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AUSSIE – the Australian United States Scandinavian Imaging Exchange: an innovative virtual integrated health research network embedded in health care

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Abstract

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Author Contributions

Owing to space restrictions, references have been omitted where scientific concepts/knowledge have been established and published by our network. JCLL wrote the first draft of this paper as network coordinator. JCLL, DV, MW & LOW formed the initial core research network. All collaborators listed as co-authors have significantly contributed to the network and authorship of this paper.

Objective—To describe the development, design and function of an innovative international clinical research network for neuroimaging research based in Australia within a joint state health service/medical school. This network focuses upon identifying neuroimaging biomarkers for neuropsychiatric and neurodegenerative disease.

Method—We describe a case study of the iterative development of the network, identifying characteristic features and methods which may serve as potential models for virtual clinical research networks. This network was established to analyse clinically–derived neuroimaging data relevant to neuropsychiatric and neurodegenerative disease, specifically in relation to subcortical brain structures.

Results—The network has harnessed synergies from the individual expertise of the component groups, primarily clinical neuroscience researchers, to analyse a variety of clinical data.

Conclusion—AUSSIE is an active virtual clinical research network, analogous to a connectome, which is embedded in health care and has produced significant research advancing our understanding of neuropsychiatric and neurodegenerative disease through the lens of neuroimaging.

Background

Clinical medical researchers in psychiatry and psychiatric neuroscience in Australia working in health care settings are generally employed either full-time or part-time in the direct provision of care. To develop high quality research programs that are funded by external grants schemes generally requires dedicated staffing and time for research which active clinicians lack, especially given that schemes such as the NHMRC are highly competitive. We describe here one model of clinical research that leverages off the skills of researchers, with relatively low infrastructure overheads, largely (but not wholly) in the absence of substantive external grants. We hope our research network will be a bootstrap to external grant funding.

With the appropriate prospective planning, ethical approval and consent it is possible for clinical researchers to collect useful clinical data during their daily practice, and then combine this with an interest in structural neuroimaging. We have been able to engage a network of collaborative researchers via a connective hub based within the ACT Health Service and ANU Medical School. This type of clinical research has been a tradition within Sweden, where we commenced our collaborations with the Karolinska Institute and Lund University, and also in Australia, at the University of Melbourne, UNSW and UWA.

In parallel, each of the clinical research centres has differential, complementary expertise in components of the analysis of structural and functional neuroimaging data. Our collaborations with specialist computational neuroscience researchers at University of North Carolina Chapel Hill (UNC), University of California Los Angeles (UCLA) and the University of Southern California (USC) have greatly expanded our scope of research.

The collaborations are focused around identifying gaps in the literature, specifically with relation to subcortical brain structures in order to understand *structure-function-symptom* relationships for the development of future biomarkers of disease. We aim to develop clinical biomarkers that may be used as surrogate outcomes in intervention and treatment trials. Studies are specifically designed to harness the required skills for a mutually planned and written publication, and a virtual project team is created out of the ensemble of skills in our network. The currency of the collaboration is shared publications, access to datasets for the projects and cross-centre skill development.

Methods

Description of the network development

The development of the network was iterative and will be described in detail as a case study from which we will distil useful principles for other clinical researchers envisaging similar research (see Table 1).

The first collaboration was the development of the interest in the role of the striatum as a structural component in parallel recurrent corticostriatal circuits subserving cognition, emotion and movement[1]. This was established via design, testing and publication of new methods to manually segment the striatum (caudate and putamen) in magnetic resonance images by our core team at ANU Medical School in conjunction with UNSW and the Karolinska Institute[2]. This led to measurement of the striatum as a marker of corticostriatal circuit integrity in post-traumatic stress disorder[3] and frontotemporal lobar degeneration (FTLD) at the Karolinska Institute[4], and in post-stroke subjects with UNSW[5].

Through innovative key collaborators at the Melbourne Neuropsychiatry Centre, Royal Melbourne Hospital (MNC), we were able to use advanced computational neuroscience shape analysis methodologies developed by colleagues at University of North Carolina, Chapel Hill[6]. This shape analysis allowed us to more accurately quantify between-group and within-group correlational differences in the shape of striatum in relation to disease or neuropsychiatric disorders with Melbourne Neuropsychiatry Unit on choreacanthocytosis[7] and Karolinska clinical data (FTLD)[4], as well as the hippocampus in FTLD[8].

Access to a larger clinical dataset at MNC of patients with FTLD and related neuropsychiatric disorders led us to explore semi-automated methods[9] for striatal segmentation with collaborators at UCLA, expanding our network, and allowing us to upscale projects in collaboration[10].

Together with our key collaborators at Karolinska Institute, we were introduced to clinical researchers at Lund University and Skåne University Hospital where the shape analysis methods could be applied to studies of progressive supranuclear palsy[11]. In turn, our collaborators at Lund have worked with us on datasets for persons suffering from FTLD and further introduced us to other researchers working on pharmacoresistant epilepsy and Parkinson disease. Through MNC we applied methods for measurement of mid-sagittal pontine to midbrain ratio to adult Niemann-Pick C disease, uncovering a biomarker associated with clinical eye movement measures in this neurometabolic disorder[12], and also studied striatal morphology in eating disorders with researchers from Hospital Clinico San Carlos Madrid and Complutense University Madrid.

Through our collaborators at Karolinska Institute, we were able to access the large European Union framework of the Leukoaraiosis and Disability in the Elderly study (LADIS) on age-related white matter disease. One of our early career researchers undertook a Master's thesis on this dataset[13]. This published work has enabled us to access the entire LADIS study in a new semi-automated analysis project with USC.

Together with our collaborators at MNC and Monash University, we have a joint PhD student project on subcortical structural morphology in Huntington disease. We also have a senior psychiatry trainee developing a study of Parkinson disease with UWA. We have used methods developed by MNC and UCLA to measure the morphology of the corpus callosum as a biomarker in FTLD.

A new early career collaborator at UWA has joined our network to develop manual segmentation methods to quantify the shape of the thalamus as a key subcortical hub, and is in turn collaborating through the network with Lund University and with USC for the shape analysis. This is a snapshot of development to this stage.

Through the Australian hub, we are connecting with and through to our US and Swedish collaborators. Much of our work has focused upon mapping a subcortical connectome[14] with the key subcortical brain structures as potential biomarkers for neurodegenerative disease. This network has resulted in approximately 20 publications in the last five years, largely through the goodwill of the clinical and neuroscience researchers involved.

Developing research capacity

Through the hub at the ANU, we have recruited clinical research students, primarily from the graduate medical school program. Medical students at the ANU have a mandatory research project as part of their course requirements, and we have hosted more than 20 such students over the last 10 years, as well as students progressing to Masters and Doctoral studies.

We have trained collaborative researchers connected via the various research hubs in structural magnetic resonance imaging research. Together with the MNC, we have hosted medical specialist psychiatric researchers from Malaysia and Spain, and facilitated exchanges.

We have jointly supervised postgraduate research students across all of our centres and plan to expand such co-supervision in future.

Project planning for our research studies

As we are located in different countries and time-zones, our planning is conducted by asynchronous communication via email, supplemented by phone-calls and yearly face-to-face meetings by the network coordinator.

Discussion

We have described an outline of the iterative development of a synergistic virtual clinical research network running on the proverbial smell of an oily rag through the generous and essential contribution of expertise, work and infrastructure from each centre. As such we have achieved collaboratively more than we could if we sought to develop in each centre the same level of expertise in our research specialities, and expanded our own contacts for sharing and developing clinical research ideas. Virtual research networks like ours can be a springboard to launch and train clinicians and neuroscience researchers in clinical research towards practical research literacy, as well as enhancing capacity for such research in healthcare settings. As the Australian hubs of the network are embedded within shared public health and university setting, we are an example of a virtual integrated health research network, and describe some principles of development in Table 2. Similar, much larger scale virtual research networks developed for genetic neuroimaging analysis, such as the ENIGMA consortium also exist[15]. In the international development context, similar virtual networks, such as Crisis Mapping, a voluntary, self-assembling association sharing data and computational methodology which collaborates with local embedded partners to map evolving world crises (disasters, conflict), also exist[16].

As with any developmental collaboration, there are strengths and pitfalls of the model, which we describe in Table 4.

The next stage in our network development will be necessarily to seek innovative ongoing funding to support our projects across and via our respective centres, towards expansion of the network to the Asia-Pacific region and further Centres.

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References

1. Looi JCL, Walterfang M. Striatal morphology as a biomarker in neurodegenerative disease. Molecular Psychiatry. 2012; 18:417–424. [PubMed: 22584865]
2. Looi J, Lindberg O, Liberg B, Tatham V, Kumar R, Maller J, Millard E, Sachdev P, Hogberg G, Pagani M. Volumetrics of the caudate nucleus: Reliability and validity of a new manual tracing protocol. Psychiatry Research: Neuroimaging. 2008; 163:279–288.
3. Looi JCL, Maller JJ, Pagani M, Högberg G, Lindberg O, Liberg B, Botes L, Engman E-L, Zhang Y, Svensson L. Caudate volumes in public transportation workers exposed to trauma in the Stockholm train system. Psychiatry Research: Neuroimaging. 2009; 171:138–143.
4. Looi JCL, Walterfang M, Styner M, Svensson L, Lindberg O, Östberg P, Botes L, Örndahl E, Chua P, Kumar R, Velakoulis D, Wahlund L-O. Shape analysis of the neostriatum in frontotemporal lobar degeneration, Alzheimer's disease, and controls. Neuroimage. 2010; 51:970–986. [PubMed: 20156566]
5. Looi JCL, Tatham V, Kumar R, Maller JJ, Millard E, Wen W, Chen X, Brodaty H, Sachdev P. Caudate nucleus volumes in stroke and vascular dementia. Psychiatry Research: Neuroimaging. 2009; 174:67–75.

6. Styner M, Oguz I, Xu S, Brechbuhler C, Pantazis D, Levitt JJ, Shenton ME, Gerig G. Framework for the Statistical Shape Analysis of Brain Structures using SPHARM-PDM. Insight Journal. 2006:1–21.
7. Walterfang M, Looi JCL, Styner M, Walker RH, Danek A, Niethammer M, Evans A, Kotschet K, Rodrigues GR, Hughes A, Velakoulis D. Shape alterations in the striatum in chorea-acanthocytosis. Psychiatry Research: Neuroimaging. 2011; 192:29–36.
8. Lindberg O, Walterfang M, Looi JCL, Malykhin N, Ostberg P, Zandbelt BB, Styner M, Paniagua B, Velakoulis D, Orndahl E, Wahlund LO. Hippocampal shape analysis in Alzheimer's disease and frontotemporal lobar degeneration subtypes. Journal of Alzheimer's Disease. 2012; 30:355–365.
9. Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, Parikshak N, Hua X, Toga AW, Jack CR, Weiner MW, Thompson PM. Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease mild cognitive impairment, and elderly controls. Neuroimage. 2008; 43:59–68. [PubMed: 18675918]
10. Looi JCL, Rajagopalan P, Walterfang M, Madsen SK, Thompson PM, Macfarlane MD, Ching C, Chua P, Velakoulis D. Differential putaminal morphology in Huntington's disease, Frontotemporal dementia and Alzheimer's disease. Australian and New Zealand Journal of Psychiatry. 2012; 46:1145–1158. [PubMed: 22990433]
11. Looi JCL, Macfarlane MD, Walterfang M, Styner M, Velakoulis D, Latt J, van Westen D, Nilssen C. Morphometric analysis of subcortical structures in progressive supranuclear palsy: in vivo evidence of neostriatal and mesencephalic atrophy. Psychiatry Research: Neuroimaging. 2011; 194:163–175.
12. Walterfang M, Macfarlane MD, Looi JCL, Abel L, Bowman E, Fahey MC, Desmond P, Velakoulis D. Pontine-to-midbrain ratio indexes ocular-motor function and illness stage in adult Niemann-Pick disease type C. European Journal of Neurology. 2012; 19:462–467. [PubMed: 22329857]
13. Macfarlane MD, Looi JCL, Walterfang M, Spulber G, Velakoulis D, Styner M, Crisby M, Örndahl E, Erkinjuntti T, Waldemar G, Garde E, Hennerici MG, Bäzner H, Blahak C, Wallin A, Wahlund L-O. Shape Abnormalities of the Caudate Nucleus Correlate with Poorer Gait and Balance: Results from a Subset of the LADIS Study. The American Journal of Geriatric Psychiatry. 2013
14. Looi JC, Walterfang M, Nilsson C, Power BD, van Westen D, Velakoulis D, Wahlund LO, Thompson PM. The subcortical connectome: Hubs, spokes and the space between - a vision for further research in neurodegenerative disease. Australian and New Zealand Journal of Psychiatry. 2013
15. ENIGMA. ENIGMA: Enhancing Neuro Imaging Genetics through Meta-Analysis. Imaging Genetics Center; USC, Los Angeles, California, USA: 2014.
16. Kilcullen, D. Out of the Mountains. New York: Oxford University Press; 2013.

Table 1

Establishing a new collaborative network

- Read broadly and consult with research colleagues in and outside your area of research interest
- Interesting research may involve application of interdisciplinary approaches, or application of established methods in a new field, or gathering together rare datasets
- Identify a novel research area that is novel, and not already heavily researched
- Develop an area of research expertise: this is essential for participation in any network – this will take time and development from your end – but is a predicate before any collaboration can exist, as you must have skills to contribute to a collaboration
- Conduct your own research projects in the area towards initial data-based publications framing your interests and displaying your skills
- Identify via the literature and through your current networks potential collaborators
- If possible ask mutual contacts (of both you and the collaborator) to introduce you to new potential collaborators: that is, leverage from your networks to build a trusted introduction
- Meet with your potential collaborators in person initially towards discussing a collaborative project: this means you need to meet on your collaborator's turf
- Begin with smaller scale collaborative projects of mutual interest to build relationships
- Discuss in detail plans for workflow and writing for the completion of the project
- Quickly and efficiently produce results from the small project to build trust
- Write and publish results together with your collaborators
- Use completed projects as a springboard to new projects
- See also Tables 2 and 3 for additional details on project and collaborative management, and be aware of strengths and pitfalls in Table 4

Table 2

The principles of our project planning

- Identifying a dataset of interest
- Identifying an interesting clinical question that we wish to explore within the dataset
- Determining the clinical data required (clinical scales, neuropsychology, demographics and neuroimaging)
- Assembling the relevant collaborators from the network
- Agreeing on a draft project plan including publication and encompassing authorship, project leads, relevant roles, timelines and outcomes (papers)
- Seeking ethical approval at origin data site, and at locally each involved site before commencement
- *Sharing only de-identified imaging and clinical data* (origin data site de-identifies data using an anonymised unique ID number for each subject for which only the origin has the key) for analysis
- Sharing processed imaging and clinical data analysed as per agreement with origin site and other agreed collaborators
- Coordinating via the central hub at ANU Medical School/ACT Health Directorate of network projects, and logistics support from the hub for each centre's self-run projects needing access to the network
- Recruiting mutually supervised clinical researchers for postgraduate degrees based upon the research projects (Masters, PhD)

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Table 3

Principles distilled from the development of the network

Trust and cooperation are fundamental:

- Identify people you can work with and trust.
- Early discussion of a project, the participants and publication authorship details are very important.
- Memoranda of understanding between collaborators can provide a vehicle through which to discuss such issues.
- Choosing collaborators to join the network is informed by those already within the network.

Bringing together a variety of skills and interests:

- Neuroimaging work requires different skill sets, from the skill required to manually trace images through to the higher level mathematical and computational skills required to develop semi-automated or automatic algorithms.
- Collaborations may develop from complementary skill sets

Having shared interests in clinical research:

- Collaborators must share research ideas and interests, whilst being flexible enough to accommodate alternative views.

Importance of coordination, logistics and good communication:

- Face to face communication is the ideal.
- Good communication can still occur through other media as long as care is taken with the logistics and technology.

Table 4

Strengths and Pitfalls of the Model

Strengths	Pitfalls
Flexibility to build specific virtual project teams	Reliant on close coordination of collaborators: face-to-face communication limited by time differences
Independent of specific collaborative funding	Collaborators must fund their own infrastructure: long-term network funding needed
Local ethical approval at origin site for de-identified data to be shared	Ethical approval still needed at each collaborative site may introduce delays
De-identified data, using anonymised unique IDs allows for safe data transfer	Imperative to maintain up-to-date databases of anonymised unique IDs, especially with prospective studies
De-identified data sent via secure cloud computing services	Limited capacity of cloud services and download times
Sharing of processed data for further analyses	Database reconciliation and version control critical
Project coordinators work across network	Requires vigilant project management and communication by coordinator
Shared student supervision across centres	Requires close support of student from primary student supervisor & coordination of supervisors
Collaborative write-up of research	Delays due to multiple collaborators and required institutional approvals