OPEN LETTER

Research priorities for neuroimmunology: identifying the key research questions to be addressed by 2030 [version 1; peer review: 2 approved]

Georgina MacKenzie[1*], Sumithra Subramaniam[1*], Lindsey J Caldwell[1,2], Denise Fitzgerald[3], Neil A Harrison[4,5], Soyon Hong[6], Sarosh R Irani[7,8], Golam M Khandaker[9-11], Adrian Liston[12], Veronique E Miron[13], Valeria Mondelli[14,15], B Paul Morgan[16,17], Carmine Pariante[15], Divya K Shah[1], Leonie S Taams[18], Jessica L Teeling[19], Rachel Upthegrove[20,21]

[1]Wellcome Trust, London, NW1 2BE, UK
[2]UK Dementia Research Institute Headquarters, London, UK
[3]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[4]Cardiff University Brain Research Imaging Centre (CUBRIC), Cardiff University, Cardiff, UK
[5]Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, UK
[6]UK Dementia Research Institute, Institute of Neurology, University College London, London, UK
[7]Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[8]Department of Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[9]MRC integrative Epidemiology Unit, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[10]Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[11]Department of Psychiatry, University of Cambridge School of Clinical Medicine, University of Cambridge, Cambridge, UK
[12]Laboratory of Lymphocyte Signalling and Development, The Babraham Institute, Cambridge, UK
[13]UK Dementia Research Institute at The University of Edinburgh, Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, UK
[14]National Institute for Health Research, Mental Health Biomedical Research Centre, South London and Maudsley NHS Foundation Trust and King's College London, London, UK
[15]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[16]UK Dementia Research Institute, Cardiff University, Cardiff, UK
[17]Systems Immunity Research Institute, Cardiff University, Cardiff, UK
[18]Centre for Inflammation Biology & Cancer Immunology, Department of Inflammation Biology, School of Immunology & Microbial Sciences, King's College London, London, UK
[19]Biological Sciences, Faculty of Natural and Environmental Sciences, University of Southampton, Southampton, UK
[20]Early Intervention Service, Birmingham Womens and Childrens NHS Foundation Trust, Birmingham, UK
[21]Institute for Mental Health, University of Birmingham, Birmingham, UK

[*] Equal contributors

v1 First published: 29 Jul 2021, 6:194
https://doi.org/10.12688/wellcomeopenres.16997.1
Latest published: 29 Jul 2021, 6:194
https://doi.org/10.12688/wellcomeopenres.16997.1

Open Peer Review

Reviewer Status ✓ ✓

Abstract

Neuroimmunology in the broadest sense is the study of interactions between the nervous and the immune systems. These interactions

Corresponding authors: Georgina MacKenzie (g.mackenzie@wellcome.org), Sumithra Subramaniam (s.subramaniam@wellcome.org)

Author roles: MacKenzie G: Writing ş Original Draft Preparation, Writing ş Review & Editing; Subramaniam S: Writing ş Original Draft Preparation, Writing ş Review & Editing; Caldwell LJ: Writing ş Review & Editing; Fitzgerald D: Writing ş Review & Editing; Harrison NA

Research priorities in neuroimmunology

By engaging with a broad spectrum of stakeholders in an open and transparent process, the following research priorities were identified collectively (Figure 1).

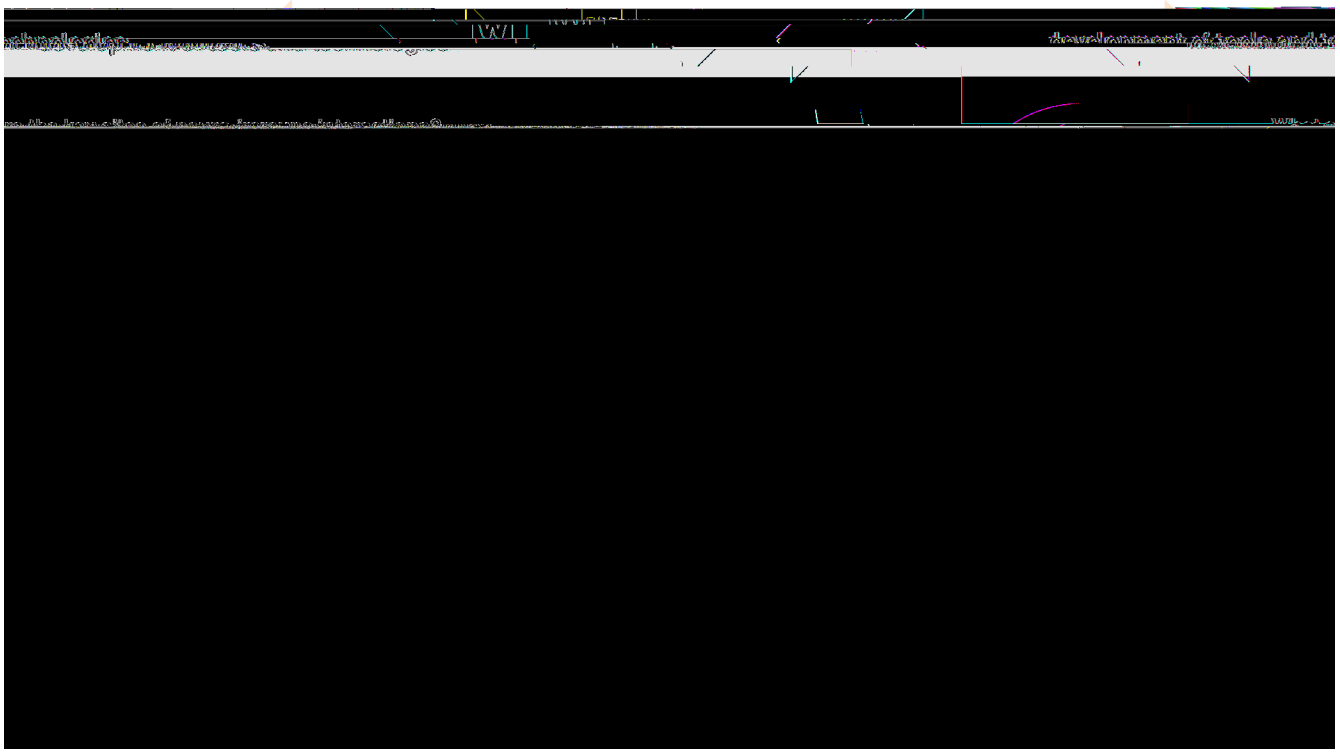
Aiming to keep the research priorities broad and applicable to the diverse researchers in the field, four cross-cutting themes were discussed that provide additional context to each question: bi-directional communication, context, translation and tool/technology development.

Bidirectional relationship of immune and nervous systems interactions

Interactions between the immune and nervous systems are bidirectional and both the neuroimmune and immune-neuro perspectives should be considered when addressing the research questions.

For example, in the immune-to-neuro direction, the presence of immune cells in the CNS was once considered a sign of neuropathology, but it is now increasingly recognised that immune signalling in the CNS is important for normal development and healthy brain function. The formation of mature neural circuits for example requires pruning of synapses by the immune system, including the classical complement pathway (initiated by C1q)[9], microglia[10] and MHC Class I[11]. By extension, inappropriate activation of the immune system can lead to excessive synapse loss and neurodegenerative disease, including Alzheimer's Disease[12]. This fine balance of immune function in the CNS is further demonstrated by the ability of antigen-specific T cells to improve neuronal survival after a CNS injury[13].

In pathological states, such as immune-mediated inflammatory diseases and autoantibody-mediated neurological conditions, immune function is unequivocally involved in neuroinflammatory damage and/or pain but, paradoxically, can also support tissue regeneration (e.g. remyelination). Inflammation can also play a role in other states and conditions, such as stress resilience and post-traumatic stress disorder (PTSD). Immune-deficient mice (severe combined immunodeficiency and nude mice) were more likely to develop PTSD than wildtype mice when subjected to stress, with improvements seen in the stress response upon transfer of T cells from wildtype donors[13]. Further roles are also proposed for T cells in learning memory and behaviour, in both antigen-specific and antigen-independent manners[13].



Ten key research questions were identified which, if addressed, would drive the field

three categories reflecting the scale of analysis (e.g. molecules, circuits) and internal and external factors that influence, or are influenced

questions will strengthen the fundamental knowledge base and ultimately drive translation (e.g. through identification of new targets,

When considering areas to prioritise, it was noted that strategies modulating the immune system to improve neurological or behavioural function are more developed than vice versa. As such, these are perhaps more likely to be taken forward in the medium term for a variety of reasons, e.g. due to challenges in developing brain penetrant drugs. However, we fully acknowledge the importance of psychological, behavioural and physical interventions that act via the nervous system to modulate immune function and their potential to be harnessed for therapeutic benefit. It has been recognised that the modulation of neural function plays a role in regulating immune responses, for example as seen in the gut-brain axis as well as strategies to modulate neurotransmitters or neuropeptides to influence health[14,15]. The immune system is also susceptible to behavioural conditioning whereby pairing of a novel aversive taste stimulus (conditioned stimulus) with an immunosuppressive drug e.g. cyclosporin (unconditioned stimulus) results in the taste stimulus itself exerting immunosuppressive properties[16,17]. Proof-of-principle data suggest that a similar behavioural conditioning approach may support an immunosuppressive drug dose-reduction strategy in renal transplant patients[18].

Activation of both the autonomic nervous system and the hypothalamo-pituitary-adrenal axis have been demonstrated to affect the immune system both directly and indirectly. For example, lymphocytes express surface receptors for neurohormones and transmitters and are exposed to neurochemicals in lymphoid organs including the spleen and in peripheral blood. Indeed, directly activating dopaminergic neurons in the mouse ventral tegmental area and characterizing the subsequent immune response after exposure to *Escherichia coli* has shown an increase in both innate and adaptive immune responses[19]. This was indexed by enhanced antibacterial activity of monocytes and macrophages, reduced bacterial load and a heightened T cell response in a mouse model of delayed-type hypersensitivity[19].

Thus, studying both neuroimmune and immune-neuro interactions will be critical to providing a holistic mechanistic understanding of these pathways that will ultimately form the foundations for innovative interventions. Furthermore, these established CNS-immune communication pathways demonstrate the potential of psychological/psycho-social interventions to improve immune health and the importance of thinking more broadly, i.e. beyond pharmacological modulators, about how neuroimmunology could inform strategies to support health.

The importance of context

Understanding the context of neuroimmune cross-talk is critical when considering the underlying mechanisms. When tackling these priorities, research teams should carefully consider and report the rationale behind the chosen experimental context(s). For example, localisation (e.g. a specific brain region or peripheral nerve terminal), age or developmental stage, and/or health or disease setting, including relapse and remission. The context itself could define which research questions are a priority to address first, or which cell types to investigate and how. For example, studying a particular cell type might be most appropriate within a specific disease setting or developmental stage.

Investigating neuroimmune relationships during homeostasis and development from pregnancy and early life through to ageing will provide significant mechanistic insights into the interactions. While the intent of the discussion was to be broadly disease-agnostic, defining where and how disease is included in the investigations was recognised to be important. The disease context has the potential to provide fundamental insights for certain common phenotypes across multiple diseases, both with relevance to aetiology of disease onset, persistence and progression. For example, insight into brain development can give significant clues into mechanisms that can be reactivated in disease (for example synaptic elimination). Indeed, neuroinflammation is beneficial in the right context and so improving our understanding of when it switches from being beneficial (e.g. instructing developmental processes, removing debris, fighting infection, promoting regeneration) to detrimental (e.g. potential maladaptive synaptic pruning, failure to sense danger, uncontrolled inflammation) to neurological health, is required. Failure to consider different contexts could lead to the unintended exclusion of important areas and overlooking of key mechanisms, for instance natural changes in neuroimmune cross-talk during critical periods of development and ageing.

Contextual elements that should be considered include the effect of genetic background, risk factors and co-morbidities (e.g. metabolic disorders and obesity, or chronic low-grade infection and changes in the microbiome), all of which can lead to chronic inflammation and an impact on the nervous system, and predate disorders such as psychosis or depression[20]. The influence of sleep and changes in neuroendocrine signalling (including glucocorticoids, androgens, oestrogens, neuropeptides and other hormones) and the impact of therapeutic interventions for chronic conditions (such as chemotherapy, immunomodulation or analgesics) are also important considerations. The impact of diversity on neuroimmune interactions, including sex and ethnicity, will also be important in gaining real understanding of the nuances of these interactions. Secondary influences, such as environmental factors, pollution, exercise, epidemics, therapeutics, poverty or stress, are increasingly recognised as playing important roles in shaping these interactions. As well as encouraging new epidemiological studies, the impact of societal factors opens the way for new collaborations with experts in the social sciences, further breaking down traditional academic siloes. While the impact of acute and chronic infection was not addressed directly when developing the priorities, infection and neuroimmune interactions are inherently linked e.g. in the maternal-immune activation model, where prenatal exposure to infection could be a driver in initiating depression or psychosis in later life, or chronic gum disease as a driver of dementia[21].

In summary, whilst reductionist and mechanistic experimental studies are pivotal, the impact of neuroimmune interactions cannot be studied in isolation, and the broader context of these interactions, be it co-morbidities, age, chronic stress or infection, need to be taken into consideration (and reported) when trying to understand the roles and functions of these interactions over time. This can add a level of complexity but is critical in providing a complete understanding.

Tools/technology development

Addressing some of the priority questions fully will require development of new tools and technologies. While there have been major advances in recent years, there will be an increasing need to continue to develop sensitive and selective tools to measure and modulate immune cells and molecules *in vivo*, particularly within the CNS. This applies to both human and animal models to study interactions in homeostasis and development as well as in disorders, where a lack of suitable tools often presents a major barrier to progress. For instance, being able to image and modulate CNS-resident or CNS-infiltrating immune cells and pathways in the living nervous system, without affecting the peripheral immune system, would be game changing, allowing questions to be asked that are not currently addressable around the dynamics of these cells and pathways *in vivo*. Genetic tools, robust target-specific monoclonal antibodies, novel biological labels and synthetic biology may all contribute to the new toolbox.

Analysis of the full repertoire of immune cells and molecules resident in the brain and nervous system will greatly benefit from the generation of detailed cell atlases that incorporate study of the peripheral immune system. This, however, may require development of new or more specific markers to study the different immune cell types in the first instance, and then progress to specific tools to track and manipulate cellular behaviour. The migratory nature and dynamic aspects of cell phenotypes of the immune compartment may provide additional challenges to cell atlas development.

Collaborations beyond the biological sciences could be one way forward to develop or optimise these much-needed methods and tools. For example, working with medical physicists to develop neuroimaging tools sensitive to discrete CNS immune cell types or with bioengineers to develop cell type-specific targeting vehicles that could deliver pharmacological modulators directly to cells of interest, would be transformative from both a discovery and clinical perspective. Computational approaches are equally needed in order to integrate and analyse the large amount of clinical and basic research data generated and develop hypotheses for further experimental testing. This includes neuroimaging and biomarker data, eHealth records and the outputs from large scale ‘omics approaches.

Translation to the clinic

Dissecting fundamental questions of neuroimmune interactions, such as those proposed here, can lead to an improved understanding of both systems and how disordered interactions can be potentially causal in major neurological disorders and mental illnesses. Increasing translational potential requires investigating changes in neuronal circuitry, synaptic plasticity, CNS development and ageing, and homeostasis and (dys)function in both human and model systems. Studying effects of immune-modulating therapies on the nervous system, behaviour, and psychopathology can help to elucidate pathophysiologic mechanisms, leading to development of novel or repurposed immunotherapies. Progress in this area has been greatest in multiple sclerosis. Several immune-modulating drugs are now available to effectively delay progression of neurodegeneration and work by influencing peripheral immune cell trafficking to the CNS or modulating immune cell activation. Natalizumab (anti-alpha-4 integrin) has been shown to block entry of peripheral immune cells into the CNS, alleviating disease progression and further highlighting the importance of studying interactions between the peripheral immune system and the CNS for therapeutic gain[22]. The high level of specificity conferred by the autoantibody-mediated diseases of the nervous system offer a direct link between neuroscience and immunology, allowing their parallel study in humans with these diseases[23].

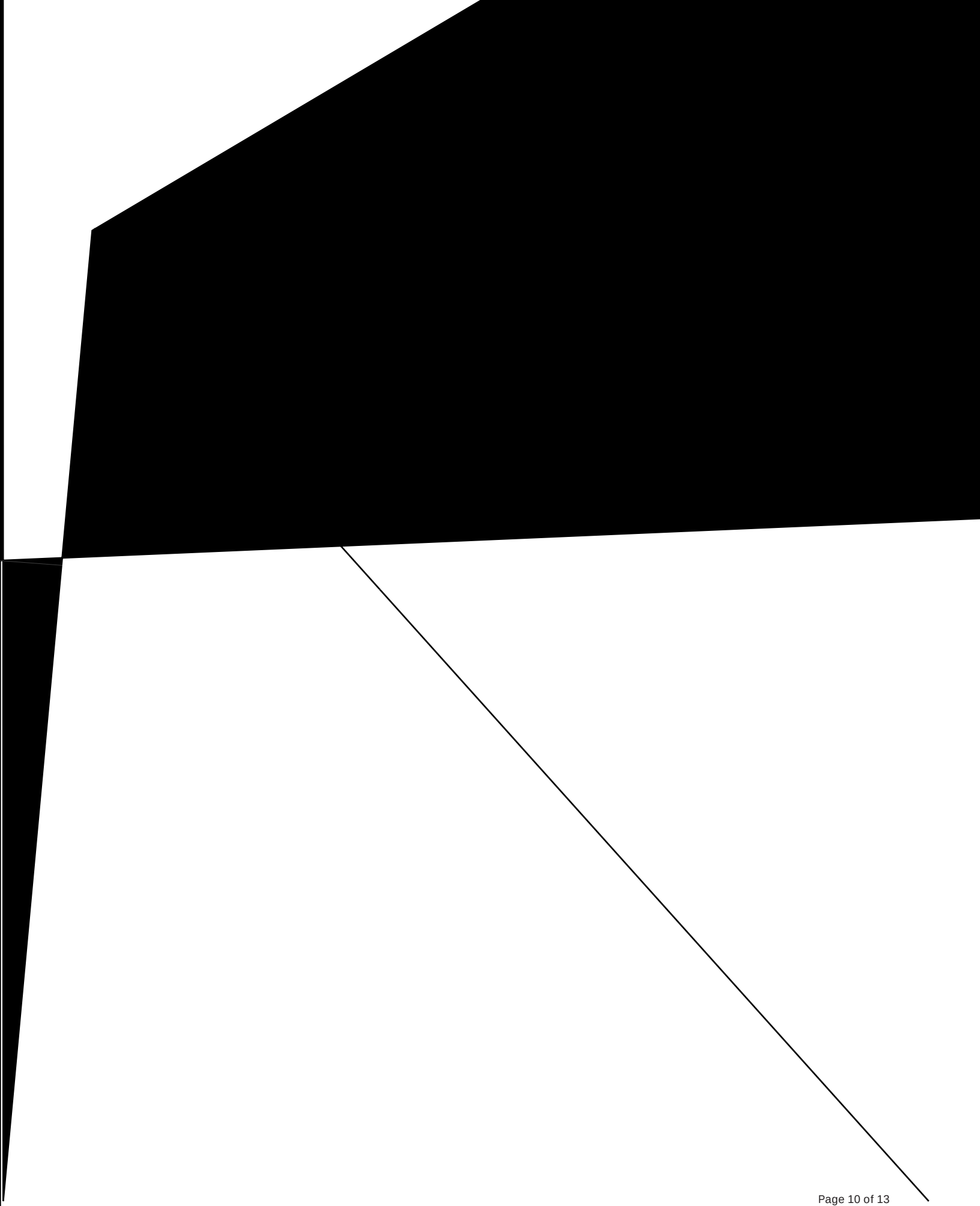
In psychiatry, interleukin (IL)-6 has been identified as a potential target in patients with depression and schizophrenia using population cohort and genetic studies[24,25]. However, patients receiving IL-6 receptor blockade (tocilizumab) as acute graft-versus-host-disease prophylaxis experienced significantly more depressive symptoms[26]

teams, galvanise collective endeavours and move neuroimmunology forward as a whole. The importance of considering the impact of context when addressing these questions is also highlighted. With multiple groups tackling each problem from different, but complementary or even synergistic angles, together they will provide an ever more granular picture of how interactions between the immune and nervous systems influence health and disease. By defining the underpinning and causal mechanisms through basic science as well as translational research in human cohorts, we anticipate impacting on health and facilitating the discovery of new diagnostic and therapeutic targets.

Achieving this vision will require the continued development of new and improved tools, open sharing and curation of data sets, multi- and inter-disciplinary teams working with colleagues in the wider biological sciences, STEM and social sciences, as well as forging partnerships with clinicians, patients and industry.

Finally, these research priorities were developed by the research community, for the research community, as an attempt to iden-

27. Khandaker GM, Oltean BP, Kaser M, :
2018; (9): e025333.
28. Nettis MA, Lombardo G, Hastings C, :
2021; (5): 939–948.
29. Krynicki CR, Dazzan P, Pariante CM, :



health disorders. There is only one question that directly asks how neural circuits, presumably from both the central and peripheral nervous systems, affect immunity. Yet, the recent review by Aysa Rolls and colleagues makes a convincing argument for brain regulation of a variety of immune events (https://doi.org/10.1038/s41577-020-0387-1).[1] As such, the case for efferent regulation of the immune system by the brain could be stronger.

Yes

Yes

Yes

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunophysiology

Reviewer Report 06 September 2021

https://doi.org/10.21956/wellcomeopenres.18768.r45229

Department of Immunology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

In this manuscript, the authors provide an overview of research directions in neuroimmunology. It's a very clear manuscript, highlighting the key research directions and main challenges in addressing them. The authors explain the rationale for selecting the directions they propose and discuss the main gaps in the field. It's a very timely piece and it summarizes the views of the authors. Thus, I can only offer a few suggestions, based on my experience as a reader, on how to increase its accessibility.

1. In the section "importance of context" -adding references to articles that exemplify the proposed research directions, can help the readers better appreciate the potential of the field.

2. For the technology part, an illustration of the challenges can be helpful.

3. Adding more questions on how the nervous system affects immunity to Figure 1 will

emphasize the bi-directional nature of the interactions. For example, how do different forms of brain activity (different areas, states) affect immune activity? Which neuronal mediators can be secreted to the periphery?

Yes

Yes

Yes

Yes

Yes

Competing Interests: No competing interests were disclosed.

Neum

Reviewer Expertise: Neuoimmunology