

Does neuroimaging research examining the pathophysiology of posttraumatic stress disorder require medication-free patients?

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Background: In an attempt to avoid unknown influence, most neuroimaging studies examining the pathophysiology of posttraumatic stress disorder (PTSD) exclude patients taking medications. Here we review the empirical evidence for relevant medications having a confounding effect on task performance or cerebral blood flow (CBF) in this population. The evidence for potentially confounding effects of psychotherapy in PTSD are also discussed. **Methods:** The literature that we reviewed was obtained through a PubMed search from 1980 to 2009 using the search terms posttraumatic stress disorder, PTSD, psychotropic medications, neuroimaging, functional magnetic resonance imaging, positron emission tomography, cerebral blood flow, CBF, serotonin-specific reuptake blocker, benzodiazepine, ketamine, methamphetamine, lamotrigine and atypical antipsychotic agents. **Results:** The empirical evidence for relevant medications having a confounding effect on task performance or CBF in relevant areas remains sparse for most psychotropic medications among patients with PTSD. However, considerable evidence is accumulating for 2 of the most commonly prescribed medication classes (serotonin-specific reuptake inhibitors and benzodiazepines) in healthy controls. Compelling data for the potentially confounding effects on brain areas relevant to PTSD for psychotherapeutic interventions are also accumulating. **Conclusion:** Neuroimaging studies examining the pathophysiology of PTSD should ideally recruit both medicated (assuming that the medication treatment has not resulted in the remission of symptoms) and unmedicated participants, to allow the findings to be generalized with greater confidence to the entire population of patients with PTSD. More research is needed into the independent effects of medications on task performance and CBF in regions of interest in PTSD. Neuroimaging studies should also take into account whether patients are currently engaged in psychotherapeutic treatment.

Introduction

In the last decade, functional neuroimaging research in posttraumatic stress disorder (PTSD) has resulted in an explosion of new data implicating the brain circuits involved in the pathophysiology of this disorder. Studies of cerebral blood flow (CBF) using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have examined neural responses to script-driven imagery, to viewing fearful, happy and

neutral faces, and to non-trauma-related scripts or pictures.¹ A recent meta-analysis has shown that PTSD patients tend to exhibit greater brain activation than healthy controls in the amygdala and insula, structures involved in fear conditioning and in the perception of bodily states, respectively. Moreover, decreased activation of the dorsal and rostral anterior cingulate and altered activation in the ventromedial prefrontal cortex, regions involved in the experience and regulation of emotion, have repeatedly been observed in patients with PTSD.¹

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In an attempt to avoid unknown influences, most neuroimaging studies examining the pathophysiology of PTSD thus far have included predominantly medication-free patients; only a few studies have included patients taking psychotropic medications.²⁻⁴

In this article, we argue that the assumption that medication use will affect the results carries with it a number of important costs that are not generally acknowledged. Moreover, in what appears to be an example of dualistic reasoning, there has been less focus on excluding patients receiving psychologic interventions for PTSD, even though these interventions may also affect neuroimaging findings. We conclude with recommendations for future investigations with regard to the use of psychotropic medications and psychotherapy in neuroimaging studies.

The primary rationale for including only medication-free patients is to eliminate the potentially confounding factor of medication use. This confounding factor may exist in 3 main forms: medication may influence task performance independent of symptom levels; medication may independently influence blood flow or blood oxygen level-dependent (BOLD) effects in areas implicated in the condition under study; and medication may independently influence neural activity that reflects the interaction between the study group and task.

To address the assumption that it is best to include only medication-free patients, we review the evidence for the first 2 types of confounding effects in PTSD by examining studies that have compared outcomes in medicated and unmedicated participants. However, it should be noted that because medication status tends not to be experimentally controlled, these comparisons may be influenced by factors correlated with medication status that could conspire to create and/or eliminate true differences. To date, no studies have examined the influence of specific medications on task performance in PTSD using neuroimaging methods.

Methods

We obtained the literature reviewed in this article through a PubMed search dating between 1980 and 2009 using the search terms posttraumatic stress disorder, PTSD, psychotropic medications, neuroimaging, functional magnetic resonance imaging, positron emission tomography, cerebral blood flow, CBF, serotonin-specific reuptake blockers, benzodiazepines, ketamine, methamphetamine, lamotrigine and atypical antipsychotic agents. In addition, we also included articles identified from the reference lists of the articles obtained in this search.

Results

Effects of psychotropic medications on task performance in PTSD

Various nonneuroimaging studies involving PTSD patients have examined medication effects in a variety of different paradigms. Two studies from the same research group examined physiologic responses to loud tones in veteran PTSD

patients⁵ and monozygotic Vietnam veteran twins discordant for combat exposure.⁶ Whereas the specific medications used in the veteran sample were not reported, the studies included as a covariate in the analysis the use of one or more potentially confounding medications, including narcotics, antidepressants, neuroleptics and benzodiazepines. Both studies found that the inclusion of patients taking prescription medications did not alter the findings of increased autonomic responses to loud tone stimuli in patients with PTSD. In the same sample of twins, the presence of reduced recall for fear extinction was also examined. Retention of extinction of conditioned fear was deficient in the PTSD group. The PTSD combat veterans showed larger skin conductance responses during extinction recall compared with their own twins as well as compared with non-PTSD combat veterans and their twins.⁶ These results were again not affected by the use of psychotropic medications, as determined by an analysis of covariance for medication status.⁷

A study of reward function in patients with combat-related PTSD used pictures of beautiful male and female faces and found no difference in responses between the medicated and unmedicated patients; both medicated and unmedicated combat-related PTSD veterans groups expended less effort by pressing a particular button to extend the viewing time of these pictures compared with Vietnam veterans without PTSD.⁸ The specific medications used in the study were not reported. A study investigating neurocognitive function, including visual memory, attention and encoding, executive function and visuospatial ability in medicated and unmedicated twins discordant for combat exposure showed that the results were not affected by current psychotropic medication use.⁹ Whereas no analysis by medication type was reported, the authors specify that 50% of medicated veterans reported benzodiazepine use, 25% reported use of a selective serotonin reuptake inhibitor (SSRI), 42% were prescribed a serotonin modulator and 25% reported taking multiple medications, which included a benzodiazepine in addition to a SSRI or a serotonin modulator in all cases.

A study of attention, learning and memory performance and estimated intellectual potential in Vietnam veterans also failed to find significant differences between medicated and unmedicated PTSD subgroups. Both groups of patients exhibited cognitive deficits on tasks of sustained attention, working memory, initial learning and estimated premorbid intelligence, but not on measures of focus of attention, shift of attention or memory savings.¹⁰ In addition, neither Golier and colleagues¹¹ nor Nixon and colleagues¹² reported a relation between memory performance and the use of psychotropic medications. The latter 2 studies did not report the specific psychotropic medications used by the participants.

Orr and colleagues¹³ examined psychophysiologic responses in a group of women with PTSD due to childhood sexual abuse by use of personal sexual abuse imagery (a method similar to script-driven imagery symptom provocation neuroimaging studies). The investigators found that the larger physiologic responses of heart rate and skin conductance in the PTSD group were not significantly different in medicated versus unmedicated subgroups; however, the

specific medications used in these studies were not reported. Similar results were found in studies examining olfactory identification as a measure of orbitofrontal integrity and qualitative block design performance in Vietnam veterans with PTSD.^{14,15} Although it is noteworthy that neither one of these studies could establish a significant correlation between medication status and task performance, interpretation of these findings is limited owing to a lack of medication-specific analyses.

In contrast, a study that examined auditory event-related potential, especially the parietal P3 amplitude, to tone stimuli in combat-related PTSD reported abnormalities in unmedicated patients ($n = 8$) that were not present in a group of patients medicated ($n = 16$) with either an SSRI ($n = 11$), trazodone ($n = 6$), lithium ($n = 1$), carbamazepine ($n = 1$), buspirone ($n = 2$), neuroleptics ($n = 4$) or benzodiazepines ($n = 1$). Medicated patients did not differ significantly from those in the control group without PTSD, and the authors suggested that psychotropic medications may normalize evoked potential-related deficits in PTSD.¹⁶ However, to substantiate this hypothesis further, carefully designed studies that analyze the specific effect of medication groups on psychophysiological parameters are warranted.

In summary, the majority of studies that involved subgroups taking or not taking psychotropic medication and studied psychophysical responses, neurocognitive functioning and reward functioning have not found a significant effect of medication on these domains, although there was a medication effect detected for auditory event-related potentials. It is noteworthy that the use of covariate analyses may not always be the most sensitive means of evaluating potential medication effects because medication use itself may covary with other clinically relevant characteristics such as severity of illness, which is not taken into account in this type of analysis. In addition, some of the studies, most of which had small sample sizes, may have lacked the power to detect a potential medication effect. This is particularly relevant for the studies discussed above that examined PTSD patients who were taking benzodiazepines or antidepressants at the time of the study, because it has been clearly demonstrated that these drugs can affect memory performance^{17,18} as well as emotional processing.¹⁹ In addition to memory, psychomotor functioning and concentration are the cognitive domains most commonly affected by commonly used prescription medications.²⁰ Furthermore, complex interactions between medication and task performance need to be considered, because some medication types may influence performance of certain tasks. To date, it is impossible to determine which medication types will influence performance of certain tasks by PTSD patients, because these influences have not directly been studied in this population. Therefore, differential interactions between medication type and task need to be taken into account when studying BOLD responses in PTSD patients. This warrants separate analysis of patients using only one type of pharmacologic agent as well as an evaluation of the potential differential effects of various psychotropic agents. To our knowledge, no PTSD neuroimaging studies have manipulated medication status and compared task

performance independent of PTSD symptoms. In addition, only a few studies have examined the effects of psychotropic medications on CBF; these are described in the next section.

Direct effects of psychotropic medications on CBF in healthy participants

Understanding the effects of psychotropic medications on CBF in brain areas associated with PTSD is important for determining the potential effects of including medicated patients in neuroimaging studies.²¹ Current psychobiologic models construe PTSD fundamentally as a disorder of fear and affect arousal regulation,²²⁻²⁵ and they implicate alterations in the amygdala, medial prefrontal cortex, anterior cingulate cortex and hippocampus. Studies have begun to examine the effects of several psychotropic medications on CBF in these brain areas in healthy participants, including SSRIs, benzodiazepines, methamphetamine, ketamine and lamotrigine (Table 1). The SSRIs and benzodiazepines are particularly relevant to PTSD because they are often used in the treatment of this condition.

During a hand sensorimotor task, a single dose of the SSRI fluoxetine and fenoflone led to more focused activation in the contralateral sensorimotor area, increased activation of the posterior supplementary motor area and a widespread decrease in bilateral cerebellar activation, as assessed by fMRI in healthy controls.^{26,27} Moreover, 1-month administration of paroxetine modulated human motor cortex excitability in healthy participants.²⁷ More recently, Peran and colleagues²⁸ examined the effects of long-term paroxetine administration (20 mg for 1 mo) on the activity of cortical areas implicated in higher-order representations of action-related language processing in healthy controls. Both verb generation and mental simulation of action showed a paroxetine-mediated hypoactivation of the left prefrontal and right medial premotor cortex and hyperactivation of the right Brodmann area (BA) 6 for less demanding verb repetition tasks. Short-term administration of citalopram (1 dose of 7.5 mg given intravenously) in healthy volunteers enhanced the right BA 47 responses and attenuated the medial orbitofrontal cortex to the no-go condition. In contrast, citalopram attenuated right BA 47 responses but attenuated right amygdala response to aversive faces.²⁹

Recently, this finding has been replicated in a randomized, placebo-controlled study.³⁰ Healthy volunteers were given either a single oral dose of citalopram (20 mg) or placebo. Amygdala activity in reaction to fearful facial expressions was significantly reduced 3 hours later in the treatment group compared with the placebo group. A similar effect was found for long-term treatment with escitalopram for 21 days,³¹ which led to a reduction in amygdala activation during an emotion face assessment task.³¹ This was also found in a placebo-controlled 7-day trial³² that used nonconscious exposure to fearful faces. These effects of SSRIs on amygdala responses to threat support the idea that antidepressants may produce relevant effects in emotion processing areas early in the course of treatment. The amygdala is known to be involved in the processing of emotional stimuli and, in

particular, the rapid detection of threat-relevant cues such as fearful facial expressions.³³

Because both depression and PTSD have been associated with hyperactivity of the amygdala,^{4,34,35,36} and converging evidence demonstrates that one mechanism by which SSRIs may exert their action is by constraining such overactivity, the effects of SSRIs on BOLD responses in paradigms examining threat-relevant cues in PTSD should be studied. Therefore, patients taking SSRIs should be included in PTSD studies.

The effects of short-term treatment with the selective norepinephrine reuptake inhibitor reboxetine were also investigated in healthy volunteers during processing of emotional faces. Compared with those taking a placebo, those taking reboxetine had a reduced amygdala response to fearful faces and increased activation to happy versus neutral facial expressions in the right fusiform gyrus.³⁷

The effects of benzodiazepines on brain activation during memory encoding tasks have been investigated.^{38,39} Studies

Table 1: Effects of psychotropic agents on brain function in healthy controls

Study	Medication (duration of use)	Healthy controls, no.	Neuroimaging method	Task	Neural effects
Loubinoux et al. ²⁶	Fluoxetine (short-term) Fenzole (short-term)	12	fMRI	• Hand sensorimotor task	• ↑ activation of posterior supplementary area • ↓ activation of bilateral cerebellum
Loubinoux et al. ²⁷	Paroxetine (1 mo)	19	fMRI	• Active/passive movement dexterity task • Sensory discrimination task	• Modulation of motor cortex excitability
Peran et al. ²⁸	Paroxetine (4 mo)	12	fMRI	• Action-related language processing	• ↓ activation of left prefrontal and right medial premotor cortex • ↑ activation of right BA 6 for less demanding and repetition tasks
Del-Ben et al. ²⁹	Citalopram (short-term)	12	fMRI	• No-go task • Adverse faces	• ↑ activation of right BA 47 to no-go • ↓ activation of right amygdala to adverse faces
Murphy et al. ³⁰	Citalopram (short-term)	26	fMRI	• Fearful facial expressions	• ↓ amygdala response to fearful facial expressions
Harmer et al. ³²	Citalopram (7 d)	24	fMRI	• Masked fearful and happy facial expressions	• ↓ amygdala responses • ↓ hippocampus response • ↓ medial prefrontal cortex masked presentations of fearful faces • ↓ recognition of fearful facial expressions assessed after the scan
Arce et al. ³¹	Escitalopram (21 d)	13	fMRI	• Emotion face assessment task	• ↓ amygdala activation
Mintzer et al. ³⁸	Triazolam (short-term)	15	PET150 – H ₂ O	• Episodic memory encoding	• ↓ memory performance associated with ↓ activation in anterior cingulate cortex, precuneus and cerebellum
Mintzer et al. ³⁹	Triazolam (short-term)	12	PET150 – H ₂ O	• Somatic, episodic memory encoding	• ↓ memory performance associated with ↓ activation in anterior cingulate, prefrontal cortex and parahippocampal gyrus
Paulus et al. ⁴⁰	Lorazepam (short-term)	15	fMRI	• Emotion face assessment task	• ↓ activation in bilateral amygdala and insula
Norbury and Mackay ³⁷	Reboxetine (7 d)	24	fMRI	• Categorization and recognition of positive and negative words	• ↑ left precuneus and right inferior frontal gyrus during categorization of positive words • ↓ left precuneus, anterior cingulate and medial frontal gyrus during recognition of positive words
Kleinschmidt et al. ⁴¹	Methamphetamine (short-term)	7	fMRI	• Dynamic gradient-echo imaging	• ↑ signal in cerebellum and subcortical grey matter structures
Holcomb et al. ⁴²	Ketamine (short-term)	23	PET H ₂ ¹⁵ O	• Resting scan	• Brain activation in the anterior cingulate and medial prefrontal cortex correlated with the psychomimetic action of ketamine
Holcomb et al. ⁴²	Ketamine (short-term)	8	fMRI	• Perception of face–non-face contrast	• No BOLD signal change in any region during ketamine administration
Li et al. ⁴⁴	Lamotrigine (short-term)	12	TMS/fMRI		• Lamotrigine diffusely inhibited cortical activation induced by TMS applied over motor cortex

BA = Brodmann area; BOLD = blood oxygen level–dependent; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; TMS = transcranial magnetic stimulation.

using PET revealed that triazolam significantly impaired memory performance and led to deactivation in brain areas previously shown to be associated with memory encoding, including the anterior cingulate cortex, precuneus and cerebellum.³⁸ These results were later replicated in a similar study which found that triazolam produced dose-related impairment in memory performance and dose-related deactivation in brain regions previously shown to be associated with memory encoding and known to show differential activity or connectivity in PTSD, such as the anterior cingulate cortex, prefrontal cortex and parahippocampal gyrus.³⁹ Dose-dependent decreases in brain activation in the bilateral amygdala and insula have also been reported in response to lorazepam (1-time dosing) as compared with placebo during an emotion face assessment task in healthy volunteers,⁴⁰ rendering these studies equally relevant for PTSD research.

The effects of methamphetamine on cerebral activity have been examined using dynamic gradient-echo imaging before, during and after intravenous administration in healthy controls. Methamphetamine was associated with fMRI signal increases in the cerebellum and subcortical grey matter structures.⁴¹

In healthy participants, ketamine has been shown to be associated with CBF increases in the anterior cingulate, medial prefrontal and inferior frontal cortices and decreases in cerebral activation in the cerebellum.⁴² In this study, brain activation in the anterior cingulate and medial prefrontal cortex was correlated with the psychomimetic action of ketamine, whereas there was no correlation with this psychologic change and the level of brain activation in the cerebellum. The consequences of ketamine and placebo and their effects on BOLD versus alterations in cognitive state in healthy participants has also been examined.⁴³ The changes in BOLD signal during perception of the face–nonface contrast exhibited widespread BOLD changes. However, in the placebo group compared with in the ketamine group, there was significantly greater BOLD signal change only in the middle occipital gyrus (BA 18) and the precentral gyrus (BA 4). The changes in BOLD signal were not significantly greater in any region during ketamine administration. The authors suggested that the BOLD signal changes represented task-dependent effects of drug or placebo, rather than task-independent effects of drug.⁴³

The effects of lamotrigine on BOLD signal changes induced by transcranial magnetic stimulation (TMS) have also been examined in healthy participants.⁴⁴ Lamotrigine at clinically relevant serum concentrations diffusely inhibited cortical activation induced by TMS applied over the motor cortex. In contrast, when TMS was applied over the prefrontal cortex, lamotrigine increased the TMS-induced activation of limbic regions such as the orbitofrontal cortex and hippocampus.

In summary, there is sufficient evidence that psychotropic drugs can influence task-dependent and task-independent cerebral blood flow in healthy participants. Additionally, several studies have shown similar effects in other psychiatric populations such as schizophrenia, depression and bipolar disorder. Schlagenhauf and colleagues state that both typical neuroleptics and olanzapine influence task-dependent blood

flow in schizophrenia patients using BOLD responses during a working memory task.⁴⁵

In a longitudinal study, schizophrenia patients exhibited significant correlations between the increase in the LORETA value of the left superior temporal gyrus during an auditory oddball task with improvements of negative symptoms after 6-month treatment with olanzapine.⁴⁶ In patients with depression, functional correlates of antidepressant treatment and symptomatic responses were identified using pre–post comparisons of activations elicited by sad facial affect processing,⁴⁷ masked emotional faces,⁴⁸ working memory tasks⁴⁹ and in combination with sleep deprivation.⁵⁰ In bipolar disorder, unmedicated patients exhibited significantly higher BOLD responses throughout the motor cortex, basal ganglia and thalamus compared with patients taking antipsychotic or mood-stabilizing medication during a motor reaction task.⁵¹ In addition, a study examining emotion processing demonstrated decreased amygdala activity in medicated versus unmedicated bipolar patients.^{52,53} These findings indicate that careful studies examining medication effects on neuroimaging results are necessary to analyze possible interaction effects between disorder and medication type. Therefore, careful examination of specific medication effects in PTSD will be essential.

Preliminary evidence of medication effects in PTSD

Several studies have begun to examine the differential effects of psychotropic drugs on brain function in PTSD. For example, investigators have examined the effects of yohimbine, an α_2 adrenoreceptor antagonist, on cerebral glucose metabolism in combat-related PTSD. The veterans with PTSD exhibited increased anxiety in response to yohimbine and decreased metabolism in the prefrontal, temporal, parietal and orbitofrontal cortex compared with healthy participants.⁵⁴ In a group of 11 patients with PTSD, treatment with citalopram was associated with decreased activation in the left medial temporal cortex, and symptomatic improvement was positively correlated with increased medial prefrontal cortex activity.⁵⁵

Whereas the effects of long-term treatment with psychopharmacologic agents on brain morphology have been investigated extensively (e.g., in schizophrenia⁵⁶), literature on neuroanatomical changes associated with pharmacotherapy in PTSD is just beginning to emerge. The neurobiology of PTSD has been hypothesized to involve alterations in glutamatergic transmission with subsequent neurotoxicity, especially involving the hippocampal region. Phenytoin, an anti-convulsant used to treat epilepsy, is believed to act by modulating glutamatergic neurotransmission and has been associated with a 6% increase in right brain volume. Moreover, increased hippocampal volume was correlated with reductions of PTSD symptom severity.⁵⁷ Animal studies have suggested that stress is associated with hippocampal volume changes, inhibition of neurogenesis and deficits in hippocampal-based memory dysfunction, and the literature is beginning to show that SSRIs promote neurogenesis and can reverse the effects of stress on hippocampal atrophy, whereas the neurobiological mediators are still being investigated.⁵⁸ In PTSD patients, treatment with the serotonin-specific reuptake

blocker paroxetine for 1 year resulted in a 5% increase in hippocampal volume and a 35% improvement in declarative memory function.⁵⁹

In conclusion, there is evidence in healthy participants that some psychotropic drugs not commonly used to treat PTSD, including methamphetamine, ketamine and clozapine, may affect brain regions that have been implicated in PTSD, including the orbitofrontal cortex, anterior cingulate cortex, amygdala and medial prefrontal cortex. Accumulating evidence suggests that some SSRIs and lamotrigine affect some of these same regions. Benzodiazepines have clearly been shown to affect memory performance and brain activation of regions that have been associated with PTSD, including the anterior cingulate cortex, prefrontal cortex and parahippocampal gyrus. It is of note that most of the above described studies were conducted in non-PTSD samples and across a variety of paradigms. As a result, the findings can only be generalized with caution to PTSD neuroimaging studies because the effects of psychotropic drugs on CBF in PTSD remain largely unknown. Given the emerging evidence of differential effects of various psychotropic agents on CBF and/or BOLD, future studies need to continue to focus on evaluating the specific effects of each psychotropic agent in healthy populations and patients with PTSD. Furthermore, no studies to date have examined the effects of adjunctive pharmacotherapeutic treatment in PTSD (even though multiple medications are often used in the treatment of PTSD⁶⁰ or the extent of placebo effects in this population.^{61,62} Because a positive placebo response is evident in up to 50% of patients with pain syndromes and depression, the influence of psychopharmacologic agents in PTSD patients should be explored in randomized, placebo-controlled trials.

Disadvantages of including medication-free patients

One disadvantage of focusing purely on medication-free PTSD patients is the risk of studying a population that does not necessarily represent all patients with PTSD. This is not such an issue if the aim is to isolate underlying mechanisms of the disorder; however, it is still important to establish whether such mechanisms can be equally well identified in patients encountered in routine clinical practice. Even though to date no studies have compared characteristics of treated and untreated PTSD patients, future studies should focus on factors that may prevent PTSD patients from seeking treatment. Several studies have examined prescribing practices in a variety of PTSD populations and have reported that 77% and 80% of domestic and military PTSD populations, respectively, received psychotropic medications,^{60,63} suggesting that medication-free PTSD patients do not represent the majority of PTSD patients.

In addition to the implications of representativeness, including only medication-free patients in PTSD research may also introduce various sample biases. Samples are likely to include patients and treating psychiatrists who can be persuaded to voluntarily discontinue medication. In many cases these patients may be less severely ill or less prone to have their anxiety exacerbated by being exposed to the scanning environment.⁶⁴⁻⁶⁶

This is particularly problematic because PTSD patients with more severe and complex symptoms are often much more difficult to treat and therefore present a greater financial burden to the health care system.^{67,68} Understanding the pathophysiology of PTSD may contribute to the development of better treatment strategies; however, if the pathophysiology differs in patients with different disease severity, the patient groups excluded from research are less likely to benefit from these advances. In fact, investigators of other psychiatric disorders such as schizophrenia and mood disorders have a long history of performing neuroimaging research with both unmedicated and medicated patients for this reason.^{69,70}

An additional disadvantage of including PTSD patients who have undergone a drug washout is that this procedure and its associated potential withdrawal symptoms, especially related to the use of antidepressant medications, may have independent effects on CBF. For example, proton magnetic resonance spectroscopy has shown that selective serotonin reuptake inhibitor discontinuation syndrome is associated with a rostral anterior cingulate choline metabolite decrease.⁷¹ Drug washouts may therefore introduce rather than eliminate a potential confounding factor. There are few neuroimaging studies that have examined the potential effects of psychotropic drug washouts and/or withdrawal symptoms on CBF, which therefore remain largely unknown.

One must also ask whether there are ethical issues raised by a protocol that involves weaning severely ill patients off any intervention, including drugs, when that intervention has been shown to be beneficial for that individual. In other conditions for which drugs have a more established role, such as schizophrenia, many institutional review boards are taking the view that this poses an unacceptable level of risk. If this view becomes commonly accepted in relation to PTSD studies, or in relation to a subset of PTSD patients, an evidence base that is restricted to unmedicated patients will need broadening to advance the field. An additional option to address this issue is to use study designs that include patients before medication treatment whenever possible.

Should neuroimaging studies include PTSD patients receiving psychotherapy?

To date, PTSD neuroimaging studies have excluded medicated PTSD patients, yet many have not excluded patients receiving psychotherapeutic interventions. This point is important in light of the increasing evidence that psychotherapeutic interventions can have profound effects on CBF. For example, in a sample of subthreshold PTSD patients who were compared with matched waiting-list subthreshold PTSD patients, a course of exposure-based and cognitive restructuring therapy led to significantly higher levels of CBF in the parietal lobes, left hippocampus, thalamus and left prefrontal cortex during memory retrieval after psychotherapy.⁷² In addition, the effects of eye movement desensitization and reprocessing therapy on CBF in a group of PTSD patients listening to a traumatic script showed that a significant tracer difference present before treatment in the uncus (BA 36) disappeared after treatment, while a significant difference appeared in the

lateral temporal pole (BA 21).⁷³ Furthermore, in a group of 8 patients with PTSD, imaginal exposure and cognitive restructuring was associated with increased activation in the rostral anterior cingulate cortex,⁷⁴ and improvements in PTSD symptom severity were correlated with increased rostral anterior cingulate activation and decreased amygdala activation. The effects of brief eclectic therapy involving trauma imagery in civilian PTSD patients were associated with decreased CBF in the right middle frontal gyrus as determined by PET. Treatment effects correlated positively with activation in the left superior temporal gyrus and superior/middle frontal gyrus.⁷⁵ Research has also shown the effects of psychotherapeutic intervention on CBF in depression,⁷⁶ obsessive-compulsive disorder,⁷⁷ panic disorder,⁷⁸ social phobia⁷⁹ and spider phobia.^{80,81} In unipolar depression,⁸² a prospective PET study revealed comparative results for psychotherapeutic (cognitive behavioural therapy) and pharmacologic (venlafaxine) treatment. Both treatments yielded a significant increase in glucose metabolism in the right occipital-temporal cortex and significant decreases in the orbitofrontal cortex and left medial prefrontal cortex. Patients who responded to either or both treatments were characterized by reduced metabolism in several prefrontal regions. In light of these results, the different inclusion standards for patients treated with psychopharmacologic agents versus psychotherapy seem anachronistic.

In summary, there appears to be compelling evidence for the potentially confounding effects on brain areas relevant to PTSD for psychotherapeutic interventions. Given these results, it appears that the effects of psychotherapy, just like those of pharmacotherapy, may confound the results of neuroimaging studies. It may therefore be important to note whether patients are currently engaged in psychotherapeutic treatment and include such information in the analyses of neuroimaging data.

Conclusion

The general principle of including medication-free psychiatric patients whenever possible is widely considered a desirable factor and may play an important role in decisions concerning the funding and publication of neuroimaging studies. At least in PTSD, however, the empirical evidence for relevant medications having a confounding effect on task performance or CBF in relevant areas remains sparse for most psychotropic medications because detailed dismantling studies are lacking. However, considerable evidence is accumulating in healthy controls for 2 of the most commonly prescribed medication classes, SSRIs and benzodiazepines.

We believe that the field will best be advanced by studies that can speak to whether findings from medication-free participants can be meaningfully applied to the actual patient population, as well as by knowing how or which medications affect which outcomes. Changing approaches to research participant protection may mean that, at some point, studying medication-free patients may become very difficult (unless patients can be accessed and studied before receiving treatment), rendering the need to investigate medication effects on neuroimaging data particularly urgent. Given the rather

substantial evidence for the effects of psychotherapy on brain function, there are also likely to be considerable benefits from comparing the separate effects of psychologic and pharmacologic intervention.

There are a number of alternative strategies that do not require discontinuing medication to remove potential confounding effects. Within-patient designs have the effect of holding medication status constant while manipulating the conditions of interest. Other studies have attempted to control for medication status by having a psychiatric control group that is receiving similar pharmacologic treatment. In the case of PTSD, patients with major depressive disorder may sometimes provide an appropriate comparison group,⁸³ although the possibility of a drug-by-disorder interaction cannot be excluded.

Furthermore, neurobiologic changes associated with the preventive prescription of psychopharmaceutical agents in acutely traumatized patients have emerged as a topic of interest. To date, studies prospectively assessing symptom severity have yielded mixed results, indicating a need for further study.⁸⁴⁻⁸⁷ Whereas the effects of long-term treatment with psychopharmacologic agents on brain morphology have been investigated in other psychiatric disorders, neuroanatomical changes associated with short- and long-term pharmacotherapy in PTSD deserve further investigation.

In addition, there are a number of testable hypotheses addressing medication effects in PTSD patients and healthy controls include. The first hypothesis is that the effects of short- and long-term administration of psychotropic medications on neural functioning during a resting state differ in PTSD patients and healthy controls. The second is that the effects of psychotropic medications on neural functioning at baseline versus during relevant cognitive tasks, such as working memory tasks,⁸⁸ differ in PTSD patients and healthy controls. Such studies will allow an examination of brain activation changes associated with task-dependent effects of the drug or placebo and task-independent effects of the drug or placebo. The third hypothesis is that the effects of psychotropic medications differ under conditions that directly trigger PTSD symptoms such as the script-driven imagery symptom provocation paradigm as compared with baseline conditions. Such studies will enable an increased understanding of the neural mechanisms underlying medication and placebo effects on specific PTSD symptoms.

Finally, to gain further insight into the underlying mechanisms of pharmacotherapeutic agents often used adjunctively in PTSD, one may determine the adjunctive effects of drug A by randomly assigning PTSD patients who are receiving drug B to also receive either drug A or placebo.

In conclusion, we make the following recommendations with regard to future research directions and the inclusion of PTSD patients currently taking psychotropic medications in neuroimaging studies. First, we agree with the findings of a recent review of similar issues in bipolar disorder,⁷⁰ which concluded that neuroimaging studies should ideally recruit both medicated and unmedicated patients to allow the findings to be generalized with greater confidence to the entire population of PTSD patients.

Furthermore, more research is clearly needed on the independent effects of medications on task performance and on blood flow in regions of interest in PTSD. Therefore, separate and comparative analyses of medicated and unmedicated patients that carefully differentiate the effects of symptom severity, task difficulty and medication influence are called for. In addition, neuroimaging studies should take account of whether patients are currently engaged in psychotherapeutic treatment and include such information in the data analyses. Future research focusing on these different areas of investigation should not only provide greater insight into the mechanisms underlying PTSD, but also shed more light on the specific effects of psychotropic medications on brain functioning in PTSD.

Because pharmacologically induced changes in BOLD signal could reflect influences not only on neural activity but also on the synaptic and metabolic signalling to the blood vessels that control the cerebral blood flow responses, studies using fMRI to investigate the effects of psychopharmaceutical agents should consider whether pharma-induced alterations of the BOLD signal reflect influences on neurovascular, rather than neural, activity. To control for nonspecific neurovascular alterations, the inclusion of a control task to assess the BOLD response in brain regions not expected to be modulated by the drug is recommended. Randomized, placebo-controlled studies that use different tasks expected to show differential activity in PTSD patients would not only allow the determination of whether the psychopharmacologic medication affects task performance but also might serve to substantiate psychobiologic models of PTSD.

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Contributors: Drs. Brewin, Friedman, Liberzon, Schnurr, Shin and Stein designed the study. Drs. Lanius and Liberzon acquired the data, which Drs. Lanius, Daniels, Friedman, McFarlane, Schnurr, Shin, Stein and Vermetten analyzed. Drs. Lanius, Brewin, Daniels, Friedman, Liberzon and Stein wrote the article. All authors reviewed the article and approved the final version submitted for publication.

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CCNP News and Views

Canadian College of Neuropsychopharmacology 2009 Award Winners

Heinz Lehmann Award

Dr. Anthony Phillips is the recipient of the 2009 Canadian College of Neuropsychopharmacology (CCNP) Heinz Lehmann Award. Dr. Phillips is a Professor of Psychiatry and Senior Scientist with the Vancouver Coastal Health Brain Research Centre, University of British Columbia. The award, donated by Eli Lilly Canada Inc., consists of a \$5000 research prize plus a \$2000 travel award, and an engraved plaque. Congratulations to Dr. Phillips!

Title of presentation: "Interference peptides to probe addiction"

Innovations in Neuropsychopharmacology Award

Dr. Sheena Josselyn is the recipient of the 2009 Canadian College of Neuropsychopharmacology (CCNP) Innovations in Neuropsychopharmacology Award. Dr. Josselyn is a Canada Research Chair in Molecular and Cellular Recognition and an EJLB Scholar. She is an Assistant Professor in the Department of Physiology and at the Institute of Medical Studies at the University of Toronto. This award is designed to recognize outstanding research innovations in the basic or clinical fields of neuropsychopharmacology. The award, donated by Wyeth Pharmaceuticals, consists of \$5000 and an engraved plaque. Congratulations to Dr. Josselyn!

Title of presentation: "Erasing fear memories"

Young Investigator Award

Dr. Jens Pruessner is the recipient of the 2009 Canadian College of Neuropsychopharmacology (CCNP) Young Investigator Award. Dr. Pruessner is an Assistant Professor in the Departments of Psychiatry and of Neurology and Neurosurgery at McGill University, and Director of the McGill Centre for Studies in Aging. This award is designed to recognize outstanding contributions in the field of research in neuropsychopharmacology by a young basic scientist or clinical investigator in Canada. The award, donated by AstraZeneca Canada, consists of a \$2500 bursary plus a \$2000 research grant and an engraved plaque. Congratulations to Dr. Pruessner!

Title of presentation: "Origin of interindividual differences in stress responsivity in human populations"

CCNP Medal

Dr. Lakshmi Yatham is the recipient of the 2009 Canadian College of Neuropsychopharmacology (CCNP) Medal. Dr. Yatham is a Professor of Psychiatry and Vice Chair for Research and International Affairs at the University of British Columbia in Vancouver. This award was established to honour individuals for a meritorious career in, and outstanding contribution to, neuropsychopharmacology in Canada as evidenced by their activities in education, administration and/or patient care. The award consists of a bronze medal engraved with the recipient's name and is sponsored by the CCNP. Congratulations to Dr. Yatham!