Brain, Behavior, and Immunity 58 (2016) 31–39

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Interferon-α acutely impairs whole-brain functional connectivity network architecture – A preliminary study

Ottavia Dipasquale [a,b,c], Ella A. Cooper [c], Jeremy Tibble [d], Valerie Voon [e,f], Francesca Baglio [b], Giuseppe Baselli [a], Mara Cercignani [c,i], Neil A. Harrison [c,g,h,*]

[a] Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy
[b] IRCCS, Fondazione don Carlo Gnocchi, Milan, Italy
[c] Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, Brighton, UK
[d] Department of Gastroenterology, Brighton & Sussex University Hospitals, Brighton, UK
[e] Department of Psychiatry, University of Cambridge, Cambridge, UK
[f] Cambridge and Peterborough NHS Foundation Trust, Cambridge, UK
[g] Sackler Centre for Consciousness Science, University of Sussex, Falmer, UK
[h] Sussex Partnership NHS Foundation Trust, Brighton, UK
[i] Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy

ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form 10 December 2015
Accepted 13 December 2015
Available online 14 December 2015

Keywords:
Cytokine
Inflammation
Interferon-α
Resting state fMRI
Graph theory
Functional connectivity
Brain network

ABSTRACT

Interferon-alpha (IFN-α) is a key mediator of antiviral immune responses used to treat Hepatitis C infection. Though clinically effective, IFN-α rapidly impairs mood, motivation and cognition, effects that can appear indistinguishable from major depression and provide powerful empirical support for the inflammation theory of depression. Though inflammation has been shown to modulate activity within discrete brain regions, how it affects distributed information processing and the architecture of whole brain functional connectivity networks have not previously been investigated.

Here we use a graph theoretic analysis of resting state functional magnetic resonance imaging (rfMRI) to investigate acute effects of systemic interferon-alpha (IFN-α) on whole brain functional connectivity architecture and its relationship to IFN-α-induced mood change. Twenty-two patients with Hepatitis-C infection, initiating IFN-α-based therapy were scanned at baseline and 4 h after their first IFN-α dose. The whole brain network was parcellated into 110 cortical and sub-cortical nodes based on the Oxford-Harvard Atlas and effects assessed on higher-level graph metrics, including node degree, betweenness centrality, global and local efficiency.

IFN-α was associated with a significant reduction in global network connectivity (node degree) ($p = 0.033$) and efficiency ($p = 0.013$), indicating a global reduction of information transfer among the nodes forming the whole brain network. Effects were similar for highly connected (hub) and non-hub nodes, with no effect on betweenness centrality ($p > 0.1$). At a local level, we identified regions with reduced efficiency of information exchange and a sub-network with decreased functional connectivity after IFN-α. Changes in local and particularly global functional connectivity correlated with associated changes in mood measured on the Profile of Mood States (POMS) questionnaire.

IFN-α rapidly induced a profound shift in whole brain network structure, impairing global functional connectivity and the efficiency of parallel information exchange. Correlations with multiple indices of mood change support a role for global changes in brain functional connectivity architecture in coordinated behavioral responses to IFN-α.

1. Introduction

Systemic inflammation rapidly impairs mood, motivation and cognition and when chronic is implicated in the etiology of depression (Dantzer et al., 2008). Arguably, the most powerful empirical support for an etiological role for inflammation in depression comes from patients with chronic Hepatitis-C infection treated with interferon-alpha (IFN-α) based therapies. Though clinically efficacious, direct and/or indirect actions of IFN-α on the brain frequently result in highly disabling behavioral changes including fatigue, mood, motivation and cognitive impairments (Capuron et al., 2002). In one third of patients these changes evolve to appear

* Corresponding author at: Clinical Imaging Sciences Centre, Brighton & Sussex Medical School, University of Sussex, Falmer BN1 9RR, UK.
E-mail address: n.harrison@bsms.ac.uk (N.A. Harrison).

http://dx.doi.org/10.1016/j.bbi.2015.12.011
0889-1591/

indistinguishable from major depression (Bonaccorso et al., 2001; Dantzer et al., 2008).

Though major depression typically only develops after many weeks of IFN-α administration, changes in mood, motivation and fatigue (and in some cases feelings of social connection and spatial memory) can be readily observed within hours of IFN-α administration (Dowell et al., 2015) and/or other experimental inflammatory challenges such as Typhoid vaccination (Harrison et al., 2009a,b, 2014, 2015a) and Lipopolysaccharide (LPS) injection (Reichenberg et al., 2001; Eisenberger et al., 2010a,b). Furthermore, inflammation also alters physiology, including the central autonomic regulation of the gastrointestinal (Pacheco-Lopez and Bermudez-Rattoni, 2011) and cardiovascular (Harrison et al., 2013) systems. This characteristic profile of inflammation-induced neuropsychological and physiological changes signifies a complex motivational reorientation and suggests that peripheral inflammation can rapidly modify the functional integration of a broad range of interconnected cortical and sub-cortical structures.

To date, rodent and human brain imaging studies have been successful in identifying a discrete set of cortical and sub-cortical structures that appear particularly sensitive to changes in peripheral inflammation. These include the amygdala, striatum (particularly ventral regions), substantia nigra, insula, sub-genual and dorsal anterior cingulate, orbitofrontal cortex and hippocampus/parahippocampus. Some structures appear to play relatively specific roles in discrete aspects of inflammation-associated behavioral change. For example, actions on the ventral striatum (Eisenberger et al., 2010b; Capuron et al., 2012; Harrison et al., 2015b) in impaired reward sensitivity, and hippocampus/parahippocampus in acute spatial memory impairment (Yirmiya and Goshen, 2011; Harrison et al., 2013) whereas other regions such as the insula, anterior and sub-genual cingulate and amygdala appear to play broader less circumscribed roles (Harrison et al., 2009a; Dowell et al., 2015). Common to many of these regions is that they form part of the extended limbic circuitry critical to complex motivational behavior, emotion, learning, and memory and the integration of behavioral and physiological allostatic responses to infection (Critchley and Harrison, 2013; McEwen and Gianaros, 2010).

However, what remains poorly understood is how inflammation modulates brain function at the network level. Broadly, even the simplest cognitive functions depend on the carefully coordinated activity of multiple spatially distributed brain areas. In this context the brain can be viewed as a complex network of nodes (discrete grey matter areas) and inter-connecting fiber pathways. Functional connectivity between nodes can be quantified by acquiring functional MRI (fMRI) data at rest then measuring how activity recorded at each node correlates with that at all other nodes. Conceptualizing the brain in this manner allows the application of advanced mathematical network analyses such as graph theory that can quantify a number of fundamental properties of complex networks. For example, node degree (the number of direct connections to all other network nodes), betweenness centrality (the number of connections between other node pairs that pass through a specific node) and network efficiency (a measure of the networks capacity for parallel information transfer).

Similar to many other complex systems, application of graph theory approaches to the human brain has shown that it follows an efficient 'small-world' functional architecture (Achard et al., 2006); i.e. individual network components (nodes) have greater local interconnections (edges) than expected for a random network, and smaller minimum path lengths between node pairs than regular or lattice type networks (Watts and Strogatz, 1998). This functional architecture affords a number of substantial benefits; it reduces wiring cost and ensures a high degree of robustness, i.e. preservation of network integrity following random damage to a node or individual connection (edge). However, such networks also have a smaller number of highly connected (hubs) and 'high centrality' nodes that provide the shortest connection path between many other node pairs (high centrality); these nodes are crucial to efficient communication (van den Heuvel et al., 2008) but also vulnerable to targeted insults that can result in a rapid reduction in network efficiency and whole brain connectivity. Whether IFN-α induces rapid, coordinated shifts in behavior through global effects on network efficiency (as may be anticipated from alterations in broadly acting neuromodulators such as dopamine or serotonin) or instead more selective actions on discrete sub-networks or high centrality/node degree regions is currently unknown.

The aim of the present study was therefore to investigate acute effects of IFN-α on the functional connectivity architecture of the human brain with a particular focus on efficiency of information transfer. We used resting state functional magnetic resonance imaging (rfMRI), a powerful technique for investigating human functional brain connectivity (Fox and Raichle, 2007) that enables examination of brain network properties without *a priori* assumptions about regions potentially affected by IFN-α.

Twenty-two patients with Hepatitis-C initiating IFN-α-based therapy underwent resting-state fMRI (rfMRI) approximately 1-week before then again 4 h after starting IFN-α-based treatment. rfMRI was parcellated into 110 cortical and sub-cortical regions then higher level graph theory metrics were used to examine effects of IFN-α on topological and weighted properties of the whole-brain network. Specifically, we looked at two complimentary metrics: (1) node degree – a measure of the number of connections (edges) of each node with the other network nodes and (2) betweenness centrality – a measure of how many shortest paths between all other network node pairs pass through any particular node (Bullmore and Sporns, 2009) [see Fig. 1]. We also assessed local and global network efficiency defined as a function of the minimum path length between nodes i.e. whether information can be directly transferred from node A to node B (short path length) or alternately must first pass through one or more intermediary nodes (longer path length). Efficiency thus provides a quantitative measure of the capacity of a network for parallel information transfer between regions. Global efficiency provides a general description of whole-brain network functioning while local efficiency gives an estimate of the importance of each individual node for network information exchange. Functional connectivity changes were also estimated to identify sub-networks particularly sensitive to the acute effects of IFN-α.

We predicted that IFN-α would acutely impair global network functional connectivity, specifically a reduction in node degree and network efficiency. We additionally predicted that highly connected (hub) nodes that make the greatest contribution to global efficiency would be particularly affected. We adopted an exploratory approach to investigate how global or local changes in network function related to acute changes in mood measured on the Profile of Mood States (POMS) questionnaire.

2. Materials and methods

2.1. Participants

Twenty-two patients (15 male, mean 48.9 ± 11.3 years) initiating IFN-α based therapy for Hepatitis-C infection were recruited. All were fluent in English, aged 18–64 years and fulfilled National Institute for Clinical Excellence (NICE) guidelines for starting pegylated IFN-α based therapy. Participants had a baseline psychiatric evaluation of current mental state and previous psychiatric history, using the MINI International Neuropsychiatric Inventory (MINI)