

Contribution of Functional Neuroimaging to Understanding Neuropsychiatric Side Effects of Interferon in Hepatitis C

SCOTT C. MATTHEWS, M.D.

MARTIN P. PAULUS, M.D.

JOEL E. DIMSDALE, M.D.

Patients with hepatitis C who are treated with interferon may develop neuropsychiatric symptoms, including fatigue and depression. The authors discuss the potential use of functional neuroimaging in the identification and treatment of these patients. The authors provide an overview of functional neuroimaging studies of fatigue and depressive symptoms in various medical and psychiatric conditions and suggest future directions for research that may increase understanding of the specific neural substrates of neuropsychiatric side effects associated with hepatitis C and interferon treatment. This knowledge may help consultation-liaison psychiatrists identify patients at high risk for developing side effects related to hepatitis C and interferon, which would allow for implementation of validated strategies for prophylactic treatment of these patients.

(Psychosomatics 2004; 45:281–286)

The sequelae of hepatitis C virus infection and its treatment are of vital public health concern and are becoming increasingly common among patients seen by consultation-liaison psychiatrists. A burgeoning literature describes the effects of hepatitis C and interferon treatment on quality of life¹ and on the development of neuropsychiatric symptoms such as fatigue and depression.^{2,3} Fatigue and depressive symptoms are also associated with many other conditions encountered in the consultation-liaison setting, including major depressive disorder, multiple sclerosis, and chronic fatigue syndrome. Functional brain imaging techniques have contributed greatly to an understanding of the brain structures involved in such symptoms, and these techniques are potentially useful tools for the identification and prophylactic treatment of consultation-liaison patients who are most vulnerable to the development of neuropsychiatric side effects. Hepatitis C is an area in which functional neuroimaging has the potential for great clinical utility.

Hepatitis C has an enormous effect on morbidity and mortality. In the United States alone, an estimated 4 million

persons have hepatitis C, of which approximately 20% are expected eventually to develop cirrhosis of the liver.⁴ Of these, approximately 25% will die from hepatic failure or require liver transplantation.⁵ Progression to cirrhosis is often silent, until patients present with symptoms of end-stage liver disease. In addition to these complications, neuropsychiatric symptoms and a decrease in quality of life are also associated with hepatitis C and interferon treatment.^{1,6}

It is interesting to note that not all patients with hepatitis C develop neuropsychiatric symptoms. For example, most investigators have reported that between 10% and 40% of patients who receive interferon treatment experience depressive symptoms.⁷ Although the vulnerability factors involved in the development of neuropsychiatric symptoms in hepatitis C and interferon treatment are not

Received Nov. 26, 2003; accepted Jan. 26, 2003. From the Department of Psychiatry, University of California, San Diego. Address reprint requests to Dr. Matthews, San Diego VA Hospital, 3350 La Jolla Village Dr., Mail Code 116-A, La Jolla, CA 92161; scmatthews@ucsd.edu (e-mail).

Copyright © 2004 The Academy of Psychosomatic Medicine.

known, functional brain imaging techniques have contributed greatly to the general understanding of the brain circuits that may be disrupted when neuropsychiatric symptoms are experienced by patients with major depressive disorder, multiple sclerosis, and chronic fatigue syndrome. An emerging literature supports the idea that this brain circuitry is also involved in interferon-induced neuropsychiatric symptoms.

In this article, we provide an overview of functional neuroimaging studies of fatigue and depressive symptoms in various medical and psychiatric conditions, describe converging evidence from these diverse clinical entities, and suggest future directions for research that may increase the understanding of the specific neural substrates involved in interferon-induced neuropsychiatric side effects. This knowledge may aid the consultation-liaison psychiatrist in identifying patients at high risk for developing side effects related to hepatitis C and interferon and allow for the implementation of validated strategies for prophylaxis⁸ and treatment³ of these patients. Before reviewing the literature regarding the brain circuitry involved in fatigue and depressive symptoms in specific patient groups, we first provide a brief overview of the diverse approaches to functional neuroimaging.

OVERVIEW OF FUNCTIONAL NEUROIMAGING

Modern functional neuroimaging techniques comprise a diverse set of methods, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). These procedures are relatively noninvasive and can provide detailed information about cortical brain activity at rest and about how brain function changes as one engages in a specific task. The characteristics of these neuroimaging techniques are summarized in Table 1.

Functional Magnetic Resonance Imaging (fMRI)

The blood-oxygen-level-dependent (BOLD) fMRI method pioneered by Ogawa and colleagues⁹ can be used

to identify signal change associated with task performance. fMRI measures relative changes in blood flow on the basis of differences in blood oxygenation and infers information about functional brain activity from these measures. Blood flow within the brain is under tight control, and when neuronal activity increases in a given cortical region, blood flow to that area increases and oxygen is delivered in order to keep up with the increased metabolic demand. However, for reasons that are incompletely understood, blood flow increases disproportionately, relative to oxygen demand, leading to a relative increase in oxygenated hemoglobin in active brain regions. The greater the ratio of oxygenated to deoxygenated hemoglobin in a given region, the greater the signal detected from that region. This phenomenon is known as the BOLD effect and is the basis of traditional fMRI experiments.⁹

In the fMRI procedure, subjects are placed inside a large magnet that exerts a powerful static magnetic field with a magnetic flux density of 1.5–4 T. This external field causes protons within the nuclei of hydrogen atoms to align either in a parallel or anti-parallel orientation with the field. Next, delivery of energy pulses results in a perpendicular magnetic field that tips protons into a higher-energy state. As the protons relax (dephase) back to their lower-energy state, a signal in the form of energy photons is emitted and quantified by the receiver coils in the scanner. The strength of the signal is dependent on the microenvironment in which the protons are located. Specifically, protons dephase more slowly in an environment with relatively more oxygenated hemoglobin. Therefore, a stronger signal is detected from active cortical regions (regions with relatively more oxygenated hemoglobin). Smaller gradient magnetic fields may also be applied to allow for three-dimensional localization of nuclei.

Emission Techniques

PET and SPECT measure biological processes such as glucose consumption and regional cerebral blood flow (rCBF). In these techniques, brain metabolism is located and quantified by administering radioactively labeled mol-

TABLE 1. Characteristics of Three Functional Neuroimaging Techniques

Characteristic	Functional Magnetic Resonance Imaging	Positron Emission Tomography	Single Photon Emission Computed Tomography
Cost	Moderate	High	Low
Spatial resolution	1–3 mm	10–16 mm	9–12 mm
Temporal resolution	4–10 seconds	1–2 minutes	3–4 minutes
Exposure of scanned subject to radiation	No	Yes	Yes

ecules that are taken up by metabolically active neurons. The nature of the process of radioactive decay differs between PET and SPECT and partially explains the greater spatial resolution of PET. However, compared with SPECT, PET is more expensive and less readily available.

PET

In contrast to fMRI, PET relies on conventional X-rays and employs radioactively labeled molecules referred to as radiopharmaceuticals. The radiopharmaceuticals are administered to subjects through inhalation or injection and disperse throughout the body and brain. As radioactive decay occurs, the positrons that are emitted collide with electrons. These collisions result in the annihilation of both particles and the production of photons that are detected by the PET scanner. The spatial localization of the annihilation can be approximated.

[¹⁸F]fluorodeoxyglucose (FDG) is the most commonly used radiopharmaceutical in PET experiments. Active neurons have higher metabolic rates and take up glucose at a higher rate than less active neurons. Similarly, regional cerebral blood flow is higher in active brain regions compared to less active brain regions. Intravenous [¹⁵O]H₂O may be administered in order to approximate rCBF. Regional glucose metabolic rate and rCBF directly relate to local functional activity in particular brain regions.

SPECT

Like PET, SPECT involves the administration of radioactively labeled tracers that decay over time while emitting a signal that is localized by the SPECT scanner. Radioactively labeled ligands accumulate in particular brain regions relative to the amount of blood flow to that area.

[^{99m}Tc]hexamethylpropyleneamine oxime (HMPAO) is rapidly taken up into the brain and is the most commonly used radiopharmaceutical in SPECT experiments. Other radiopharmaceuticals are also employed for a variety of clinical purposes. [^{99m}Tc]ethylcysteine dimer (ECD) is stable in vitro for several hours, which allows for the study of episodic phenomenon such as seizures. [²⁰¹Tl]chloride is often administered in SPECT studies to image brain tumors. Xenon-133 may be used to study rCBF; however, the spatial resolution of this technique is less than that of [¹⁵O]H₂O PET.

Collectively, these techniques have been used to identify a network of brain regions that is involved in the development of neuropsychiatric symptoms.

FUNCTIONAL BRAIN IMAGING STUDIES OF NEUROPSYCHIATRIC SYMPTOMS

The anterior cingulate cortex and the prefrontal cortex have been implicated frequently in the development of fatigue and depressive symptoms in various medical and psychiatric conditions. The anterior cingulate cortex is a structure with multiple functions and at least two functional subdivisions. The ventral anterior cingulate cortex is critical for integration of emotional information¹⁰ and modulation of the autonomic nervous system.^{11,12} The dorsal anterior cingulate is intimately involved in cognitive processes such as response inhibition¹³ and error processing,¹⁴ and is also involved in modulation of the autonomic nervous system.¹¹ Given the role of this structure in integrating cognitive and emotional information, it is not surprising that dysfunction of the anterior cingulate cortex has been associated with the development of neuropsychiatric symptoms in several psychiatric and medical conditions.

Functional subdivisions have also been identified within the prefrontal cortex, a structure that is critically involved in the regulation of mood and affect.¹⁵ The ventromedial prefrontal cortex is intimately involved in the anticipation of positive and negative stimuli,¹⁶ and the dorsolateral prefrontal cortex and orbital prefrontal cortex are involved in spatial working memory and reward expectation.¹⁷ Various functional imaging evidence supports the role of the prefrontal cortex in mediating fatigue and depressive symptoms in various conditions.

Studies of Depressive Symptoms

Many functional neuroimaging studies of major depressive disorder (MDD) used PET or fMRI and have described altered brain activation in the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex. These studies are summarized later in this section. Major depressive disorder has also been associated with altered brain activation in the amygdala, a structure in the medial temporal lobe that is important for face recognition,¹⁸ as well as integration of emotional responses and modulation of the autonomic nervous system.¹⁹ Hyperactivation of this structure has been consistently demonstrated in major depressive disorder.²⁰

In a review of the neuroimaging literature, Drevets *et al.*²¹ described a convergence of findings from various studies suggesting that less activation in the dorsolateral prefrontal cortex is associated with MDD. More recent studies have provided consistent results. Using fMRI and

an affective task, Davidson et al.¹⁵ demonstrated that subjects with MDD had significantly less left-sided dorsolateral prefrontal cortex activation, relative to healthy comparison subjects. This study also revealed that differences in activation in the rostral anterior cingulate cortex helped predict future antidepressant treatment response.

In considering how activation of the anterior cingulate cortex is affected in MDD, it is important to keep in mind the subdivisions of this brain region. Less activation in the dorsal anterior cingulate cortex has been repeatedly observed in PET and fMRI studies of subjects with MDD. Conversely, hyperactivation has been observed in the ventral (subgenual) anterior cingulate cortex of subjects with MDD. Mayberg et al.²² conducted a PET study and reported the intriguing finding that greater activation in the ventral anterior cingulate cortex before treatment predicted a positive response to antidepressant medication. Davidson et al.¹⁵ replicated these findings using fMRI.

In summary, the functional neuroimaging literature supports the notion that MDD is associated with disruption of a neural circuit that involves multiple cortical and subcortical components. The dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, as well as the ventral anterior cingulate cortex and amygdala, are key components of this circuit. Altered patterns of activation and deactivation in these functionally and anatomically connected brain regions have been found in patients with MDD, and this evidence suggests that this disorder may alter these circuits. Emerging evidence suggests that similar brain circuitry is involved in interferon-induced depression.

Studies of the Effects of Interferon in Hepatitis C

Surprisingly few neuroimaging studies have examined the effects of interferon on brain activation in hepatitis C. We review one such study and then highlight other studies that have used neuroimaging to investigate fatigue in chronic medical conditions. Juengling et al.²³ studied the effect of interferon on brain activation and the development of depressive symptoms in 11 subjects treated with interferon- α for chronic hepatitis C infection. Neuropsychological testing and FDG PET were performed before and after 12 weeks of interferon treatment. Significant changes in brain activation were observed at week 12. Specifically, bilateral dorsolateral prefrontal cortex hypometabolism was observed at week 12, relative to baseline, in all subjects. In a covariance analysis, this hypometabolism was correlated with changes in scores on the Beck Depression Inventory. Before interferon treatment, one of the 11 sub-

jects met the criteria for depression, whereas six of 11 were depressed at week 12. The authors noted that hypometabolism in the prefrontal cortex was seen in both the depressed and the nondepressed subjects before interferon treatment, and they speculated that this characteristic may constitute a predisposing factor for interferon-associated neuropsychological syndromes.

Studies of Fatigue

Chronic fatigue syndrome is characterized by fatigue accompanied by several associated physical or cognitive symptoms for a period of 6 months or longer. Poor concentration and impaired memory are among the most frequently encountered symptoms. Although the neurobiology of these symptoms remains incompletely understood, functional neuroimaging studies have revealed that the prefrontal cortex and anterior cingulate cortex are critically involved in mediating fatigue in chronic fatigue syndrome.

SPECT experiments in chronic fatigue syndrome have revealed hypoperfusion in a variety of brain regions, including the anterior cingulate cortex and prefrontal cortex. Schmaling et al.²⁴ implemented an auditory working memory paradigm and observed a relative increase in task-related left anterior cingulate cortex activity in chronic fatigue syndrome patients, relative to healthy comparison subjects. Baseline differences in brain activation were also reported in this study. Specifically, decreased anterior cingulate cortex activity and decreased global activation were observed at baseline in chronic fatigue syndrome patients, relative to comparison subjects. Related SPECT studies have observed frontal lobe hypometabolism in chronic fatigue syndrome.²⁵

The literature on PET studies also contains evidence of altered prefrontal cortex activation in chronic fatigue syndrome. Tirelli et al.²⁶ reported that subjects with chronic fatigue syndrome had significant hypometabolism in the right mediofrontal cortex and brainstem, compared to healthy subjects. This study also included several subjects with MDD, who were found to have severe hypometabolism in the medial and upper frontal regions bilaterally, although they had normal metabolism in the brainstem.

We are unaware of fMRI studies in chronic fatigue syndrome, but this technique has been used to study fatigue in other conditions. For example, Filippi et al.²⁷ used fMRI to study the pathogenesis of fatigue related to multiple sclerosis. In their study, 15 healthy comparison subjects and 29 patients with multiple sclerosis (15 patients with fatigue and 14 patients without fatigue) performed a simple motor

task while fMRI was conducted. The multiple sclerosis patients with and without fatigue had differences in brain activation in many areas, including the cingulate and frontal cortex. Specifically, multiple sclerosis patients with fatigue had significantly greater activation in the contralateral cingulate motor area and significantly less activation of several areas of the prefrontal cortex, including the contralateral middle frontal gyrus and the ipsilateral orbitofrontal cortex. Further, significant negative correlations were found between fatigue scores and relative activations in the ipsilateral orbitofrontal cortex and thalamus as well as the contralateral intraparietal sulcus, but no significant changes were found in prefrontal cortex activation.

CONVERGING FINDINGS AND FUTURE DIRECTIONS

Converging functional neuroimaging evidence supports the hypothesis that common neural circuitry is involved in the development of fatigue and depression in diverse conditions. The anterior cingulate cortex and prefrontal cortex are key components of this circuitry. Intact functioning in these regions during cognitive and affective challenge tasks may indicate that subjects are less likely to develop fatigue and depression. Conversely, a preexisting weakened neural circuit may make a subject more vulnerable to developing such symptoms.

The dorsolateral prefrontal cortex may be particularly important in the development of depressive symptoms. Lower levels of activation in this region have been observed in patients with interferon-induced depression and in patients with MDD, relative to healthy comparison subjects. Future fMRI studies with a region-of-interest approach are needed to fully understand how interferon administration affects activation in the dorsolateral prefrontal cortex and how this process relates to the development of depressive symptoms. Similarly, fMRI studies are needed to investigate the role of the anterior cingulate cortex in interferon-induced depression. Hyperactivation in the ventral anterior cingulate cortex has been shown to predict future antidepressant treatment response in MDD. Specific investigation of this structure in subjects who are taking

interferon may allow prospective identification of patients at risk for interferon-induced depression and initiation of prophylactic treatment for these patients.

Functional neuroimaging studies of fatigue have identified several regions of the prefrontal cortex and anterior cingulate cortex as critical for mediating fatigue associated with chronic fatigue syndrome and multiple sclerosis. Future fMRI studies may allow the identification the specific subregions within these structures that are important in mediating fatigue in these conditions. The specific structures involved in interferon-related fatigue are unknown. The temporal and spatial resolution of fMRI and the development of tasks that specifically probe the functions of the dorsolateral prefrontal cortex, anterior cingulate cortex,²⁸ and other regions of critical brain circuitry may make it possible to fully elucidate the neural substrates of interferon-induced neuropsychiatric side effects. Thus, functional brain imaging has enormous potential for revolutionizing psychosomatic medicine and may soon become another diagnostic tool for clinicians in the consultation-liaison setting.

This review was intended to summarize the current understanding of the brain circuits involved in the development of neuropsychiatric symptoms and to guide future research in this area to allow better diagnosis and treatment of the sequelae of hepatitis C and interferon treatment. The fact remains that neuropsychiatric symptoms may be a characteristic of hepatitis C, interferon treatment, or both, and further research is needed to address this issue. The extensive literature on the neuropsychology of HIV and its treatment may help to shed light on this area. Careful characterization of patients who have successfully been treated for hepatitis C may also be illustrative. In addition, careful comparisons between patients who do and do not develop interferon-induced neuropsychiatric side effects may contribute greatly to the understanding of the pathophysiology of these symptoms in hepatitis C. Given the prevalence of hepatitis C and the disabling nature of its associated neuropsychiatric side effects, collaboration between consultation-liaison psychiatrists, hepatologists, and psychologists is essential for advancing knowledge and making key contributions to patient well-being.

References

1. Bianchi G, Loguercio C, Sgarbi D, Abbiati R, Chen CH, Di Pierro M, Disalvo D, Natale S, Marchesini G: Reduced quality of life in patients with chronic hepatitis C: effects of interferon treatment. *Dig Liver Dis* 2000; 32:398-405
2. Lerner DM, Stoudemire A, Rosenstein DL: Neuropsychiatric toxicity associated with cytokine therapies. *Psychosomatics* 1999; 40:428-435
3. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, Hill J, Gulati M, Thornton AJ, Schultz RL, Valentine AD, Meyers CA, Howell CD: A prospective study of the incidence and open-label treatment

Neuropsychiatric Side Effects in Hepatitis C

- of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry* 2002; 7:942–947
4. Alberti A, Pontisso P: Hepatitis viruses as aetiological agents of hepatocellular carcinoma. *Ital J Gastroenterol* 1991; 23:452–456
 5. Seeff LB: Natural history of hepatitis C. *Hepatology* 1997; 26(3 suppl 1):21S–28S
 6. Fried MW: Side effects of therapy of hepatitis C and their management. *Hepatology* 2002; 36(5 suppl 1):S237–S244
 7. Dieperink E, Willenbring M, Ho SB: Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. *Am J Psychiatry* 2000; 157:867–876
 8. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH: Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; 344:961–966
 9. Ogawa S, Lee TM, Kay AR, Tank DW: Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 1990; 87:9868–9872
 10. Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL: The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry* 1998; 44:1219–1228
 11. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ: Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 2003; 126:2139–2152
 12. Matthews SC, Paulus MP, Simmons AN, Nelesen RA, Dimsdale JE: Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage* (in press)
 13. Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL: The counting Stroop: an interference task specialized for functional neuroimaging: validation study with functional MRI. *Human Brain Mapping* 1998; 6:270–282
 14. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD: Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998; 280:747–749
 15. Davidson RJ, Irwin W, Anderle MJ, Kalin NH: The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am J Psychiatry* 2003; 160:64–75
 16. Bechara A, Damasio AR, Damasio H, Anderson SW: Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994; 50:7–15
 17. Hikosaka K, Watanabe M: Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. *Cereb Cortex* 2000; 10:263–271
 18. Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK: Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry* 2000; 47:769–776
 19. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR: Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry* 2003; 53:494–501
 20. Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, Axelson D, Whalen PJ, Casey BJ: Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry* 2001; 58:1057–1063
 21. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME: Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 1997; 386:824–827
 22. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT: Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 1997; 8:1057–1061
 23. Juengling FD, Ebert D, Gut O, Engelbrecht MA, Rasenack J, Nitzsche EU, Bauer J, Lieb K: Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl)* 2000; 152:383–389
 24. Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS: Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosom Med* 2003; 65:129–136
 25. Costa DC, Tannock C, Brostoff J: Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 1995; 88:767–773
 26. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G: Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* 1998; 105:54S–58S
 27. Filippi M, Rocca MA, Colombo B, Falini A, Codella M, Scotti G, Comi G: Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* 2002; 15:559–567
 28. Bush G, Shin LM, Holmes J, Rosen BR, Vogt BA: The Multi-Source Interference Task: validation study with fMRI in individual subjects. *Mol Psychiatry* 2003; 8:60–70