Available online at www.sciencedirect.com
ScienceDirect
Brain, Behavior, and Immunity 22 (2008) 870–880
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C

Matthias Majer [a], Leonie A.M. Welberg [b], Lucile Capuron [a,c], Giuseppe Pagnoni [a], Charles L. Raison [a], Andrew H. Miller [a,*]

[a] *Department of Psychiatry and Behavioural Sciences, Winship Cancer Institute, Emory University School of Medicine, 5th Floor, Room C5006, 1365-C Clifton Road, Atlanta, GA 30322, USA*
[b] *Macmillan Publishers Limited, London, UK*
[c] *Laboratoire de Psychoneuroimmunologie, Université Bordeaux II, Bordeaux, France*

Received 28 November 2007; received in revised form 21 December 2007; accepted 23 December 2007
Available online 6 February 2008

Abstract

Interferon (IFN)-alpha has been used to investigate pathways by which innate immune cytokines influence the brain and behaviour. Previous studies suggest that altered basal ganglia function may contribute to IFN-alpha-induced neuropsychological and behavioural changes. To further examine IFN-alpha effects on neuropsychological functions related to basal ganglia (as well as other brain regions), and explore the relationship between altered neuropsychological function and IFN-alpha-induced depression and fatigue, a selected subset of the Cambridge Neuropsychological Test Automated Battery was administered to 32 hepatitis C patients at baseline (Visit 1) and following ~12 weeks (Visit 2) of either no treatment ($n = 12$) or treatment with IFN-alpha plus ribavirin ($n = 20$). Symptoms of depression and fatigue were assessed using the Montgomery-Asberg Depression Rating Scale and the Multidimensional Fatigue Inventory. Compared to control subjects, patients treated with IFN-alpha/ribavirin exhibited significant decreases in motor speed as measured in the simple and five-choice movement segments of the CANTAB reaction time task and slower response times in the rapid visual information processing task, a task of sustained attention. Decreased motor speed on the five-choice movement segments of the reaction time task was in turn correlated with increased symptoms of depression and fatigue ($R = 0.47$, $p < 0.05$ and $R = 0.48$, $p < 0.05$, respectively). IFN-alpha/ribavirin treatment had no effects on executive function, decision time in the reaction time task, or target detection accuracy in the sustained attention task. Motor slowing and its correlation with psychiatric symptoms suggest that altered basal ganglia function may contribute to the pathogenesis of IFN-alpha-induced behavioural changes.

Keywords: Interferon-alpha; Hepatitis C; Neuropsychological tests; Motor slowing; Depression; Fatigue; Basal ganglia; Dopamine

1. Introduction

Interferon (IFN)-alpha is an innate immune cytokine with potent antiviral and anti-proliferative properties that is used to treat viral infections such as hepatitis C and certain cancers including malignant melanoma and renal cell carcinoma (Dorr, 1993; Kirkwood, 2002). Despite therapeutic efficacy in these illnesses, IFN-alpha administration causes marked behavioural changes that overlap with major depression including depressed mood, anhedonia, anergia/fatigue, psychomotor slowing, cognitive dysfunction, anxiety/irritability, anorexia, sleep alterations and increased sensitivity to pain (Loftis and Hauser, 2004; Maddock et al., 2005; Reichenberg et al., 2005; Asnis and De La Garza, 2006; Lotrich et al., 2007). Given IFN-alpha's effects on behaviour and its ability to activate the innate immune response including the release of other innate immune cytokines such as interleukin (IL)-6, IFN-alpha has been used as a model to study the influence of innate immune cytokines on the brain.

* Corresponding author. Fax: +1 404 727 3233.
E-mail address: amill02@emory.edu (A.H. Miller).

0889-1591/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2007.12.009

A number of pathophysiologic mechanisms underlying the neurobehavioural effects of IFN-alpha have been proposed (Capuron et al., 2004). One mechanism by which IFN-alpha is believed to induce behavioural symptoms is through alteration of dopamine neurotransmission and basal ganglia function. For example, animal studies have shown that chronic IFN-alpha administration induces a robust depression in motor activity and reduces dopamine concentrations in the mouse brain (Dunn and Crnic, 1993; Shuto et al., 1997). Moreover, Parkinson-like motor symptoms have been described in patients treated with IFN-alpha for chronic hepatitis C (Mizoi et al., 1997), and levodopa, an intermediate in dopamine biosynthesis, has been shown to significantly ameliorate IFN-alpha-induced akathisia, a symptom of "inner" motor restlessness often associated with dopamine blockade by antipsychotic medications (Sunami et al., 2000). IFN-alpha administration also has been demonstrated to reduce psychomotor speed in normal volunteers (Smith et al., 1988). Interestingly, IFN-alpha-induced decreases in motor speed as assessed by movement time in the five-choice reaction time task of the Cambridge Neuropsychological Test Automated Battery after 5 days of IFN-alpha treatment were found to significantly correlate with the development of depressive symptoms after 1 month of intravenous (iv) IFN-alpha therapy for cancer (Capuron et al., 2001). Of note, no such relationship was found in patients receiving subcutaneous (sc) administration of IFN-alpha for cancer treatment. Of direct relevance to the effects of IFN-alpha on brain regions involved in the regulation of motor activity and dopamine neurotransmission is a recent study by Capuron et al. (2007), which revealed that self-reported symptoms of fatigue were positively correlated with increased glucose metabolism in basal ganglia nuclei, including the putamen and nucleus accumbens, in patients receiving high dose IFN-alpha therapy for malignant melanoma.

Aside from evidence of IFN-alpha effects on neuropsychological and neurobiological correlates of basal ganglia function and dopamine neurotransmission, IFN-alpha has been shown to affect other brain regions and other domains of cognitive performance. Indeed, EEG data has shown significant slowing of frontal lobe waves in cancer patients receiving high doses of IFN-alpha therapy (Rohatiner et al., 1983; Smedley et al., 1983). Similarly, decreases in prefrontal cortex glucose metabolism as revealed by positron emission tomography have been described in patients receiving IFN-alpha for hepatitis C and malignant melanoma (Juengling et al., 2000; Capuron et al., 2007). In addition, neuropsychological testing has indicated diminished executive function and slowing of cognitive processes in patients receiving IFN-alpha for cancer or hepatitis C (Meyers et al., 1991; Pavol et al., 1995; Valentine et al., 1998; Scheibel et al., 2004; Hilsabeck et al., 2005; Lieb et al., 2006). Nevertheless, the effects of IFN-alpha on cognitive function have not been consistent, with some studies failing to find cognitive effects of IFN-alpha treatment (Panitch et al., 1986; Mapou et al., 1996; Caraceni et al., 1998). Disparate results across studies may reflect differences in the dose or duration of IFN-alpha therapy, its mode of administration (iv vs. sc), the severity of the underlying illness for which the patient is receiving IFN-alpha therapy, concurrent medications, and the use of a matched control group in the study design.

To further explore the relationship between IFN-alpha-induced changes in neuropsychological functions relevant to the basal ganglia and the development of behavioural alterations during IFN-alpha therapy, we measured neuropsychological function and behaviour in patients with hepatitis C before and after ~12 weeks of IFN-alpha therapy. Hepatitis C patients awaiting IFN-alpha therapy who were studied in parallel served as controls. Based on the previous literature, we hypothesised that IFN-alpha-induced changes in the performance of neuropsychological tasks associated with basal ganglia function, in particular those assessing psychomotor speed and response latencies, would be associated with the development of depression and fatigue, thereby supporting a role for cytokine effects on basal ganglia function as a mechanism for cytokine-induced behavioural change.

2. Methods

2.1. Subjects

Thirty-two HCV-positive subjects (18 males, 14 females) between the ages of 30 and 56 were enrolled in the study. Subjects were required to be serum positive for anti-HCV antibodies or HCV-RNA by reverse transcription-polymerase chain reaction. Exclusion criteria included decompensated liver disease; liver disease from any cause other than HCV; unstable cardiovascular, endocrinologic, hematologic, renal or neurologic disease (as determined by medical history, physical exam and laboratory testing); history of schizophrenia, bipolar disorder or a diagnosis of major depression or substance abuse/dependence within six months of study entry [as determined by the Structured Clinical Interview for DSM-IV (SCID)] and/or a score <24 on the Mini Mental State Examination (a standard, 27-item assessment of general cognitive functioning), indicating more than mild cognitive impairment (Folstein et al., 1983). Patients were required to be off all psychotropic medications (antidepressants, antipsychotics, mood stabilizers, narcotics and benzodiazepines) for at least 2 weeks prior to study entry and at least 2 weeks prior to any neuropsychological assessments (8 weeks for fluoxetine). All patients provided written, informed consent before enrolment, and the study was *a priori* approved by the Emory University Institutional Review Board.

2.2. Design

A prospective, longitudinal design was used to examine neuropsychological function and behaviour in patients with HCV prior to (Visit 1), and following, 12 weeks (Visit 2) of either no treatment (control group) or treatment with IFN-alpha plus ribavirin (treatment group). All subjects who underwent treatment with IFN-alpha received either pegylated IFN-alfa-2a (PEGASYS®, Roche; 180 μg/week, s.c.; $n = 7$) or pegylated IFN-alfa-2b (Pegintron®, Schering Plough; 1.5 μg/kg weekly, s.c.; $n = 13$) and ribavirin (800–1400 mg/d). Participation in the control vs. treatment group as well as type of IFN-alpha administered was determined by patients and their physicians and was not controlled by study protocol. Following study enrolment, all subjects underwent a 14-h adaptation night in the Emory University General Clinical Research Center (GCRC) to become familiarized with the GCRC environment prior to study evaluation. Within two weeks of the adaptation night, subjects

underwent their baseline (Visit 1) evaluation in the Emory University GCRC. After 12 weeks, subjects returned to the GCRC for their second assessment (Visit 2). At Visits 1 and 2, subjects were admitted to the GCRC the night prior to evaluation to allow for accommodation to the GCRC environment and to control for the effects of sleep and wake times on neuropsychological performance. Lights out occurred at 10 pm, and all subjects were awakened at 7:15 am and served breakfast before neuropsychological testing, which took place between 9 and 10 am. Where appropriate, subjects who developed depressive symptom severity warranting psychiatric intervention prior to 12 weeks immediately underwent their second GCRC assessment (Visit 2) and were then referred for psychiatric evaluation. Urine drug screens were conducted at each visit to rule out substance abuse.

2.3. Neuropsychological testing

At both Visits 1 and 2, neuropsychological performance was assessed using a selected subset of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992), a battery of neuropsychological tests using a portable computer with touch screen. Four CANTAB tests were selected to assess specific domains of neuropsychological function (psychomotor speed, attention, and executive function). Completion of the chosen tests (including the instructions) took approximately 30 min, and the test order was counterbalanced across all subjects. The following tests of the CANTAB were employed:

2.3.1. Psychomotor speed

The *Reaction Time (RTI)* test was used to evaluate psychomotor speed, which has been associated with basal ganglia function (Mink, 1996). The test includes simple and five-choice reaction time segments and provides distinction between reaction (or decision) time and movement latencies. Reaction (or decision) time is the speed with which the subject releases the press pad in response to the onset of a stimulus. Movement time (motor speed) is the time taken to touch the stimulus on the computer screen after the press pad had been released.

2.3.2. Attention

To assess sustained attention, the *Rapid Visual Information Processing* (RVIP) test was used. Digits (ranging from 2 to 9) appeared one at a time (100 digits/min) in the center of the computer screen in random order. Subjects were asked to press a response pad when they detected any one of three number sequences ('2-4-6', '4-6-8', '3-5-7'). Performance accuracy was estimated from the target sensitivity score A' (ranging from 0.00 to 1.00; bad to good). Performance speed was assessed by measuring the mean latency for correct responses.

2.3.3. Executive function

Two tests were used to evaluate executive function. (a) The *Intra/Extra Dimensional Attentional Shift* (IED) task is a test of rule acquisition and reversal, and assesses the subject's visual discrimination and attentional set shifting abilities. In this test, the subject is required to maintain attention to a reinforced stimulus presented in different configurations (intra-dimensional shift, IDS) and then must shift attention to a previously irrelevant stimulus (extra-dimensional shift, EDS). This test is sensitive to cognitive dysfunction in Parkinson's disease, basal ganglia lesions and frontal lobe deficits (Owen et al., 1991; Swainson and Robbins, 2001). Subjects progress through the test by satisfying a set of learning criteria at each stage (nine stages in total). The number of completed stages, the total number of errors (adjusted to the number of completed stages), the number of errors made prior to the extra-dimensional shift phase (Pre-ED errors), and the number of errors made within the extra-dimensional shift phase (EDS errors) were used as performance indices. (b) The *Stockings of Cambridge* (SOC) task was used to evaluate spatial planning/problem solving. The task makes substantial demands on executive function and is sensitive to frontal lobe damage (Robbins et al., 1998). The test is based on the "Tower of London" task and contains incremental levels of difficulty. For each problem, the computer touch screen showed two displays of colored balls, and the subject was told to move the balls in the lower display in a minimum number of moves until they matched the target configuration. Subjects were told to solve the problem in their minds before making the first move. Analysis of the test controls for motor speed. Subjects' executive abilities were estimated from the time taken to move the first ball to solve a problem [initial thinking time (ITT)], the time taken after the initial move [subsequent thinking time (STT)], the number of problems solved in the minimum possible number of moves (# perfect solutions), and the average number of moves made for each solution (# moves).

2.4. Behavioural assessment

Depression was evaluated using the mood disorders module of the SCID and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS is a 10-item, clinician-administered scale that assesses the severity of depressive symptoms, including sadness, inner tension, concentration difficulties, inability to feel, pessimistic thoughts, suicidal thoughts, reduced sleep, reduced appetite and lassitude. To evaluate the presence and severity of fatigue, subjects completed the 20-item Multidimensional Fatigue Inventory (MFI-20) at each assessment (Smets et al., 1995). Consistent with recent data regarding the structure of fatigue in medically ill patients, the MFI assesses five dimensions of fatigue, including general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. Four items contribute to each subscale with a five-point rating per item. Accordingly, the total score of each subscale ranges from 4 (best) to 20 (worst). In addition to scores for each subscale, a total score can be derived by summing the five-subscale scores (Wichers et al., 2005a).

2.5. Statistical analysis

Chi-square or Fisher's exact test was used to compare distributions of the following variables between IFN-alpha-treated and control subjects: sex, race, education, history of depression and history of substance abuse. *t*-tests were used to compare age as well as depression and fatigue scores at Visit 1 of IFN-alpha-treated and control subjects. Neuropsychological and behavioural assessments of IFN-alpha-treated and control patients were evaluated using repeated measures analysis of covariance (ANCOVA) with visit (Visit 1 vs. Visit 2) as a within-subject factor and treatment (IFN-alpha vs. control) as a between-subjects factor. Because age has been strongly associated with neuropsychological test performance in the CANTAB (Robbins et al., 1998; Rabbitt and Lowe, 2000), statistical analyses were conducted using age as a covariate in order to reduce inter-subject variability. Other covariates included in the analyses were level of education (# years of college) and history of depression. Where ANCOVAs were significant, post hoc comparisons were performed using Tukey's test of significance. Correlations between measures of neuropsychological functioning and symptom scores of depression and fatigue in the sample were determined using the Spearman test due to the non-continuous nature of the MFI-20 and MADRS data. To limit the influence of outliers on statistical analyses of specific cognitive tests, subjects whose task performance at baseline included repeated ($\geqslant 4$) instances of responses three standard deviations (SD) above or below the sample mean were excluded from the analysis of that task. Accordingly, two control subjects were excluded from the analysis of the reaction time task. For all statistical tests, significance was set at $p < 0.05$, two-sided.

3. Results

3.1. Demographic and clinical characteristics of the study sample at baseline

As shown in Table 1, there were no significant differences between IFN-alpha-treated and control subjects in

Table 1
Demographic and clinical characteristics of the study sample

Variable	Control ($n = 12$)	IFN-alpha ($n = 20$)	p Value
Sex	6 males, 6 females	12 males, 8 females	0.71
Age (range)	48.3 (40–54)	47.6 (30–56)	0.71
Race	6 black	10 black	
	5 white	8 white	
	1 other	2 other	0.98
Education College (1 or more years)	10	12	0.24
History of depression	0	4	0.13
History of substance abuse	6	11	0.71

MADRS, Montgomery-Asberg Depression Rating Scale; MFI, Multidimensional Fatigue Inventory.

terms of sex (Fisher's exact test, $p = 0.71$), age ($t(30) = 0.36$, $p = 0.71$;), race ($X^2(2) = 0.02$, $p = 0.98$), education (Fisher's exact test, $p = 0.24$), history of depression (Fisher's exact test, $p = 0.13$) and history of substance abuse (Fisher's exact test, $p = 0.71$). There were also no differences between groups in level of depression and fatigue at Visit 1 (MADRS score: $t(30) = 0.31$, $p = 0.75$; MFI total score: $t(29) = 0.40$, $p = 0.68$) (Table 2). Two subjects treated with IFN-alpha/ribavirin developed depressive symptoms severe enough to warrant GCRC evaluation before 12 weeks (one subject at 4 weeks and one subject at 11 weeks). Accordingly, the average length of time from Visit 1 to Visit 2 was shorter for the treatment group than the control group (mean length from Visit 1 to Visit 2 (±SD): 11.1 (±2.7) weeks vs. 12.9 (±1.2) weeks, respectively, $t(30) = 2.16$, $p < 0.05$).

3.2. Neuropsychological performance

3.2.1. Reaction time task

Using 2-way repeated measures ANCOVA controlling for age, level of education and past history of major depression, no main effects or interactions were found for IFN-alpha/ribavirin treatment or Visit on reaction (decision) time in the simple- or five-choice CANTAB reaction time task. In contrast, while there were no main effects of IFN-alpha/ribavirin treatment or Visit on movement times in the CANTAB reaction time task, there was a significant interaction between these variables (treatment × Visit) for both simple- and five-choice reaction time tasks ($F(1,27) = 8.97$, $p < 0.01$ and $F(1,27) = 4.68$, $p < 0.05$, respectively). Post hoc analysis revealed that IFN-alpha/ribavirin-treated patients exhibited significantly slower simple- and five-choice movement times at Visit 2 vs. Visit 1 (both $p < 0.01$) (Fig. 1). Moreover, IFN-alpha/ribavirin-treated patients exhibited significantly slower simple and five-choice movement times at Visit 2 compared to controls (both $p < 0.05$). Delta movement times (Visit 2–Visit 1) for each group were as follows: IFN-alpha/ribavirin-treated subjects: Δsimple movement time, ΔsMT (±SD) = 91.3 (±120.5), Δchoice movement time, ΔcMT = 68.1 (±101.2); control subjects: ΔsMT = −66.7 (±158.4), ΔcMT = −35.4 (±156.0). Slower simple movement times compared to five-choice movement times (for both visits and both patients groups) may be secondary to an order effect, since the simple reaction time condition always precedes the five-choice reaction time condition in the CANTAB reaction time task.

3.2.2. Attention—rapid visual information processing

Two-way repeated measures ANCOVA revealed no significant differences between IFN-alpha/ribavirin-treated patients and controls on RVIP performance accuracy as measured by signal A'. Nevertheless, there was an interac-

Table 2
Mean (±SD) depression and fatigue scores in IFN-alpha-treated and control subjects

Behavioural assessment	Control ($n = 12$)			IFN ($n = 20$)		
	Visit 1	Visit 2	Delta	Visit 1	Visit 2	Delta
MADRS	4.0 (5.1)	3.2 (3.7)	−0.9 (2.5)	4.7 (5.5)	12.8 (10.0)[a,*]	8.1 (10.1)
MFI						
Total	42.8 (15.3)	37.7 (16.0)	−4.0 (7.6)	40.5 (14.7)	59.8 (21.3)[a,*]	19.2 (16.3)
GF	10.3 (4.1)	8.2 (4.0)	−2.0 (2.1)	9.8 (3.8)	14.0 (4.6)[a,*]	4.2 (4.1)
PF	9.0 (3.4)	8.6 (4.0)	−0.4 (1.8)	8.9 (4.1)	12.6 (4.7)[a,*]	3.6 (3.6)
RA	8.3 (3.4)	7.1 (3.4)	−1.2 (1.3)	7.6 (4.2)	11.7 (5.0)[a,*]	4.1 (3.9)
RM	7.2 (3.0)	6.7 (2.6)	−0.5 (2.1)	7.4 (2.9)	11.5 (4.4)[a,*]	4.1 (3.4)
MF	7.9 (3.3)	7.1 (3.7)	−0.8 (2.1)	6.8 (2.6)	10.0 (5.0)[a,*]	3.2 (4.5)

SD, standard deviation; MADRS, Montgomery-Asberg Depression Rating Scale; MFI, Multidimensional Fatigue Inventory; GF, general fatigue; PF, physical fatigue; RA, reduced activity; RM, reduced motivation; MF, mental fatigue.
[a] Significantly different from Visit 1 ($p < 0.01$ using Tukey test).
[*] Significantly different from respective control value ($p < 0.01$ using Tukey test).

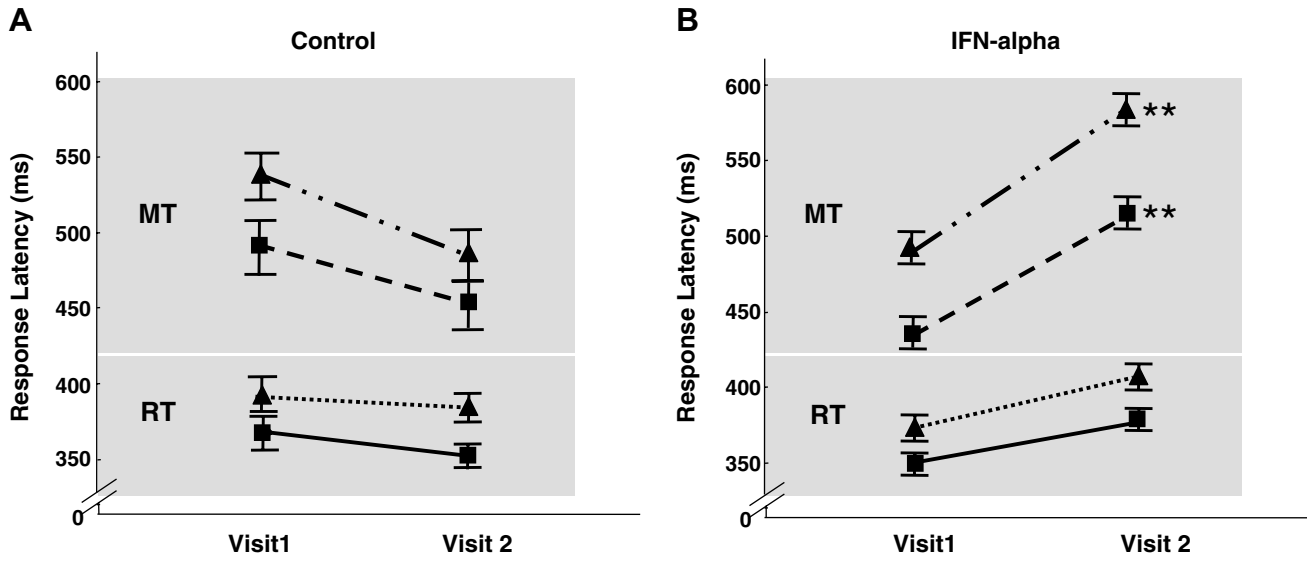

Fig. 1. Change in motor speed in control and IFN-alpha/ribavirin-treated patients. (A) Mean (±SEM) simple and five-choice movement times in the reaction time task are depicted at baseline (Visit 1) and after ~12 weeks (Visit 2) in control (Panel A) and IFN-alpha/ribavirin-treated (Panel B) patients. Motor slowing was observed from Visit 1 to Visit 2 in IFN-alpha-treated but not control subjects. $^{**}p < 0.01$ Visit 2 vs. Visit 1 (Tukey's test); dot-dashed lines—simple movement time; dashed lines—choice movement time; dotted lines—choice reaction time; solid lines—simple reaction time. RT, reaction time; MT, movement time.

tion between the effects of IFN-alpha treatment and Visit on the mean latency to correct responses ($F(1,29) = 13.9$, $p < 0.01$). Post hoc analysis revealed that control patients, but not IFN-alpha treated patients, showed significantly faster responses at Visit 2 compared to Visit 1 ($p < 0.01$) (Fig. 2). Change in mean latency (Δlatency) for correct responses on the RVIP task from Visit 1 to Visit 2 were as follows: IFN-alpha/ribavirin-treated-subjects: Δlatency (±SD) = 35.1 (±78.8) ms; control subjects: Δlatency = −90.8 (±108.1) ms (Fig. 2).

3.2.3. Executive function-intra-/extra dimensional set shift and stockings of Cambridge

IFN-alpha/ribavirin treatment did not affect rule-learning capacity or set shifting as measured in the IED test (Table 3). No main effects of IFN-alpha treatment or Visit

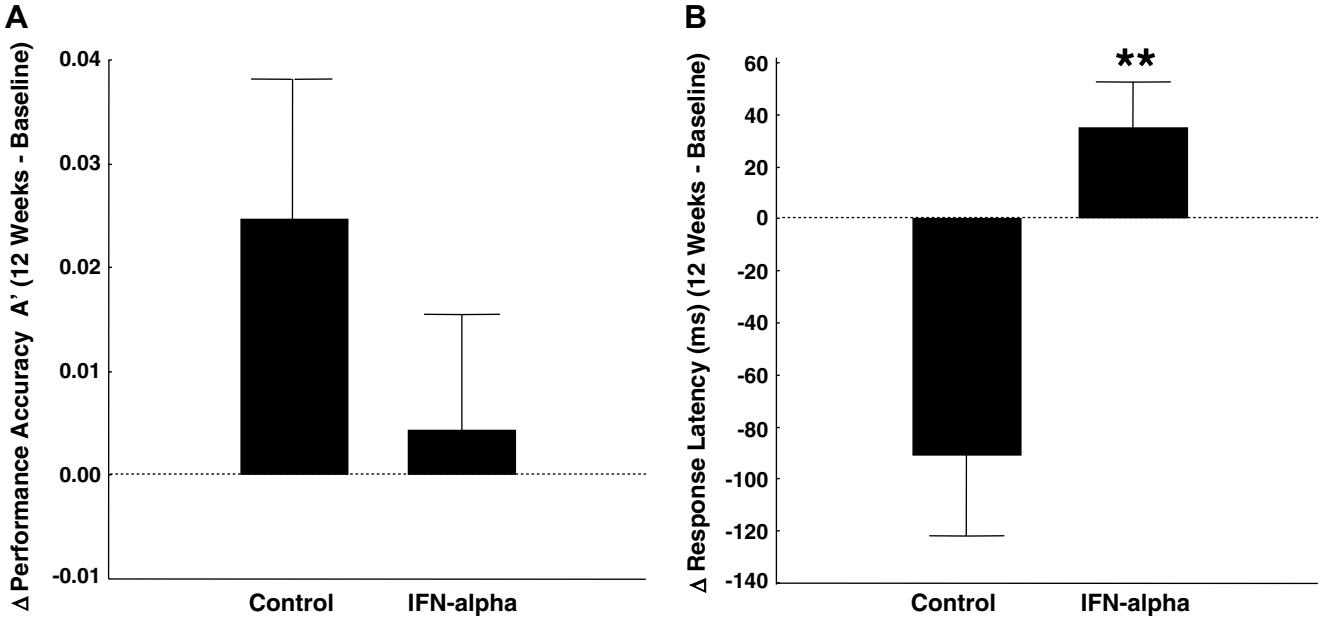

Fig. 2. Change in sustained-attention in control and IFN-alpha-treated patients. Comparison of the mean (±SEM) change in performance accuracy A' (panel A) and response latency (panel B) in the Rapid Visual Information Processing (RVIP) test in control and IFN-alpha/ribavirin-treated subjects are indicated. Control patients, but not IFN-alpha-treated patients, showed faster responses at Visit 2 compared to Visit 1. There were no significant differences between IFN-alpha-treated and control patients in performance accuracy A'; $^{**}p < 0.01$ vs. controls (Tukey's test).

Table 3
Effects of IFN-alpha treatment on measures of executive function

Neuropsychological tests	Controls ($n = 12$)		IFN-alpha ($n = 20$)	
	Visit 1	Visit 2	Visit 1	Visit 2
Intra/extra dimensional shift				
EDS errors	14.0 (3.8)	11.3 (3.2)	12.2 (2.6)	12.4 (2.4)
Pre-ED errors	8.2 (1.3)	6.8 (1.1)	6.3 (0.7)	6.3 (1.1)
# Stages completed	8.5 (0.3)	8.4 (0.3)	8.5 (0.2)	8.5 (0.2)
Total # errors (adjusted)	30.6 (6.4)	27.1 (6.0)	26.9 (4.8)	28.4 (4.6)
Stockings of Cambridge				
ITT (s)—4	4.4 (0.8)	4.2 (1.0)	4.6 (0.7)	5.3 (0.7)
ITT (s)—5	4.9 (1.3)	3.0 (0.5)	5.9 (1.2)	5.7 (1.2)
# Moves—4	7.3 (0.5)	7.5 (0.4)	7.9 (0.3)	7.1 (0.4)
# Moves—5	6.0 (0.4)	5.7 (0.2)	5.5 (0.2)	5.7 (0.2)
STT (s)—4	1.7 (0.4)	1.3 (0.3)	1.7 (0.3)	1.6 (0.3)
STT (s)—5	1.0 (0.2)	0.5 (0.1)	1.5 (0.3)	1.2 (0.4)
# Perfect solutions	6.7 (0.5)	7.3 (0.4)	6.5 (0.4)	7.3 (0.5)

Data are shown as means (±SEM); EDS errors: the number of errors made within the extra-dimensional shift phase; pre-ED errors: the number of errors made prior to the extra-dimensional shift phase; ITT, initial thinking time: the time taken to move the first ball to solve a problem; STT, subsequent thinking time: the time taken after the initial move.

on IED task performance were observed, nor was there an interaction between these factors. IFN-alpha/ribavirin treatment also had no effect on executive function as measured in the SOC task (Table 3). No main effects of treatment or Visit on SOC task performance were observed, nor was there an interaction between these factors.

Of note, no differences were found between patients treated with pegylated IFN-alfa-2a (PEGASYS®) vs. pegylated IFN-alfa-2b (Pegintron®) on any of the neuropsychological measures. Moreover, no differences were found in neuropsychological test performance in IFN-alpha-treated patients with a past history of depression vs. those without.

3.3. Behavioural symptoms

3.3.1. Depression

Three patients treated with IFN-alpha/ribavirin developed symptom criteria for DSM-IV major depression during the study. In addition, MADRS scores exhibited significant increases in symptoms of depression in IFN-alpha/ribavirin-treated patients vs. controls. Two-way ANOVA on MADRS scores with Visit as a repeated measures factor revealed a significant main effect of treatment ($F(1,30) = 6.39$, $p < 0.05$) and Visit ($F(1,30) = 4.91$, $p < 0.05$) as well as a significant interaction between these factors ($F(1,30) = 8.81$, $p < 0.01$). Post hoc analysis indicated that IFN-alpha/ribavirin-treated patients scored higher on the MADRS at Visit 2 than at Visit 1 ($p < 0.01$). In addition, MADRS scores at Visit 2 were higher in IFN-alpha/ribavirin-treated subjects compared to control patients ($p < 0.01$). Of note, no differences in change in MADRS scores from Visit 1 to Visit 2 were found between IFN-alpha-treated patients with and without a past history of major depression or patients treated with pegylated IFN-alfa-2a vs. pegylated IFN-alfa-2b.

3.3.2. Fatigue

IFN-alpha/ribavirin treatment increased all dimensions of fatigue as measured in the MFI. Two-way repeated-measures ANOVA yielded a significant interaction between treatment and Visit for all dimensions of fatigue ($p < 0.01$, all dimensions). Post hoc analysis revealed that IFN-alpha/ribavirin-treated patients reported increased scores at Visit 2 for general, physical and mental fatigue as well as for reduced activity and reduced motivation compared to Visit 1 (baseline) scores ($p < 0.01$, all dimensions). In addition, general fatigue and reduced motivation scores at Visit 2 were significantly higher in IFN-alpha/ribavirin-treated patients than control subjects ($p < 0.05$).

Of note, fatigue and depression scores were inter-correlated. For example, change in total MFI scores from Visit 1 to Visit 2 were significantly correlated with changes in MADRS scores ($R = 0.51$, $p = 0.025$). Furthermore, among the various dimensions of fatigue, changes in general fatigue ($R = 0.47$, $p = 0.042$), physical fatigue ($R = 0.61$, $p = 0.005$), and mental fatigue ($R = 0.45$, $p = 0.049$) were significantly correlated with changes in MADRS scores, while changes in reduced activity and reduced motivation were not. No significant differences in changes in MFI scores were found between patients receiving pegylated IFN-alfa-2a vs. pegylated IFN-alfa-2b or patients with or without a past history of depression.

3.4. Relationship between IFN-alpha induced neuropsychological alterations and symptoms of depression and fatigue

To evaluate the relationship between IFN-alpha/ribavirin-induced alterations in neuropsychological performance and IFN-alpha/ribavirin-induced increases in depression and fatigue, changes in simple and five-choice movement time as well as latency for correct responses in the RVIP task were correlated with changes in MADRS and MFI scores within the group of IFN-treated/ribavirin-treated patients. As shown in Fig. 3, increased symptoms of depression (ΔMADRS score) as well as fatigue (ΔMFI total score) were significantly correlated with IFN-alpha-induced motor slowing (ΔcMT) ($R = 0.47$, $p < 0.05$ and $R = 0.48$, $p < 0.05$, respectively). Within the dimensions of fatigue, IFN-alpha induced motor slowing (ΔcMT) correlated significantly with increased general fatigue ($R = 0.56$, $p < 0.05$), as well as with reduced activity ($R = 0.51$, $p < 0.05$) and reduced motivation ($R = 0.47$, $p < 0.05$). No significant correlations were found between simple movement time on the reaction time task or response latency on the RVIP task and IFN-alpha/ribavirin-induced changes in any of the depression or fatigue measures. Finally, patients who developed major depression during IFN-alpha/ribavirin therapy ($n = 4$) exhibited significantly greater decreases in motor speed on the five-choice movement segment of the reaction time task (ΔcMT) compared to IFN-alpha/ribavirin-treated patients who did not develop depression ($n = 26$) (168.3

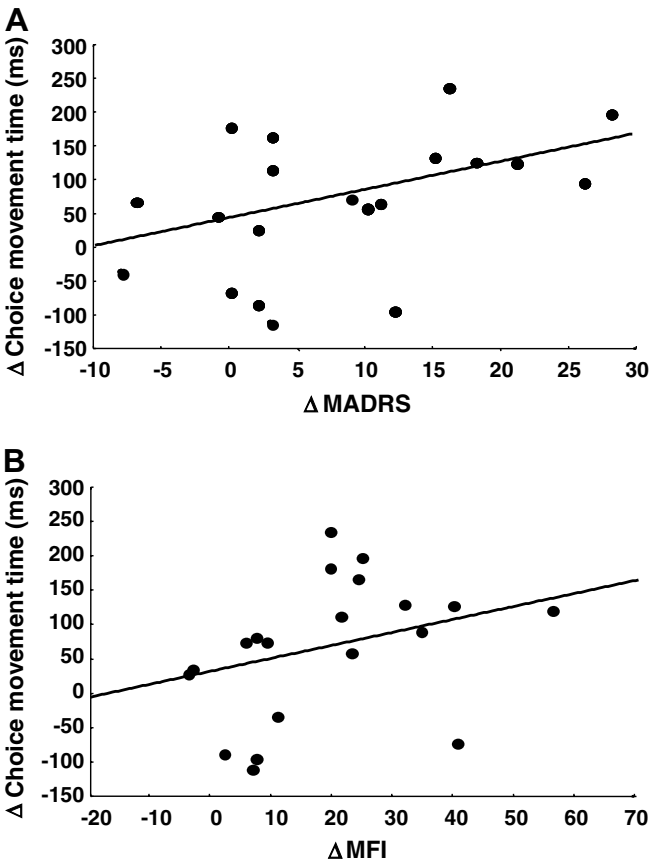

Fig. 3. Association between changes in motor speed and changes in symptoms of depression and fatigue in IFN-alpha/ribavirin-treated patients. Top panel: correlation of Δchoice movement time and ΔMADRS ($n = 20$) ($R = 0.47$, $p < 0.05$); Bottom panel: correlation of Δchoice movement time and ΔMFI ($n = 20$) ($R = 0.48$, $p < 0.05$). Δ, delta; MADRS, Montgomery-Asberg Depression Rating Scale; MFI, Multidimensional Fatigue Inventory.

(SD ± 63.5) ms vs. 12.87 (±124.8) ms; $t(28) = 2.4$, $p = 0.022$). There were no significant differences between these two groups in simple movement time or response latency in the RVIP task.

4. Discussion

The findings from the current study indicate that IFN-alpha/ribavirin treatment was associated with significant motor slowing (as manifested by decreased simple and five-choice movement times), which was, in turn, correlated with the development of symptoms of depression and fatigue. Decision time in the reaction time, target detection accuracy during sustained attention, and executive function were not affected by IFN-alpha/ribavirin treatment.

The data reported herein replicate and expand previous work in patients undergoing IFN-alpha treatment for cancer, in which motor slowing, as reflected by increased five-choice movement times on the CANTAB reaction time task after five days of IFN-alpha treatment was correlated significantly with the subsequent development of depressive symptoms after 1 month of IFN-alpha therapy (Capuron et al., 2001). In the current study, we show that motor slowing persists for up to three months of IFN-alpha treatment and correlates with both symptoms of depression and fatigue.

While motor slowing in IFN-alpha-treated patients may in principle be attributable to several factors (including functional alterations in motor and premotor cortices, as well as midbrain structures regulating general level of arousal) (Johnson and Ebner, 2000; Berridge and Waterhouse, 2003), there are reasons to consider involvement of the basal ganglia. The basal ganglia are traditionally regarded as the brain structures that regulate initiation of movement and motor speed (Alexander et al., 1986; Middleton and Strick, 2000). Indeed, patients with basal ganglia pathology have been found to exhibit decreased motor speed on a number of neuropsychological tasks including the CANTAB reaction time task (Sahakian, 1990; Gauntlett-Gilbert and Brown, 1998). Relevant to IFN-alpha, widespread alterations (increases) in glucose metabolism in basal ganglia nuclei including the putamen, globus pallidus, and nucleus accumbens have been demonstrated in IFN-alpha-treated subjects in two brain imaging studies using positron emission tomography (Juengling et al., 2000; Capuron et al., 2007). These findings are consistent with similar increases in resting state glucose metabolism in the basal ganglia of patients with Parkinson's disease (Wichmann and DeLong, 1999), where it is believed that disinhibition of dopaminergic inhibitory circuits leads to increased oscillatory burst activity in relevant basal ganglia nuclei (and thus increased metabolic activity). Consistent with correlations between decreases in motor speed (possibly reflecting altered basal ganglia function) and the development of fatigue in the current study, IFN-alpha-induced changes in basal ganglia metabolic activity, specifically in the putamen and nucleus accumbens, were correlated with symptoms of fatigue (Capuron et al., 2007).

As noted above, some neuropsychological functions that involve the basal ganglia, including set shifting, were unaffected by IFN-alpha/ribavirin treatment. One explanation for these findings is that IFN-alpha primarily influences the "motor loop" described by Alexander et al. (1986), which regulates psychomotor speed and involves the putamen, substantia nigra, thalamus and supplementary motor area. This "motor loop" is distinct from circuits interconnecting basal ganglia and prefrontal cortex that have been shown to be involved in higher executive functions, such as rule learning and task switching (as in the IED shift task), which appear to be largely dependent on prefrontal cortical function (Monchi et al., 2001).

One mechanism by which IFN-alpha may influence basal ganglia function is through effects on central dopamine (DA) pathways (Smith and Kieval, 2000). For example, IFN-alpha administration to mice induced a robust depression in motor activity, which was associated with

decreased DA as measured in whole brain homogenates (Shuto et al., 1997). Moreover as noted previously, IFN-alpha administration has been associated with symptoms of Parkinson's disease that were alleviated by levodopa. In addition, in a recent study of rhesus monkeys, IFN-alpha-induced decreases in the dopamine metabolite, homovanillic acid, was associated with depressive-like huddling behaviour in these animals (Felger et al., 2007).

IFN-alpha may influence DA neurotransmission through a number of pathways including effects on the synthesis, release and reuptake of DA. For example, IFN-alpha administration to rats has been shown to decrease central nervous system concentrations of tetrahydrobioperin, an important enzyme co-factor for tyrosine hydroxylase, the rate limiting enzyme in the synthesis of DA (Kitagami et al., 2003). Another potential pathway involves IFN-alpha-induced changes in kynurenic acid, a tryptophan metabolite, which can affect DA release. Through activation of the enzyme, indolamine 2,3 dioxygenase (which breaks down tryptophan to kynurenine), IFN-alpha treatment has been associated with increased plasma concentrations of kynurenine (especially in depressed patients), which is metabolized to kynurenic acid (KA) (Capuron et al., 2003). Of relevance to DA, intrastriatal administration of KA has been shown to dramatically reduce extracellular DA in the rat striatum (Wu et al., 2007), indicating a neuromodulatory role of KA on DA neurotransmission in addition to the previously proposed neuroprotective actions of this metabolite during cytokine (IFN-alpha) administration (Wichers et al., 2005b). Yet another pathway by which IFN-alpha and innate immune cytokines may influence DA metabolism is through activation of mitogen activated protein kinase (MAPK). Activation of MAPK signaling pathways have been shown to up-regulate the activity and cell surface expression of the DA reuptake pump, which in turn may decrease DA synaptic availability (Moron et al., 2003). Finally, IFN-alpha has been shown to bind to opioid receptors on nigrostriatal, mesolimbic and mesocortical dopaminergic neurons, causing presynaptic DA release (Ho et al., 1992; Dafny et al., 1985; Di Chiara and Imperato, 1988). Long-term IFN-alpha-induced DA release may lead to a compensatory reduction in the number and/or sensitivity of DA receptors (Cooper et al., 2003) and ultimately *decreased* dopaminergic tone.

IFN-alpha effects on DA and the basal ganglia may contribute to the development of IFN-alpha-induced depression and fatigue. Considerable attention has been focused on the role of DA in the pathophysiology of depressive disorders (Dunlop and Nemeroff, 2007). For example, rodent models of depression demonstrate altered mesolimbic DA system function and, importantly, certain antidepressants act to enhance DA neurotransmission (Willner et al., 1992). Furthermore, several studies, including postmortem investigations, have shown that depressed patients, particularly those with psychomotor retardation, exhibit reduced concentrations of DA metabolites, primarily homovanillic acid, both in the cerebrospinal fluid and in brain regions that mediate mood and motivation (Mendels et al., 1972; Roy et al., 1992; Brown and Gershon, 1993; Reddy et al., 1992; Klimek et al., 2002). Several neuroimaging studies have also found evidence of reduced DA transmission in depressed patients, including compensatory up-regulation of D_2 receptors (D'Haenen and Bossuyt, 1994; Shah et al., 1997; Ebert et al., 1996; Martinot et al., 2001; Meyer et al., 2001; Tremblay et al., 2005). Interestingly, in one study (Shah et al., 1997), reduced DA transmission, as indicated by increased binding of the dopamine $D_{2/3}$ ligand ^{123}IZBM in the striatum, was correlated with motor slowing in the reaction time task of the CANTAB in depressed patients. Regarding fatigue, it has been suggested that reduced nucleus accumbens dopamine may contribute to symptoms of fatigue in patients with depression (Salamone et al., 2003, 2005). Moreover, treatment with levodopa or other pharmacological agents that increase dopamine release (e.g. stimulants) improve fatigue in patients with basal ganglia disorders as well as in IFN-alpha-treated patients with malignant melanoma (Lou et al., 2003; Schwartz et al., 2002). Chaudhuri and Behan have proposed that altered basal ganglia function is a primary mechanism of central fatigue, with fatigue representing a fundamental behavioural characteristic of diseases that affect the basal ganglia, including Parkinson's disease, multiple sclerosis, cortical stroke, and HIV/AIDS (Chaudhuri and Behan, 2000). Finally, although we propose that motor slowing is a reflection of altered basal ganglia function leading to fatigue, it should be noted that decreased motor speed may be a consequence of fatigue and/or decreased motivation during neuropsychological testing. Nevertheless, the lack of more widespread, non-specific effects of IFN-alpha/ribavirin treatment on other neuropsychological functions and the specificity of effects within the reaction time task (i.e. effects on movement time but not reaction time) suggests that the motor alterations may be relatively specific to IFN-alpha administration and its effects on cognitive function as opposed to representing a more non-specific lack of motivation or inability to perform cognitive tasks.

The preserved performance in tests of executive/frontal cortex functions as measured by the CANTAB tasks Stockings of Cambridge and Intra/Extra Dimensional Attentional Shift is in contrast with some studies that found impairment in planning abilities (Adams et al., 1984) and cognitive flexibility (Meyers et al., 1991; Pavol et al., 1995) in IFN-alpha-treated subjects. Nevertheless, the findings reported herein are consistent with other studies, which found no IFN-alpha-induced impairment in executive function. For example, in a study by Amodio et al. (2005), IFN-alpha treatment of HCV-infected patients was not associated with decreases in executive function as measured by the trail making test (Part B), verbal fluency test or Stroop test. In addition, in two studies in cancer patients, IFN-alpha administration was not associated

with worsening of executive function after one or three months of initiation of IFN-alpha therapy (Bender et al., 2000; Capuron et al., 2001). The explanation of the discrepant findings is not clear, but is likely related to multiple contributing factors including the duration of therapy, the dose of IFN-alpha, the severity of co-morbid medical illnesses, the variety of diseases treated and the lack of a control group.

Several strengths and limitations of the current study warrant consideration. The longitudinal study design allowed patients to serve as their own controls, thus reducing the potential effects of baseline variables such as age, sex and education that have been associated with performance on neuropsychological tests in prior studies (Boone et al., 1993; Van der Elst et al., 2005). In addition, non-IFN-alpha-treated subjects studied in parallel allowed for a control of the effects of repeated testing (i.e. "practice effects"), which have been associated with improved test performance (Lowe and Rabbitt, 1998). Moreover, no patients were on psychotropic medication at the time of neuropsychological assessment. Finally, patients' neuropsychological functioning was measured using an automated test battery that assesses distinct neuropsychological domains that have been shown to probe different brain regions (Baker et al., 1996; Coull et al., 1996; Lazeron et al., 2000; Owen et al., 1996a,b; Robbins et al., 1998). In terms of study limitations, it is possible that the effects of HCV on the brain may have contributed to the results. Some studies have suggested that HCV may have independent effects on cognitive function (Forton et al., 2006). It also remains possible that HCV infection may have augmented the neuropsychological effects of IFN-alpha. The additional treatment with ribavirin also may have interacted with IFN-alpha administration. Indeed, a previous report suggested that ribavirin alone may contribute to depressive symptoms (Asnis et al., 2004). Nevertheless, the findings from the current study are consistent with our previous work on non-infected cancer patients treated with IFN-alpha monotherapy which showed a relationship between motor slowing and development of depression. Furthermore, patients receiving pegylated IFN-alfa-2a and 2b were enrolled. No controlled data are available to indicate whether the incidence of neuropsychological alterations is different between these two types of interferon. However, no significant differences between these preparations were found, although given the small sample size, these results should be interpreted with caution. It also should be noted that although all patients were free of psychotropic medications, caffeine intake was not restricted. Therefore, the potential influence of differential caffeine consumption on the results cannot be determined. Finally, because complementary assessments of basal ganglia function using techniques such as neuroimaging were not included in the current study, a direct link between the observed alterations in motor speed and basal ganglia function cannot be established.

Acknowledgments

This work was supported in part by funding from the National Institute of Mental Health (K05-MH069124, R01-HL073921, and R01-MH067990) and the Emory General Clinical Research Center (MO1-RR00039).

References

Adams, F., Quesada, J.R., Gutterman, J.U., 1984. Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. J. Am. Med. Assoc. 252, 938–941.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Amodio, P., De Toni, E.N., Cavalletto, L., Mapelli, D., Bernardinello, E., Del Piccolo, F., Bergamelli, C., Costanzo, R., Bergamaschi, F., Poma, S.Z., Chemello, L., Gatta, A., Perini, G., 2005. Mood, cognition and EEG changes during interferon alpha (alpha-IFN) treatment for chronic hepatitis C. J. Affect. Disord. 84, 93–98.

Asnis, G.M., De La Garza 2nd, R., Miller, A.H., Raison, C.L., 2004. Ribavirin may be an important factor in IFN-induced neuropsychiatric effects. J. Clin. Psychiatry 65, 581.

Asnis, G.M., De La Garza 2nd, R., 2006. Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches. J. Clin. Gastroenterol. 40, 322–335.

Baker, S.C., Rogers, R.D., Owen, A.M., Frith, C.D., Dolan, R.J., Frackowiak, R.S.J., Robbins, T.W., 1996. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 34, 515–526.

Bender, C.M., Yasko, J.M., Kirkwood, J.M., Ryan, C., Dunbar-Jacob, J., Zullo, T., 2000. Cognitive function and quality of life in interferon therapy for melanoma. Clin. Nurs. Res. 9, 352–363.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84.

Boone, K.B., Ghaffarian, S., Lesser, I.M., Hill-Gutierrez, E., Berman, N.G., 1993. Wisconsin card sorting test performance in healthy, older adults: relationship to age, sex, education, and IQ. J. Clin. Psychol. 49, 54–60.

Brown, A.S., Gershon, S., 1993. Dopamine and depression. J. Neural Transm. Gen. Sect. 91, 75–109.

Capuron, L., Ravaud, A., Dantzer, R., 2001. Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. Psychosom. Med. 63, 376–386.

Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H., 2003. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. Biol. Psychiatry 54, 906–914.

Capuron, L., Ravaud, A., Miller, A.H., Dantzer, R., 2004. Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. Brain Behav. Immun. 18, 205–213.

Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., Berns, G.S., Nemeroff, C.B., Miller, A.H., 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology 32, 2384–2392.

Caraceni, A., Gangeri, L., Martini, C., Belli, F., Brunelli, C., Baldini, M., Mascheroni, L., Lenisa, L., Cascinelli, N., 1998. Neurotoxicity of interferon-alpha in melanoma therapy: results from a randomized controlled trial. Cancer 83, 482–489.

Chaudhuri, A., Behan, P.O., 2000. Fatigue and basal ganglia. J. Neurol. Sci. 179 (S 1–2), 34–42.

Cooper, J., Bloom, F.E., Roth, R.H., 2003. The Biochemical Basis of Neuropharmacology. Oxford University Press, New York.

Coull, J.T., Frith, C.D., Frackowiak, R.S., Grasby, P.M., 1996. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34, 1085–1095.

Dafny, N., Prieto-Gomez, B., Reyes-Vazquez, C., 1985. Does the immune system communicate with the central nervous system? Interferon modifies central nervous activity. J. Neuroimmunol. 9, 1–12.

D'Haenen, H.A., Bossuyt, A., 1994. Dopamine D2 receptors in depression measured with single photon emission computed tomography. Biol. Psychiatry 35, 128–132.

Di Chiara, G., Imperato, A., 1988. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244, 1067–1080.

Dorr, R.T., 1993. Interferon-alpha in malignant and viral diseases. A review. Drugs 45, 177–211.

Dunlop, B.W., Nemeroff, C.B., 2007. The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 64, 327–337.

Dunn, A.L., Crnic, L.S., 1993. Repeated injections of interferon-alpha A/D in Balb/c mice: behavioral effects. Brain Behav. Immun. 7, 104–111.

Ebert, D., Feistel, H., Loew, T., Pirner, A., 1996. Dopamine and depression—striatal dopamine D2 receptor SPECT before and after antidepressant therapy. Psychopharmacology (Berlin) 126, 91–94.

Felger, J.C., Alagbe, O., Hu, F., Mook, D., Freeman, A.A., Sanchez, M.M., Kalin, N.H., Ratti, E., Nemeroff, C.B., Miller, A.H., 2007. Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. Biol. Psychiatry 62, 1324–1333.

Folstein, M.F., Robins, L.N., Helzer, J.E., 1983. The mini-mental state examination. Arch. Gen. Psychiatry 40, 812.

Forton, D.M., Taylor-Robinson, S.D., Thomas, H.C., 2006. Central nervous system changes in hepatitis C virus infection. Eur. J. Gastroenterol. Hepatol. 18, 333–338.

Gauntlett-Gilbert, J., Brown, V.J., 1998. Reaction time deficits and Parkinson's disease. Neurosci. Biobehav. Rev. 22, 865–881.

Hilsabeck, R.C., Hassanein, T.I., Ziegler, E.A., Carlson, M.D., Perry, W., 2005. Effect of interferon-alpha on cognitive functioning in patients with chronic hepatitis C. J. Int. Neuropsychol. Soc. 11, 16–22.

Ho, B.T., Huo, Y.Y., Lu, J.G., Tansey, L.W., Levin, V.A., 1992. Opioid-dopaminergic mechanisms in the potentiation of D-amphetamine discrimination by interferon-alpha. Pharmacol. Biochem. Behav. 42, 57–60.

Johnson, M.T., Ebner, T.J., 2000. Processing of multiple kinematic signals in the cerebellum and motor cortices. Brain Res. Rev. 33, 155–168.

Juengling, F.D., Ebert, D., Gut, O., Engelbrecht, M.A., Rasenack, J., Nitzsche, E.U., Bauer, J., Lieb, K., 2000. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. Psychopharmacology 152, 383–389.

Klimek, V., Schenck, J.E., Han, H., Stockmeier, C.A., Ordway, G.A., 2002. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. Biol. Psychiatry 52, 740–748.

Kirkwood, J., 2002. Cancer immunotherapy: the interferon-alpha experiment. Semin. Oncol. 29, 18–26.

Kitagami, T., Yamada, K., Miura, H., Hashimoto, R., Nabeshima, T., Ohta, T., 2003. Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: role of nitric oxide as a signal crossing the blood-brain barrier. Brain Res. 978, 101–104.

Lazeron, R.H., Rombouts, S.A., Machielsen, W.C., Scheltens, P., Witter, M.P., Uylings, H.B., Barkhof, F., 2000. Visualizing brain activation during planning: the tower of London test adapted for functional MR imaging. Am. J. Neuroradiol. 21, 1407–1414.

Lieb, K., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Janssen, G., Schaefer, M., 2006. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): results from a prospective study. Eur. Psychiatry 21, 204–210.

Loftis, J.M., Hauser, P., 2004. The phenomenology and treatment of interferon-induced depression. J. Affect. Disord. 15, 175–190.

Lotrich, F.E., Rabinovitz, M., Gironda, P., Pollock, B.G., 2007. Depression following pegylated interferon-alpha: characteristics and vulnerability. J. Psychosom. Res. 63, 131–135.

Lou, J.S., Kearns, G., Benice, T., Oken, B., Sexton, G., Nutt, J., 2003. Levodopa improves physical fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study. Mov. Disord. 18, 1108–1114.

Lowe, C., Rabbitt, P., 1998. Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge neuropsychological test automated battery. International study of post-operative cognitive dysfunction. Neuropsychologia 36, 915–923.

Maddock, C., Landau, S., Barry, K., Maulayah, P., Hotopf, M., Cleare, A.J., Norris, S., Pariante, C.M., 2005. Psychopathological symptoms during interferon-alpha and ribavirin treatment: effects on virologic response. Mol. Psychiatry 10, 332–333.

Martinot, M., Bragulat, V., Artiges, E., Dolle, F., Hinnen, F., Jouvent, R., Martinot, J., 2001. Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. Am. J. Psychiatry 158, 314–316.

Mapou, R.L., Law, W.A., Wagner, K., Malone, J.L., Skillman, D.R., 1996. Neuropsychological effects of interferon alfa-n3 treatment in asymptomatic human immunodeficiency virus-1-infected individuals. J. Neuropsychiatry Clin. Neurosci. 8, 74–81.

Mendels, J., Frazer, A., Fitzgerald, R.G., Ramsey, T.A., Stokes, J.W., 1972. Biogenic amine metabolites in cerebrospinal fluid of depressed and manic patients. Science 175, 1380–1382.

Meyer, J.H., Kruger, S., Wilson, A.A., Christensen, B.K., Goulding, V.S., Schaffer, A., Minifie, C., Houle, S., Hussey, D., Kennedy, S.H., 2001. Lower dopamine transporter binding potential in striatum during depression. Neuroreport 12, 4121–4125.

Meyers, C.A., Scheibel, R.S., Forman, A.D., 1991. Persistent neurotoxicity of systemically administered interferon-alpha. Neurology 41, 672–676.

Middleton, F.A., Strick, P.L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Rev. 31, 236–250.

Mink, J.W., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. Prog. Neurobiol. 50, 381–425.

Mizoi, Y., Kaneko, H., Oharazawa, A., Kuroiwa, H., 1997. Parkinsonism in a patient receiving interferon alpha therapy for chronic hepatitis C. Rinsho Shinkeigaku 37, 54–56.

Monchi, O., Petrides, M., Petre, V., Worsley, K., Dagher, A., 2001. Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J. Neurosci. 21, 7733–7741.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Moron, J.A., Zakharova, I., Ferrer, J.V., Merrill, G.A., Hope, B., Lafer, E.M., Lin, Z.C., Wang, J.B., Javitch, J.A., Galli, A., Shippenberg, T.S., 2003. Mitogen-activated protein kinase regulates dopamine transporter surface expression and dopamine transport capacity. J. Neurosci. 23, 8480–8488.

Owen, A.M., Doyon, J., Petrides, M., Evans, A.C., 1996a. Planning and spatial working memory: a positron emission tomography study in humans. Eur. J. Neurosci. 8, 353–364.

Owen, A.M., Evans, A.C., Petrides, M., 1996b. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cereb. Cortex 6, 31–38.

Owen, A.M., Roberts, A.C., Polkey, C.E., Sahakian, B.J., Robbins, T.W., 1991. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 2, 993–1006.

Panitch, H.S., Gomez-Plascencia, J., Norris, F.H., Cantell, K., Smith, R.A., 1986. Subacute sclerosing panencephalitis: remission after treatment with intraventricular interferon. Neurology 36, 562–566.

Pavol, M.A., Meyers, C.A., Rexer, J.L., Valentine, A.D., Mattis, P.J., Talpaz, M., 1995. Pattern of neurobehavioral deficits associated with interferon alfa therapy for leukemia. Neurology 45, 947–950.

Rabbitt, P., Lowe, C., 2000. Patterns of cognitive ageing. Psychol. Res. 63, 308–316.

Reddy, P.L., Khanna, S., Subhash, M.N., Channabasavanna, S.M., Rao, B.S., 1992. CSF amine metabolites in depression. Biol. Psychiatry 31, 112–118.

Reichenberg, A., Gorman, J.M., Dieterich, D.T., 2005. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. AIDS 19, 174–178.

Robbins, T.W., James, M., Owen, A.M., Sahakian, B.J., Lawrence, A.D., McInnes, L., Rabbitt, P.M., 1998. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J. Int. Neuropsychol. Soc. 14, 474–490.

Rohatiner, A.Z., Prior, P.F., Burton, A.C., Smith, A.T., Balkwill, F.R., Lister, T.A., 1983. Central nervous system toxicity of interferon. Br. J. Cancer 47, 419–422.

Roy, A., Karoum, F., Pollack, S., 1992. Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. Arch. Gen. Psychiatry 49, 447–450.

Sahakian, B.J., 1990. Computerized assessment of neuropsychological function in Alzheimer's disease and Parkinson's disease. Int. J. Geriatr. Psychiatry 5, 211–213.

Sahakian, B.J., Owen, A.M., 1992. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J. R. Soc. Med. 85, 399–402.

Salamone, J.D., Correa, M., Mingote, S., Weber, S.M., 2003. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. J. Pharmacol. Exp. Ther. 305, 1–8.

Salamone, J.D., Correa, M., Mingote, S.M., Weber, S.M., 2005. Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. Curr. Opin. Pharmacol. 5, 34–41.

Scheibel, R.S., Valentine, A.D., O'Brien, S., Meyers, C.A., 2004. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J. Neuropsychiatry Clin. Neurosci. 16, 185–191.

Schwartz, A.L., Thompson, J.A., Masood, N., 2002. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. Oncol. Nurs. Forum 29, E85–E90.

Shah, P.J., Ogilvie, A.D., Goodwin, G.M., Ebmeier, K.P., 1997. Clinical and psychometric correlates of dopamine D2 binding in depression. Psychol. Med. 27, 1247–1256.

Shuto, H., Kataoka, Y., Hoikawa, T., Fujihara, N., Oishi, R., 1997. Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. Brain Res. 747, 348–351.

Smedley, H., Katrak, M., Sikora, K., Wheeler, T., 1983. Neurological effects of recombinant human interferon. Br. Med. J. Clin. Res. Ed. 286, 262–264.

Smets, E.M., Garssen, B., Bonke, B., De Haes, J.C., 1995. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J. Psychosom. Res. 39, 315–325.

Smith, A., Tyrrell, D., Coyle, K., Higgins, P., 1988. Effects of interferon alpha on performance in man: a preliminary report. Psychopharmacology (Berl) 96, 414–416.

Smith, Y., Kieval, J.Z., 2000. Anatomy of the dopamine system in the basal ganglia. Trends Neurosci. 23, 28–33.

Sunami, M., Nishikawa, T., Yorogi, A., Shimoda, M., 2000. Intravenous administration of levodopa ameliorated a refractory akathisia case induced by interferon-alpha. Clin. Neuropharmacol. 23, 59–61.

Swainson, R., Robbins, T.W., 2001. Rule-abstraction deficits following a basal ganglia lesion. Neurocase 7, 433–443.

Tremblay, L.K., Naranjo, C.A., Graham, S.J., Herrmann, N., Mayberg, H.S., Hevenor, S., Busto, U.E., 2005. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. Arch. Gen. Psychiatry 62, 1228–1236.

Valentine, A.D., Meyers, C.A., Kling, M.A., Richelson, E., Hauser, P., 1998. Mood and cognitive side effects of interferon-alpha therapy. Semin. Oncol. 25, 39–47.

Van der Elst, W., van Boxtel, M.P., van Breukelen, G.J., Jolles, J., 2005. Rey′s verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. J. Int. Neuropsychol. Soc. 11, 290–302.

Wichmann, T., DeLong, M.R., 1999. Oscillations in the basal ganglia. Nature 400 (6745), 621–622.

Wichers, M.C., Koek, G.H., Robaeys, G., Praamstra, A.J., Maes, M., 2005a. Early increase in vegetative symptoms predicts IFN-alpha-induced cognitive-depressive changes. Psychol. Med. 35, 433–441.

Wichers, M.C., Koek, G.H., Robaeys, G., Verkerk, R., Scharpé, S., Maes, M., 2005b. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Mol. Psychiatry 10, 538–544.

Willner, P., Muscat, R., Papp, M., 1992. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci. Biobehav. Rev. 16, 525–534.

Wu, H.Q., Rassoulpour, A., Schwarcz, R., 2007. Kynurenic acid leads, dopamine follows: a new case of volume transmission in the brain? J. Neural Transm. 114, 33–41.