashback intensity were found in bilateral dorsolateral prefrontal, right fusiform and right medial temporal cortices. Unfortunately, it is difficult to compare the two studies, given the different imaging methods chosen.

Another study by the Brewin group (Kroes, Whalley, Rugg, & Brewin, 2011) investigated 28 PTSD patients using structural MRI measures of brain volume. Overall, brain volumes failed to relate to PTSD severity. However, greater flashback *intensity* re-experiencing scores correlated with reduced volumes in the middle temporal and inferior occipital cortices. Furthermore, increased *frequency* of flashbacks was related to reduced volume in the insula/parietal operculum and in the inferior temporal gyrus. These findings are generally described as abnormalities in the ventral stream by the authors (Kroes et al., 2011; Osuch et al., 2001). Together these results give some general support to the idea that active dorsal streams (S-Reps) are accompanied by reduced ventral activity (C-Reps) during flashbacks.

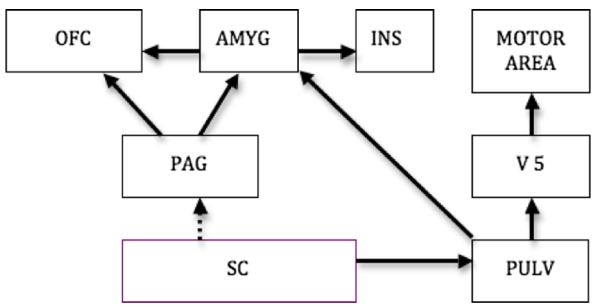
Acceptance of this theoretical implication cannot account for the fact that this pattern of activation is found in the presence of imminent danger in healthy individuals (Mobbs et al., 2010; Rigoli, Ewbank, Dalgleish, & Calder, 2016; Shuhama et al., 2016) and PTSD patients without recorded flashbacks (Grupe, Wielogosz, Davidson, & Nitschke, 2016; Geng et al., 2018). Although it may be the studies contain a variety of stimulus provocation, some of which include uncertain anticipation of electric shock, there are some notable differences in these studies compared to the flashback studies. Given a review of studies there seems to be some consistency that shows a reduction of vmPFC and often a reduced HC with imminent danger. Also it is the reasonable assumption that during the cognitive deliberation of impending danger there is activity in the dorsolateral PFC (Grupe & Nitschke, 2013). In studies with highly anxious individuals there is, what appears to be, a rebound of vmPFC and HC activity when a stimulus predicting safety is shown. Whether this is the case or not, the flashback studies failed to show changes in vmPFC when comparing emotive stimuli and neutral items this may be because the hypervigilance is also high in the control conditions. It is likely that, given that patients with PTSD typically help with the preparation of the traumatic vignettes used in research studies, they would be hypervigilant in the scanner even when neutral material appears. Stimulus overgeneralisation (Anastasides et al., 2015) and false positives are not uncommon (Whalley et al., 2013). There is also evidence that high levels of fear in highly anxious individuals without PTSD may also show indiscriminate fear conditioning (van Well et al., 2012). However, the anticipation of threat and hypervigilance may be a key contributing feature that requires further focus of investigation (American Psychiatric Association, 2013; Brewin et al., 2017; Bryant et al., 2005).

The mechanism for expected stimuli allows cortical representation even prior to the presentation of the stimulus. This expedites target detection of an anticipated stimulus, and also suppression of stimuli that are of less interest (Andrewes, 2016, pp.113-114; Chelazzi, Miller, Duncan, & Desimone, 1993; Desimone & Duncan, 1995; Sussman, Weinberg, Szekely, Hajcak, & Mohanty, 2017; Sussman, Jin, & Mohanty, 2016). This allows for quicker recognition and orientation to stimuli that is expected to be a threat with the extended mechanism described in Box 2.

Box 2: The superior colliculus a trigger for flashbacks?

The extreme stress and arousal suffered by patients with PTSD during *flashbacks* is likely to involve the superior colliculus. The superior colliculus is located in the tectum (roof) of the brain stem in the upper mid-brain. It has been implicated in the generation of defensive behaviours elicited by visual, tactile and auditory sensory areas. In non-human and human studies, the superior colliculus is part of a network associated with flight, fight or freeze. The superior colliculus is functionally dedicated to orienting towards incoming information from the retina and fast tracking this information to the amygdala and the cortical motor areas via the pulvinar of the thalamus. (Almeida et al., 2015; da Silva et al., 2018; Evans et al., 2018; Forcelli et al., 2017; Holmes at al., 2012; Izquierdo & Murray, 2004; Li et al., 2018; Ohman, 2005; Ohman et al., 2007). The superior colliculus is a detector that responds to conscious or unconscious sensory input and while it has been attributed to be most sensitive to moving targets in the periphery, there is a similar sensitivity to central foveal information in humans during the presentation emotional provocative material e.g. snake bodies and emotional faces (Almeida et al., 2015).

The superior colliculus is innervated by the noradrenergic system from the locus coeruleus (also in the mid brain) that is active during a fear response in rodents (Li et al., 2018). The large cells of the magnocellular pathway allow rapid transmission from the superior colliculus to the amygdala via the pulvinar and possibly more directly to the emotional system of the periaquaductal grey area (PAG) (Forcelli et al., 2017). Research interest in the superior colliculus stems from the study of blindsight, in which patients with gross damage to the visual cortex can respond correctly to information presented in the blind visual field, despite the experience of being blind. The perception is degraded and associated with low frequency vision. When these blindsight patients are presented emotional material, this acts on the amygdala and anterior insula (Burra et al., 2017: Celeghin et al.,2018; de Gelder et al., 2005). The superior colliculus has, with its magnocellular pathway, quick access to motor areas and the amygdala that exceeds the speed of the more detailed perception using the lateral geniculate parvocellular pathway (Koller et al., 2018; Silverstein & Ingvar 2015; Tamietto et al., 2012). Therefore, this phylogenically old network is ideally suited for both the threat detection and a fast reaction necessary for survival. Below shows the efferent pathways attributed to the superior colliculus (SC). The transmission to the emotional system includes the amygdala (AMYG), the orbitofrontal cortex (OFC), the insula (INS) and the preiaquaductal grey matter (PAG). Also connected via the Pulvinar (PULV) is the extrastriate visual area, V5, that projects to the motor areas. The nature of the direct connection between the SC and PAG (Bitterncourt et al., 2005; Evans et al., 2018; Forcelli et al., 2017) is to be further understood as a possible "short low road".



The Flashback Mechanism and the Superior Colliculus

It is important to be reminded of the realistic nature of the flashback experience that is even hallucinogenic in its description. For example, Hellawell and Brewin (2002) describe a patient's behaviour during flashbacks as sometimes being reminiscent of someone who is under physical attack, in which the patient suddenly turns away or crosses their arms protectively in front of them. There may be a brief calling out, and in some cases, stasis (interpreted as freezing).

As described in Box 2, stressful avoidance associated with flashbacks have their equivalence in behaviours found in non-human studies with the stimulation of the superior colliculus (SC). While what is known concerning the function of the SC network describes an active defensive response function, the network must be extended to further understand the reality of the re-experience of trauma. The superior colliculus is sensitive to unconditioned and conditioned threat that has been learned as part of the original experience of the trauma (e.g. in the above vignette, the patient reported sensitivity to strip lighting). There are robust inputs from both visual and motor areas into the SC that would satisfy a hypervigilance mechanism referred to above in which the patient has an ongoing readiness to respond to stimuli that may be somewhat loosely associated with the original traumatic event (Basso & May, 2017). This vigilant readiness for threat must be assumed to be guided by top-down attention in which expectancies are determined by memories of trauma and is a prominent feature of PTSD (American Psychiatric Association, 2013; proposed ICD 11, Brewin et al., 2017). The SC is influenced by structures such as the posterior parietal cortex and frontal eye fields to determine saccade search that selects targets that may be potentially threatening (Shen, Valero, Day, & Paré, 2011). The anticipated image of the autobiographical memory may exist, without a contribution from the primary visual cortex (Bridge, Harrold, Holmes, Stokes, & Kennard, 2012) and although reduced, there may also be easy activation of the parahippocampal area (Sakamoto et al., 2005).

Recent studies have drawn attention to the PAG and its interaction with the amygdala and the vmPFC as part of extreme emotional reaction to stimulus provocation (Harricharan et al., 2016; Nicholson, Friston, et al., 2017; Rigoli et al., 2016; Shuhama et al., 2016).

In summary, there is some support for brain stem activity being associated with flashbacks (Osuch et al., 2001), but the time-line for this activity is likely to be brief and may provide some challenge to neuroimaging in terms of the required spatial and temporal acuity. Most support for the *flashback* being triggered by this phylogenetically old brain area comes from the inevitability of its involvement in a condition where there is hypervigilance and a primal reaction to feared aspects of the environment. But there is also an argument for the SC model on the grounds that there is allowance for the by-passing of primary visual areas in this model. The by-passing of areas associated with conscious visual perception would allow for the dominance of the imagined traumatic event that existed prior to any feared presentation. In this way the re-experiencing of the traumatic episode is immersive, and the reality of this experience may not be challenged by existing conscious external perception, after the initial triggering of the traumatic memory. Secondly, there is quick access to motor areas from the superior colliculus, which allows immediate defensive behaviour (Whalley et al., 2013). This last aspect is in keeping with the sensory representation of dorsal activity and a detecting attention mechanism described by Brewin et al. (2010). The function of this network satisfies the hypervigilance requirements of an automatic and *involuntary* attention to stimulus associated with the traumatic event. Finally, the sensory input of the superior colliculus, with its dependence on the magnocellular pathway, is degraded and therefore the flashback may be initiated by stimuli that is weakly associated with the traumatic event (Whalley et al., 2013; Morey et al., 2015).

This prototype model provides many of the features that would be expected given the posited synergy of hypervigilance with the flashback reaction. Increased understanding of this enigmatic feature of PTSD may in the future encourage research in approaches to treatment that compensate for this symptom. In the next section there is a discussion of what is known concerning the neuropsychology of PTSD that might similarly influence an approach to therapeutic intervention.

Reflections on Therapeutic Interventions

What can be Learned from the Neuropsychology Profile of PTSD

The intractable nature of PTSD is evident from the rather poor response of these patients to therapy with around 30% to 50% of patients' still show persisting symptoms following intervention (Bradley, Greene, Russ, Dutra, & Westen, 2005). One of the most popular treatments for PTSD is *exposure* treatment, which is used as a compensation for poor extinction associated with reduced vmPFC activity. While this therapeutic approach is successful with around 50% of rape trauma victims, the success rate is remarkably reduced in the case of other trauma following combat experience, at around 18% (Bradley et al., 2005).

As part of *exposure* treatment the patient is subjected to reminders of trauma while being relaxed and supported by the therapist. Eventually this counter-conditioning therapy does rely on the need to identify conditioned stimuli, and this may prove difficult in some patients whose conditioning seems to be wide-ranging and indiscriminate. *Prolonged exposure therapy* is designed to overcome spontaneous

remission, and, as practised, may include many cognitive behavioural features of therapy that, with homework exercises, focuses the patient on triggers and strategies that may improve results (Mørkved et al., 2014; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010).

One possible remediation approach is to consider other functional contributions of the vmPFC apart from the animal studies of extinction. As previously indicated, the vmPFC with the hippocampus provide contextual autobiographical information that may place the original traumatic episode as an event occurring in the past, and may not be seen as important in the verifiable context of veridical memory (Feng, Feng, & Chen, 2013). In this way cognitive behavioural approaches such as *rescripting* (Raabe, Ehring, Marquenie, Olff, & Kindt, 2015; Slofstra, Nauta, Holmes, & Bockting, 2016) or cognitive processing therapy (Schumm, Dickstein, Walter, Owens, & Chard, 2015), that encourage the patients' attention to scenarios with a more rational perspective, should be effective. It is possible that both rescripting and exposure approaches are equally effective (Langkaas et al., 2017) but for different reasons. It might be predicted that *exposure* therapy would be superior in terms of trauma related stimuli while *rescripting* would improve self-image (Mancini & Mancini, 2018) and create a more favourable and rational attitude to the traumatic event. Also, there are now a large number of studies that show some success with strategies of reappraisal (Buhle et al., 2014; Etkin et al., 2015). Such studies show increased activation of lateral frontal areas that are seen as part of the process of cognitive control of emotions (e.g. Beidel et al., 2017).

Finally, there seems to be a case for treating patients with the dissociative sub-type of PTSD with a different approach, since dissociation may undermine the new-learning required of therapy (Ebner-Premier et al., 2009). Many of the strategies advocating reappraisal include the instructions to distance themselves from the source of threat. In this vein, 89% of the participants in McIsaac and Eich's study (2004) who adopted the observer vantage point did so to spare themselves the horror of having to relive the trauma again through their own eyes. Similarly, Williams and Moulds (2007) found that in a high dysphoric sample suffering depression, seeing an intrusive memory from an observer perspective allowed them to feel more detached. However, in can be argued that this strategy of avoidance does not deal with the source of the threat that requires acknowledgement (Dutra & Wolf, 2017). Therefore paradoxically, the under activity of structures such as the amygdala, insula and dorsomedial ACC/PFC areas may have to be initially normalised. Some evidence of this is present in a study of patients who were successfully treated for a depersonalization disorder (see Medford et al., 2016). While there is some support for dealing with the complexity of the PTSD case with a staged based or more comprehensive treatment (e.g. Cloitre, Petkova, Wang, & Lu Lassel, 2012; Cloitre, Jackson, & Schmidt, 2016; Doré et al., 2016) such an approach remains to be confirmed.

Factors Maintaining PTSD and Early Pre-emptive Treatment

In a long-term follow-up study of patients diagnosed with PTSD, 22% showed a worsening of symptoms over 2 years and 10% showed a gradual worsening of symptoms over 6 years (Bryant et al., 2015). The intensity of PTSD symptoms may increase or reduce over time, and this is in keeping with a disorder that is dependent on an on-going interaction with current and past experiences. The accretion of the pathogenesis of PTSD and worsening of symptoms, when it is confirmed, may occur soon after diagnosis. Bryant and colleagues (Bryant et al., 2017) found evidence of a consolidating constellation of PTSD symptoms in over 850 PTSD patients; such symptoms as intrusive memories and nightmares coalesced into a PTSD profile at a 12-month follow-up, compared to the initial assessment. That is, they were more clearly showing an increased statistical inter-relationship between symptoms. There is also the possibility that, in some cases, symptoms may be increased by everyday cognitive rehearsal and appraisals of the traumatic event that appear to strengthen the phobic response (Bryant et al., 2017; Cheung & Bryant, 2017; Dunmore, Clark, & Ehlers, 2001; Elsesser, Sartory, & Tackenberg, 2005).

The question remains as to whether the persistence of this disorder or even the delayed expression of the disorder is due to the repeated experience and rehearsal of the post traumatic response or exacerbated by further trauma. If this is the case, then early treatment would be warranted. The relationship between trauma experience and the increased vulnerability to symptoms seems to be most strongly revealed in the effects of childhood trauma and the consequent increased incidence of PTSD. Maltreatment and stressful experiences during childhood may make a diagnosis of PTSD more likely later in life. For example, a history of childhood sexual or physical abuse is more likely to result in PTSD in military service personnel (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Dannlowski et al., 2012). Also, compared to those with no history of trauma exposure, a history of two or more traumatic events involving assaultive violence in childhood has been associated with a nearly fivefold greater risk that a traumatic event in adulthood would lead to PTSD (Breslau, Chilcoat, Kessler, & Davis, 1999). Schalinski and colleagues (Schalinski et al., 2016) have also found that the amount of adverse experiences (e.g. childhood neglect and other types of abuse), irrespective of age of experience, predicts PTSD in adulthood. Thus, trauma associated with childhood abuse and repeated military experience compound to increase the incidence of PTSD (Dedert et al., 2009). These studies are strongly indicative of a progressive disorder in

some individuals they are not prospective and therefore it might be difficult to claim cause and effect.

A prospective studies by Admon and colleagues (Admon, Leykin, et al., 2013; Admon, Lubin, et al., 2013) have shown that military men with increased chronic exposure to combat and trauma also exhibit increased amygdala arousal and a reduction in hippocampal volume and reduced connectivity between the hippocampus and the vmPFC and these personnel are more likely to be diagnosed with PTSD. They found that a smaller hippocampal volume on the first assessment prior to exposure had no influence on the other outcome variables such as a diagnosis of PTSD. Also, Felmingham and colleagues found a relationship between hippocampal volume reduction and length of time since diagnosis (Felmingham et al., 2009). On the positive side, an increase in volume of some of these structures such as the hippocampus is found following treatment (Felmingham, Kemp, & Williams, 2007; Thomaes et al., 2014).

The progressive nature of PTSD is such that a continued exposure to trauma and the re-experiencing of symptoms are likely to increase the severity of disorder, and also these experiences area associated with changes in neuroanatomical and neurocircuitry profile (see also Lanius et al., 2011, p.335). This has prompted PTSD to be likened to the epileptic concept of *kindling*. This cumulative evidence argues that, irrespective of congenital factors, early intervention is recommended. Therefore, while *routine* post-trauma debriefing is generally contra-indicated (McNally, Bryant, & Ehlers, 2003; Rose, Bisson, Churchill, & Wessely, 2002), there is developing support for early and pre-emptive therapeutic intervention for patients when they have been identified with acute stress disorder at the stage when they are in hospital or when PTSD is first diagnosed. With this approach, there is some preliminary evidence of reducing the further development of symptoms (Kearns, Ressler, Zatzick, & Rothbaum, 2012; Rothbaum et al., 2012).

Also, in favour of pre-emptive therapy are the results of "inoculation training" of at-risk military personnel and has been found to reduce the likelihood of developing PTSD. Such approaches may include neurofeedback, which places the activity within certain areas such as the amygdala under the individual's control (Hourani et al., 2016; Denny & Ochsner, 2014; Nicholson et al., 2017; Paret et al., 2016). However, while a past history of trauma would have to be acknowledged, there are as yet not many inexpensive ways of predicting vulnerability in PTSD. Heart rate variability and somatic arousal assessment following injury may show some promise in this area, although further research is required (O'Donnell, Creamer, Elliott, & Bryant, 2007).

At another level of description, Arnsten and colleagues (Arnsten, Raskind, Taylor, & Connor, 2015) argues that an excessive stress response associated with levels of catecholamines, such as noradrenaline, have two effects. First there is a strengthening of primary sensory input to areas including the amygdala and striatum, since high arousal of the amygdala consolidates the memory of trauma. Arnsten reports that this causes the effect of creating a habitual response dominated by the amygdala and a progressive atrophy of the medial PFC, thereby exacerbating the symptoms of the PTSD (Arnsten et al., 2015). Arnsten and colleagues suggest that this turns the organism from a reflective to a reactive reflexive state; a state that may be countered by using drugs such as propanol, prazosin and guanfacine or clonidine (see Arnsten et al., 2015). It is of interest, that the SC is also innervated by the noradrenergic system from the locus coeruleus (Li et al., 2018). These biochemical approaches provide some promise, but the timing of administration is obviously important to coincide with initial encoding and learning that may occur, just following trauma. In this vein, there is some evidence that children who have received acute administrations of morphine after severe burns eventually have lower rates of PTSD (Saxe et al., 2001; Stoddard et al., 2009).

Also an issue to be considered are sleep disruptions such as nightmares that are highly prevalent symptoms found in PTSD patients (Ohayon & Shapiro, 2000). Pace-Scott and colleagues (Pace-Schott, Germain, & Milad, 2015) make the case that the delayed onset of PTSD may be due to sleep disruption and notably poor REM sleep. REM sleep and dreaming have been found to encourage the process of extinction following aversive conditioning (Pace-Schott, Verga, Bennett, & Spencer, 2012; Pace-Schott et al., 2015; Schiller & Delgado, 2010). There is a strong relationship between sleep disruption and PTSD severity (Germain, McKeon, & Campbell, 2017; Lipinska, Timol, Kaminer, & Thomas, 2014). Nardo and colleagues (Nardo et al. 2016) found a significant relationship between sleep disruptions and the size of salience structures and blood flow within the same structures that are associated with stimulus provocation. Germain et al. (2017) argue that this is evidence is enough to consider treatment for the reduction of sleep disruptions (Morgenthaler et al., 2018).

In summary, there is some evidence for the view that neuropsychological understanding may assist with approaches to therapy. It was argued that part of the rather dismal record of treatment may be blamed on a reliance on non-human research and classical extinction learning model. The human research shows the breadth of contribution of the vmPFC to social interaction and autobiographical memory. Therefore therapy aimed at compensating for the reduced influence of the vmPFC is an approach that has been shown to be useful. Knowing the neuropsychological mechanism for dissociative PTSD may also have a positive influence in promoting a two-stage or a different approach in which the patient learns to cope with confrontation.

The proposal that PTSD may be maintained in some individuals by experience pre and post diagnosis was seen to be a

good case for early treatment and or other pre-emptive therapies. Also, the problem of sleep disruption may be considered a focus for treatment. Like *flashbacks*, nightmares might encourage brain reorganisation towards a neural habitual reaction to fears. REM dreaming has an activation of brain areas including the brain stem, with shut-down the visual sensory input that may contribute to their sense of reality and have commonalities with the proposed model of *flashbacks*.

In the present review, we initially described the modulating relationship of the vmPFC on the amygdala as part of model of emotional dysregulation. This model was described earlier on the grounds of neuroimaging research, but we were able to describe human research that directly revealed emotional disinhibition following lesions to vmPFC. Further, we presented evidence that within patients with lesions to the vmPFC, lesions to the rACC area provide the most impact on excessive emotional reaction. There was a description of PTSD+D patients that showed an over control of symptoms which again revealed the vmPFC in a controlling role. In a discussion of the enigmatic area of flashbacks, the difficulties of research in this area provided limited empirical data. This prompted a prototype model on the basis of extant human and non-human literature arguing that hypervigilance may prime the PTSD patient to anticipate the reoccurrence of the traumatic event. In this way holding autobiographical features of trauma "online" for detection. An associated trigger received by the SC would then set off a bottom–up response prior to any slower primary visual cortex processing. The application of these findings in understanding the disorder of PTSD was then applied to the discussion of an appropriate therapeutic response to PTSD based on the model provided in Fig. 4 and on the potential progressive nature of the disorder. This was ventured in a brief way and used as a way of a more comprehensive understanding of the contribution of the vmPFC.

Lastly, it is of interest to note that the *dual inhibition model* proposed here may be similarly relevant to other psychiatric disorders such as attentional deficit hyperactivity disorder, autism spectrum disorders, borderline personality and has some similarities with the core mechanism ascribed to depression, which is a common comorbidity with PTSD (Drysdale et al., 2017; Hwang et al., 2016; Kamphausen et al., 2013; Lassalle et al., 2017; Maier et al., 2014: Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Onoda & Yamaguchi, 2015; Minzenberg, Fan, New, Tang, & Siever, 2007; Monk et al., 2010). While there are obviously differences, all these disorders have emotional over activity associated with a poor vmPFC regulation as a feature of their neuroimaging profile. Future research may use Biomarkers associated with imaging profile that might allow the tailoring of treatment approaches to the patient following the recent approach with depression (Dunlop et al., 2017).

Finally, it is possible that the dual inhibition model also applies to core emotional constituents of normal emotional development that determines hyperemotional reactivity versus emotional stability (Pitskel, Bolling, Kaiser, Crowley, & Pelphrey, 2011). For example, Clauss et al. (2014) studied young adults who were classified as having a highly inhibitive temperament; being shy, cautious, and avoidant of new situations, around 50% of this group would normally, in the course of time, be diagnosed with social anxiety. However, those in this group that had a high *resilience* to a social anxiety disorder showed a fMRI profile that involved high connectivity between the rACC and the amygdala and AI respectively and a high activation of the rACC, which is in keeping with inhibition of anxiety using the current model. The evidence provided here acknowledges that the interaction between the vmPFC, and its sub-areas, with the amygdala and the PAG is a key to studying emotional reactivity and should be considered in a number of disorders and normal individuals. This might be seen as a neural circuitry base upon which further symptoms, peculiar to a disorder, might be explored.

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Compliance with Ethical Standards

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

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