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Acute Changes in Striatal Microstructure Predict the Development of Interferon-Alpha Induced Fatigue

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ABSTRACT

BACKGROUND: Interferon-alpha (IFN-α) is a key mediator of antiviral immune responses used clinically for hepatitis C treatment. Though effective, IFN-α induces marked behavioral changes that, when severe, can appear indistinguishable from major depression. Curiously, fatigue and motivational impairment evolve rapidly, suggesting acute engagement of immune-brain communicatory pathways, yet mood impairments typically emerge later, after weeks of treatment. Whether this reflects prolonged modulation of motivational processes underpinning fatigue or separate neurobiological mechanisms is currently unclear.

METHODS: Here, we used quantitative magnetization transfer (qMT) imaging, an advanced microstructural neuroimaging technique sensitive to effects of inflammation, in a prospective study design to measure acute brain changes to IFN-α and relate these to later development of discrete behavioral changes. Twenty-three patients initiating IFN-α treatment for hepatitis C underwent qMT imaging and blood sampling at baseline and 4 hours after their first IFN-α injection. Comprehensive behavioral and psychological assessments were completed at both scanning sessions and at treatment weeks 4, 8, 12, and 24.

RESULTS: IFN-α injection stimulated an acute inflammatory cytokine response and evoked fatigue that peaked between 4 and 12 weeks, preceding mood change by 4 weeks. In the brain, IFN-α induced an acute change in striatal microstructure that additionally predicted development of fatigue but not mood symptoms.

CONCLUSIONS: Our findings highlight qMT as an in vivo biomarker of central effects of peripheral inflammation. We demonstrate exquisite sensitivity of the striatum to IFN-α, implicate striatal perturbation in IFN-α-induced fatigue, and dissociate this from mechanisms underlying IFN-α-induced mood symptoms, providing empirical support for distinct neural substrates mediating actions on motivation and mood.

Keywords: Depression, Fatigue, Imaging, Inflammation, Insula, Interferon, Striatum

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Interferon-alpha (IFN-α) is a type I interferon released by specialized leucocytes (plasmacytoid dendritic cells) in response to viral stimulation (1) as well as virally infected cells and promotes a broader antiviral immune response. Externally administered IFN-α is also used clinically in the treatment of hepatitis C. Despite good clinical efficacy, direct and/or indirect actions on the brain result in often highly disabling behavioral changes including fatigue, mood, motivation, and cognitive impairments (2). When severe, these changes can appear indistinguishable from major depression and provide powerful empirical support for inflammatory theories of depression (3,4). A striking feature of IFN-α-based treatment, though one rarely utilized experimentally, is that the impact on individual behavioral domains follows markedly different temporal trajectories. Changes in fatigue and motivation typically emerge within hours of the first IFN-α injection, suggesting the rapid engagement of immune-brain communicatory pathways and motivational processes. However, mood and cognitive effects are rarely prominent before 4 weeks of treatment, suggesting either a separate neurobiological mechanism or alternatively the secondary emergence of affective symptoms following prolonged modulation of motivational processes underpinning fatigue (2). Thus, the experimental investigation of early effects of IFN-α on the brain offers a unique window into the neurobiological mechanisms underlying IFN-α-induced depression, allowing the identification of neural processes that are acutely susceptible to IFN-α and predict the later emergence of discrete symptom clusters.

To date, most studies investigating the neurobiology of IFN-α-induced behavioral change utilize cross-sectional study designs, typically after 4 to 12 weeks of IFN-α treatment when the full spectrum of behavioral change is evident (5–8). These provide important insights into the neural processes and structures susceptible to chronically administered IFN-α; however, their cross-sectional design limits the characterization of causal relationships between IFN-α-induced changes in the

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brain and the subsequent development of discrete behavioral changes that evolve with different temporal dynamics. In contrast, prospective studies enable the differentiation of changes induced by IFN-α from those resulting from the behavior itself. In one example, Capuron *et al.* (9) showed that acute reactivity of adrenocorticotropic hormone and cortisol to IFN-α injection can differentiate individuals who later develop depression. Further, by measuring the response well before the development of depression, they demonstrated this to be a key neurobiological process selectively engaged by IFN-α, rather than a consequence of the depression induced (which may alone cause hypothalamic-pituitary-adrenal axis hyperactivity) (10). Prospective studies investigating acute actions of IFN-α may also help identify and offer treatment to individuals most susceptible to the behaviorally impairing effects of IFN-α early in their treatment.

Here, we used a prospective study design to investigate the relationship between acute actions of IFN-α on the brain and subsequent behavioral change. We used quantitative magnetization transfer (qMT) imaging, an advanced structural magnetic resonance imaging (MRI) technique that exploits the phenomenon of magnetization transfer (MT) between free and macromolecular bound protons, to detect changes in microstructural environment. Molecules rich in hydroxyl and/or carboxyl groups appear to play a predominant role in MT (11). Though the precise molecules mediating MT change cannot be determined, it is noteworthy that metabolites such as lactate (which contains a hydroxyl and carboxyl group) as well as pH have previously been implicated (12,13). qMT has also been shown previously to be sensitive to the central effects of peripheral inflammation in both rodents (14,15) and humans (16).

We recruited 23 patients initiating IFN-α-based treatment for hepatitis C infection and followed them over their 6-month duration of treatment. Of these patients, 19 completed repeat qMT imaging at both baseline and 4 hours after their first IFN-α injection. Blood samples were obtained immediately after both scanning sessions to characterize the profile of cytokine changes induced acutely by IFN-α. Comprehensive clinical assessments were completed at both scanning sessions and at 4, 8, 12, and 24 weeks of treatment to quantify and characterize symptoms of fatigue and depression.

Key aims were to determine first whether IFN-α induces acute microstructural reorganization within the brain and second whether the pattern of evoked changes provides evidence for activation of an indirect (neurally mediated) or direct immune-brain communicatory pathway. We next aimed to investigate whether acute changes in brain microstructure also predict the later development of fatigue and motivational change. Finally, we tested if acute changes within systems supporting motivational behavior (and linked to expression of fatigue) additionally contributed to the later development of mood change. A subaim was to further characterize the nature of IFN-α-induced fatigue, in particular its relationship to subjective sleepiness or the propensity to fall asleep.

Unlike the reported central response to inflammation induced using bacterial antigens (16–20), the human literature concerning response to chronic IFN-α provides little support for engagement of typical interoceptive pathways to insula (5,6,21). Instead, there appears to be a particular sensitivity of striatal structures. It is currently unclear whether this reflects habituation of interoceptive pathways during chronic IFN-α treatment or, alternatively, more direct actions of IFN-α on subcortical structures as suggested by rodent studies (22,23). To address this, we investigated the acute effects of IFN-α on bilateral insula (the cortical terminus of human interoceptive pathways) (24,25) and the striatum, a structure sensitive to chronic IFN-α but not typically implicated in neurally mediated interoception (24). Given the acute onset of fatigue and motivational impairment, we predicted that acute changes in ventral striatal microstructure would additionally predict the evolution of fatigue but not necessarily later mood symptoms.

METHODS AND MATERIALS

Participants

Twenty-three individuals (17 male subjects, mean 48.8 ± 10.9 years) initiating IFN-α-based therapy for hepatitis C were recruited. All were fluent in English, aged 18 to 64 years, and fulfilled National Institute for Health and Care Excellence guidelines for starting IFN-α-based therapy. Participants had a baseline psychiatric evaluation of current mental state and previous psychiatric history, using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (26). Participants were excluded if they were receiving treatment for depression at study enrollment, had a history of psychotic or autoimmune illness, had not abstained from substance abuse for at least 6 months, were co-infected with human immunodeficiency virus, or had any cause for liver disease other than hepatitis C. The study was approved by the Cambridge Central National Research Ethics Committee. All subjects provided written informed consent.

Study Design

The study utilized a prospective cohort design. Participants were evaluated at baseline (mean 7 days before treatment), 4 hours after their first IFN-α injection, and weeks 4, 8, 12, and 24 of IFN-α-based therapy. Psychopathological symptoms were evaluated at each visit using the Profile of Mood States (POMS) questionnaire (27), Epworth Sleepiness Scale (ESS) (28), fatigue visual analog scale (fVAS), Hamilton Depression Rating Scale (HAMD), State and Trait Anxiety Inventory (STAI), and M.I.N.I. MRI followed by blood sampling, blood pressure, and temperature was repeated at baseline and 4 hours after the first IFN-α injection to index acute effects of IFN-α on brain microstructural environment and circulating cytokines, respectively. Of the total cohort, 19 participants (14 male participants, mean 44.4 ± 10.7 years) completed both MRI sessions and 20 participants (17 male participants, mean 49.6 ± 11.2 years) completed both blood samples. One female participant was later excluded from the image analysis due to metal-induced artifact. All participants completed all clinical evaluations.

Behavioral Analyses

Effects of IFN-α on global fatigue were measured using the fVAS and fatigue subcomponents of tiredness, vigor, and subjective sleepiness with the POMS and ESS. Actions on depressive and anxiety symptoms were additionally recorded using the M.I.N.I., HAMD, and STAI. Effects of IFN-α on all psychopathological symptoms and the relationship between different behavioral domains were analyzed in SPSS