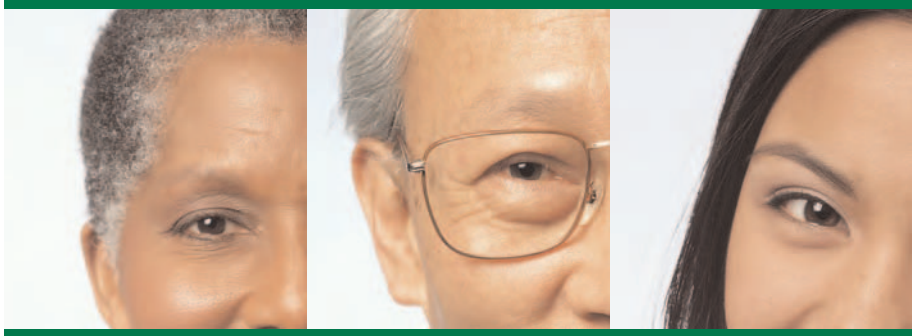
Final Report

Myer Foundation Mental Health Project

The Australian Psychosis Research Network



PROPOSALS for ESTABLISHMENT and FUNDING

Sponsored by The Myer Foundation 2004

Final Report

Myer Foundation Mental Health Project

For consideration by the
Myer Foundation Mental Health Program
Steering Group
July 2004

Proposals for the Establishment of an Australian Psychosis Research Network

Proposals for Funding

With thanks for the generous support of
The Myer Foundation

Final Report

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The statistics used to convey the size of the social, economic and public health problem represented by the psychotic disorders never seem to quite communicate the human misery these diseases inflict on the individual sufferer.

Last week a patient with schizophrenia told me that she was "the origin of all sin", something she had been for more than ten years. She said that she was responsible for everything that was bad in the world and that she could no longer tolerate the profound despair and hopelessness she felt. She said she was looking "for an exit", meaning she wanted to die. She had not come to the hospital for treatment but instead with the hope that we would put her out of her misery by euthanasia.

The patient had not had a moment's relief from the way she felt in more than a decade. The tragedy for me as a clinician is that the treatments I could offer most likely would not be very effective.

Research is the only way to defeat these dreadful illnesses. Now that the scientific tools for conquering them are available, we must apply them in the best way to produce results.

Patients with psychotic disorder will not ask us to do this for them – it is up to us to make sure that there is no delay in finding the means to prevent or cure these diseases.

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Professor of Hospital and Community Psychiatry
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Executive Summary

Disorders such as schizophrenia and bipolar disorder affect at least two percent of the Australian population and cause severe lifelong mental incapacity that starts in the teenage years. Currently, more than 70% of the disability associated with the psychoses is completely untreatable. Virtually all of our treatments are non-specific – only research can offer the prospect of targeted treatments that act on specific brain systems.

Australia has world renowned research centres in the neurosciences and genetics. It also has leading psychosis research groups and high quality neuroimaging facilities co-located with clinical services. Despite these favourable conditions for a major research effort into psychotic disorders, there is presently little coordination or strategic direction to mount such an effort.

Although psychotic disorders are complex, the range of sophisticated scientific technology needed to understand them has recently become available. The development of this technology raises ethical questions over failing to apply it systematically to the study of psychotic disorders that seriously affect the health of so many Australians who have historically suffered widespread discrimination, including at the level of resource allocation to both health services and research.

This document calls for the establishment of an Australian Psychosis Research Network (APRN) that will provide strategic direction and coordination for a national program of clinical, neuroscience, and genetic research into the psychotic disorders.

This nationally coordinated effort will create a critical mass of technical and clinical infrastructure, promote standardisation of measurement across research centres, support multi-centre studies of large representative clinical cohorts and their long term follow-up, enable integration of research databases nationally, and establish multi-disciplinary meeting processes for scientific exchange.

More than 4,000 new cases of psychotic disorder arise in Australia annually, the majority involving young people. Associated stigma and the legal and ethical prohibitions against media exposure of such patients results in these illnesses never receiving the degree of public attention warranted by their prevalence.

These activities will take Australian psychosis research into a new era of discovery and position it to more effectively benefit from and contribute to international biosciences.

APRN has three strategic aims:

- *Build pathways for discovery, from gene to therapy, by vertical integration of scientific activity across each level of research expertise and resource*
- *Achieve critical mass within each level of research expertise by horizontal integration of collaborating research centres across institutions, and across states and territories*
- *Actively engage consumers and carers, clinicians and policy-makers, and the general public in the promotion and development of psychosis research*

The seven research programs proposed are estimated to cost $10.47 million annually (this

excludes non-research functions) and are listed below:

1. **Cellular and molecular neuroscience ($2.5 million)**
2. **High-field magnetic resonance ($1.1 million)**
3. **Genetic epidemiology ($4.45 million)**
4. **Drug development ($300,000)**
5. **Novel therapeutics, psychosocial intervention and rehabilitation ($980,000)**
6. **Research into practice ($150,000)**
7. **Collaborative senior research fellowships ($990,000)**

The network will also support consumer development, community awareness, and marketing and promotion functions (initially costing $350,000 annually). If managed as an independent organisation these functions (covering scientific and non-scientific management) will cost a further $510,000 annually.

Hence, if fully implemented, the total annual budget of APRN is $11.33 million. Staged implementation is proposed so that in the first triennium an effective annual budget could range from $1 million to $5 million, the level being determined by available funding. It is assumed that APRN will initially be unable to attract competitive funding. Its successful establishment will require strong stakeholder support. The limited sponsorship of a small number of widely respected philanthropic trusts may be instrumental in eliciting broader stakeholder and community support, and offer critical leverage in seeking recurrent government funding.

Background

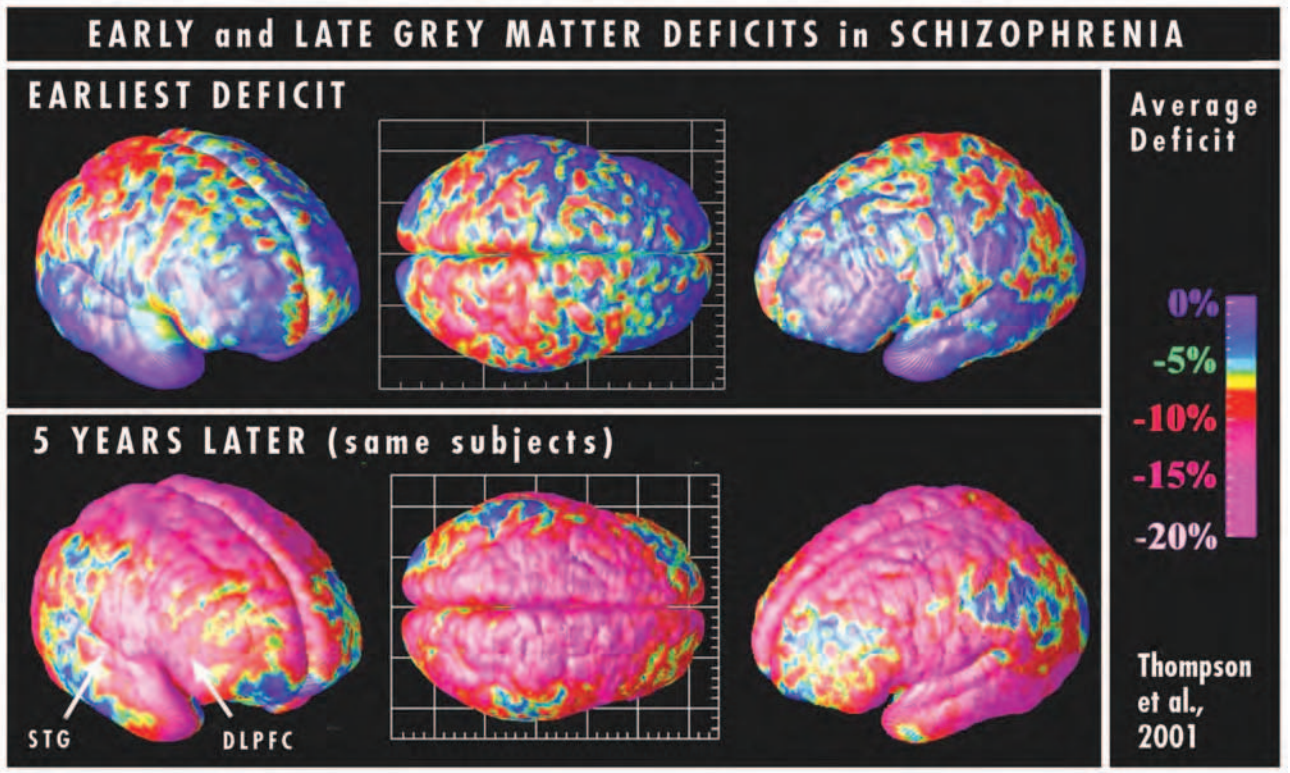


Figure 1. *These brain images are from young people with schizophrenia. Despite five years of continuous treatment, a wave of destruction (shown by the "hot" colours) has affected large areas of their brains (compare upper and lower panels).*

Psychotic disorders are chronic and relapsing psychiatric diseases that cause major disability. The characteristic symptoms are delusions, hallucinations, mood disorder and cognitive impairment.

This group of disorders includes schizophrenia, bipolar disorder (manic-depressive illness), and schizoaffective disorder.

More than two percent of the world's population is affected by psychotic illness. Most are struck down in their youth and do not recover. One in ten suicide.

A range of effective treatments has improved the lives of patients, so that today few require long-term institutionalisation. Though most patients live in the community, many are severely disabled and their families are under great strain.

Psychotic disorder contributes to many contemporary social problems including youth suicide, homelessness, and substance abuse. Few patients obtain full-time employment and 85% are dependent on government welfare benefits.

In financial terms, the cost of psychotic disorder to the Australian community is at least $2.62 billion annually and, to the Australian Government $1.70 billion annually. Although there are other public health problems of the scale of the psychotic disorders, there are two overriding reasons why increased research effort is justified in this field.

First, unlike dementia, cancer or cardiovascular disease that primarily disable or shorten the lives of older people, psychotic disorders usually permanently disable young people. Second, in the case of schizophrenia recent data indicates that current

approaches to treatment avert only about 13% of the total aggregated burden due to this disease, and that even if services were given unlimited funding they could only aim to avert about 22% of the total aggregated disability *(Andrews et al. 2003, Brit J Psychiatry, 183, 427-435)*.

This point is graphically illustrated in Figure 1. which shows the failure of treatment to arrest the progress of the destructive processes affecting the brain in schizophrenia.

Not only is current treatment relatively ineffective, Andrews et al. (2003) showed that it is extremely inefficient, costing in the order of $200,000 to avert one year of disability.

Now that the scientific tools are available to conquer the psychotic disorders, these findings represent nothing short of a public health emergency, demanding immediate action.

Only a decade ago the causes of Alzheimer's disease were virtually unknown and there were no effective treatments. Substantial funding in the last ten years has resulted in an understanding of the molecular basis of Alzheimer's disease and, currently preventative treatments are in clinical trial.

The community now needs to recognise that schizophrenia and bipolar disorder also require a concerted research effort aimed at prevention. As with Alzheimer's disease, usually those affected by these disorders cannot advocate for themselves. This heightens our responsibility to take urgent action on their behalf.

Until very recently one could not be confident that increased investment in research into psychotic disorders would yield results as quickly as it has for Alzheimer's disease. The reason for this is that although the general location of a number of putative susceptibility genes for the psychoses had been found, not a single gene was precisely identified.

Fortunately, in the last two years this situation has fundamentally changed with the discovery of eight to ten putative susceptibility gene variants. It cannot be over-emphasised how the prospects for discovery in the psychotic disorders have been radically changed by this advance.

For schizophrenia, there is increasing evidence that variants of the following genes mediate or modify susceptibility to the disease:

1. *NRG-1 also known as neuregulin-1*
2. *DTNBP-1 also known as dysbindin*
3. *G72 (a novel primate gene)*
4. *DAAO short for D-aminoacid oxidase*
5. *RGS-4, short for regulator of G-protein signalling-4*
6. *PRODH, short for proline dehydrogenase*
7. *DISC-1, short for Disrupted In Schizophrenia-1*
8. *GRM-3 encoding a metabotropic glutamate receptor*
9. *PPP3CC encoding the calcineurin gamma subunit*
10. *COMT, short for catechol-O-methyl transferase*

All of the above genes play a role in brain development and maturation, probably through their influence on synaptic neuroplasticity. The investigation of the functional significance of these genes in a multi-level, multidisciplinary research program using a combination of genomics, proteomics, animal models, *in vivo* neuroimaging and spectroscopy, and clinical studies has the potential to identify preventative approaches to the treatment of psychotic disorders.

Aims and Strategic Issues

This proposal aims to establish an Australian collaborative research network for psychotic disorders that:

- ***Builds pathways for discovery, from gene to therapy, by vertical integration of scientific activity across each level of research expertise and resource***

- ***Achieves critical mass within each level of research expertise by horizontal integration of collaborating research centres across institutions, and across states and territories***

- ***Actively engages consumers and carers, clinicians and policy-makers, and the general public, in the promotion and development of psychosis research***

Available treatments for the psychoses are non-specific, affecting only the secondary symptoms. For major improvements in clinical outcome, we must move from non-specific to specific treatments that directly target the primary underlying disorders. To do this, findings at the level of cellular and molecular neuroscience and genetics must be related to clinical research into psychotic disorders – indicating the need for collaboration between basic scientists and clinical researchers.

Basic scientists and clinicians usually work in isolation from one another. This allows the level of specialisation necessary to conduct, on the one hand, sophisticated neuroscience studies and, on the other, highly refined measurement in the clinic. Scientific journals encourage this narrow focus, and the explosion in research information makes it difficult to keep up with one's own field. Therefore, infrastructure, resources, and incentives are needed to create a broader multidisciplinary approach for the study of psychotic disorders.

The fields that are relevant to psychosis research include molecular and cellular neuroscience, epidemiological genetics, neuroimaging, drug design, cognitive neuroscience, and therapeutics. These fields go from the 'micro' (molecular neuroscience) through to the 'macro' (therapeutics). Pathways for treatment discoveries are built by vertical integration of these levels of research, so that there is a tightly interlocking chain of research supporting the application of fundamental (basic) research findings to the development of therapeutics.

The Research Program

The US National Institutes of Health (NIH) have highlighted the need to better link research to clinical practice and, developed the notion of translational research. Translational research seeks to translate advances from the bench or animal laboratory into clinical application. In relation to cancer research, NIH developed funding models called Specialised Programs of Research Excellence (SPOREs). SPOREs conduct translational research that requires interdependence between basic and clinical investigators in both the planning and implementation of research and emphasise the application of basic research findings to patients and populations. SPOREs must demonstrate effective integration of basic and applied research that translates into areas of early detection, diagnosis, therapy, and prevention. They must represent all the required levels or areas of research expertise and infrastructure. If this model is to be applied to psychotic disorders, it will need to include; genomics, proteomics, anatomical and chemical neuropathology, structural and functional neuroimaging, in vivo chemical imaging including spectroscopy, drug design, endophenotypic measurement, clinical assessment, and novel therapeutics *(see Figure 2)*.

Typically, psychosis research is carried out on small groups of patients – often groups as small as 10 to 20 are compared with similar sized groups of healthy subjects. This research is useful in looking for promising leads. But because of the low

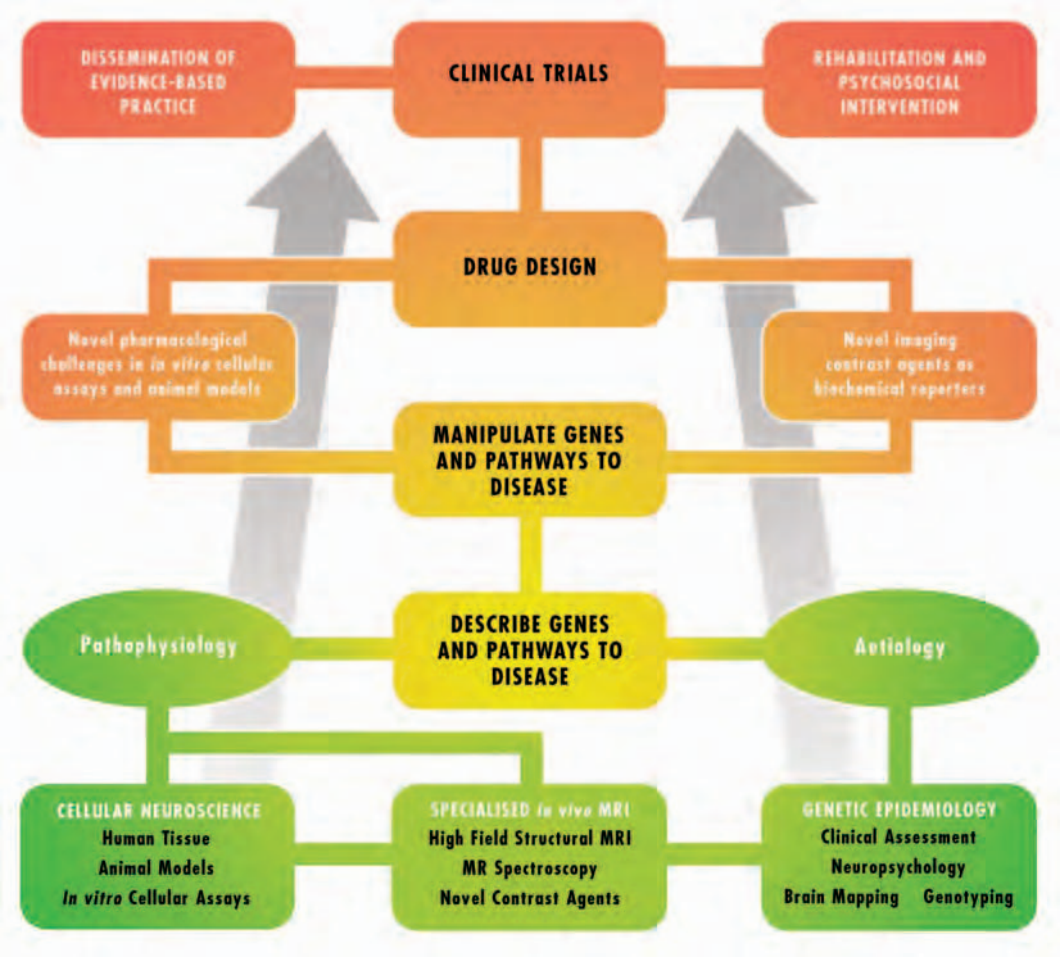


Figure 2. *APRN's integrated translational research.*

precision of clinical measurement and the high complexity of psychotic disorder, major advances require multi-centre recruitment of much larger samples – with 100's or even 1000's of subjects per group. The assessment of these large samples includes clinical ratings, neuropsychological testing, functional brain mapping, and genotyping.

To permit carriage of large-scale studies using multi-modal assessments, centres expert in these techniques must horizontally integrate within each specialised knowledge area to ensure standardisation of measurement across centres and regions. This will drive collaborative networking of these and clinical centres to ensure uniform clinical assessment with across-centre reliability; standardisation of imaging data acquisition equipment and sequences, and analysis software, across magnetic resonance imaging (MRI) sites; integration of large-scale databases; and, centralised genotyping and genetic analysis procedures.

Similar considerations apply to the molecular and cellular neuroscience investigation of psychotic disorders, using postmortem brain tissue or animal models. Research progress can be accelerated if a number of complementary technical approaches to assessing cellular and molecular structure are done concurrently in the same specimens, rather than each being done separately as is usually the case.

As many neuroscience centres specialise in only one technical approach, horizontal integration of several groups will enable a more comprehensive assessment of abnormalities in tissue from the same set of brains or the same animal model, and provide converging evidence in support of a particular finding. Horizontal integration of groups so that they use the same animal model can rapidly create converging evidence, and efficiencies, by applying several different technical approaches to the study of the same animal model. The power offered by multi-centre

recruitment of clinical subjects, the application of multiple cellular and molecular assays to the same specimens, and the coordinated investigation of animal models, will be the driving force for the horizontal integration of Australian research centres at all levels.

We propose that the integration of research centres can be achieved by funding the infrastructure necessary for groups to collaborate. Key elements of this infrastructure to be supported are: regular scientific meetings across disciplines; standardisation of data collection and analysis; and coordinated supply of postmortem brain tissue and animal models.

A number of across-centre senior research fellow positions will be supported to provide additional collaborative 'glue' to the network. These senior research fellowships will not only generate future leaders in the field of collaborative psychosis research and attract additional competitive funding but will create career pathways in psychosis research for senior scientists. Whenever possible this proposal will aim to support the development of psychosis researchers professionally, and to promote the importance of neuroscience and psychosis research to the broader community.

Although collaborative infrastructure is essential to create a network, without a number of large-scale milestone projects to drive scientists to work together, the collaboration will remain sterile and will not capitalize on the increased research capacity created. Because of the duration and scale of these projects, they are unattractive proposals for existing competitive funding processes. Therefore one or two large-scale genetic epidemiological studies, and a coordinated neuroscience program investigating cellular and molecular mechanisms in psychosis will be funded. These major studies will build on local strengths in the fields of neuroscience, genetics, and psychosis research. But to ensure that there are no gaps in the pathway to discovery afforded by the translational research model, critical weaknesses in the Australian research context, for example high field MRI, and drug design, will be strengthened by targeted investment.

No matter how robust the collaborative organisation might be, a research endeavour of the scope proposed will inevitably become unfocused if it does not have a guiding principle to give overall direction to the research program. It is essential to articulate a common theme that can be applied at all levels of research and has enough specificity to offer a driving principle to discovery.

We propose to build up our research program around the genes that have been recently implicated in the development of the psychotic disorder – and their likely functional roles in terms of synaptic plasticity. By gathering converging evidence from each of the levels of research about the functional significance of these genes, this project will contribute to the international effort to define the precise role of the genes in psychotic disorder.

Viewed from a global perspective, this nationally coordinated project would be ideally equipped to participate in international research collaborations, and well positioned to benefit from overseas funding and technology transfer.

From research to better practice

Because the time required for translation of a fundamental research discovery into an advance in therapeutics can be in the order of a decade, this proposal will include research with potential near-term improvements by seeking to extract therapeutic value from existing knowledge.

An example of this is the investigation of whether clinical outcomes can be improved by varying the order or combination of currently available treatments, especially studies of combined antipsychotic drug and psychosocial intervention or adjunctive pharmacological therapies. Studies such as these will ensure that the work is relevant to today's patient, as well as those of the next generation. Hence, a range of research projects that offer a mix of near-term, medium-term, and long-term outcomes will be included.

In a related fashion, the proposal will have a focus on the dissemination of evidence-based practice to support rapid translation of new ideas from research into clinical application. This activity has

been called *Research into practice* and involves efforts in continuing education for clinicians and managers in addition to evaluation of the effectiveness of strict adherence to agreed-upon treatment guidelines and protocols.

Finally, a national research collaboration of the scale and scope proposed requires well developed scientific management and meeting processes. Indeed, regular meetings of the scientists will be the creative powerhouse for the entire endeavour. This thinking must also be informed by consumer and community concerns.

In summary, we have carefully considered the local context to identify the best way of establishing a national program of collaborative research into psychotic disorder, and attempted to address the main issues. *To be realistic, our proposal will not attract competitive funding, under current project and program grant schemes of the NHMRC in the forseeable future,* irrespective of the merit of the strategic approach and research proposals. The scope of this proposal is beyond these funding processes. Also, limited progress in developing a scientific basis for discovery, related to past difficulties in defining what areas to research, has worked against resource allocation on the scale required. With recent advances in genetics and the neurosciences, and technologies such as brain imaging, the prospects for discovery in the psychotic disorders have fundamentally changed. However, attitudes towards increased funding are changing too slowly to keep pace with these developments. It will take more than good science to get a project like this up. Therefore, we aim to address the long-term structural impediments to funding research into psychotic disorder and propose to vigorously engage stakeholders and involve the broader community.

Bringing the community along

Strategic alliances with stakeholders and community organisations are considered much more important for attracting long-term funding for psychosis research, compared with other areas of medical research, especially because of the nature of these disorders. Patients have been stigmatised, and their disorders and needs misunderstood on a scale unequalled with any other diseases. It is not hard to see why – the symptoms are difficult to describe to the non-sufferer, and they are readily misinterpreted as self-inflicted, or to reflect moral weakness, or even to be simple laziness.

There are no laboratory tests to tell who has psychotic disorder and even the legitimacy of the diagnosis has been questioned. There are no plaster casts, shaven heads, or wheel chairs, to objectify the disability. Indeed, the disease is usually brought to the public's attention through neglect or treatment failure – the homeless 'bag lady' who inhabits the inner city; the gifted young person who inexplicably becomes an incorrigible drug addict; or sadly on occasion, the perpetrator of a senseless or macabre assault.

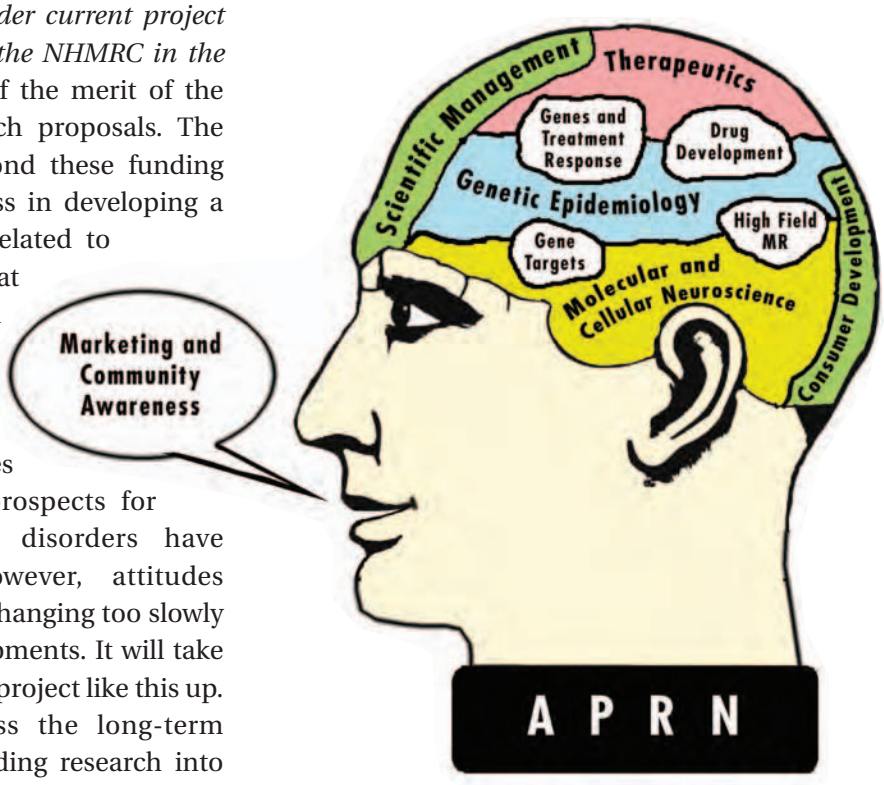


Figure 3. *APRN's integrated organisational functions*

Tragically, in about half of patients, the disease prevents the patient appreciating that they have an illness. Understandably, many not only reject the notion that they need treatment and services, but

they cannot understand why they need research and do not lobby for it. *We must advocate on their behalf and with them.*

Compounding the impact of poor insight on effective self-advocacy is consumer resource limitations. A problem with psychosis is that its full impact is not obvious until early adulthood – an age when the community expects people to look after themselves, but when patients have few resources to do so. The resources of families are rapidly exhausted by the illness of their sick relative. Hence, patients with psychosis do not attract the paternalistic sympathy that sick children do, yet they and their families are usually unable to lobby effectively for themselves. Moreover stigma inhibits relatives making public that psychosis affects their family. Psychosis is a 'hidden' disease, encouraging the general public to conclude that these disorders are rare and will not affect them personally, and that research is not a priority.

The true picture could not be further removed from this perception. Estimates of the lifetime prevalence of schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, psychotic depression, and other psychoses, are in the order of 2-3% of the general population. These figures can be doubled when the non-psychotic disorders genetically related to the psychoses are added – all of which typically have their onset in adolescence and produce lifetime disability.

Though few Australians (4%) think mental illness is a major health problem *(Highet et al, 2002, Med J Aust, 176, S63-68)* the reality is that mental disorder is among the top three public health problems today – and by 2020 is predicted to represent the single most costly health sector.

We propose to support a consumer development program with a particular focus on the creative and artistic abilities of patients and their relatives. This consumer program will include regional arts and crafts workshops for consumers, and arts and crafts exhibitions, competitions, and prizes in each state and territory. These state-based competitions will build to a national arts and crafts competition and a prestigious national creative arts prize.

The aim of the consumer development program is to convey an image of consumers as valuable members of the community worthy of our greatest compassion. The time is right for rapid change in the public's attitude to psychotic disorder – mainstream films such as "A Beautiful Mind" and "Shine" have prepared the community for this change. Much of the community's attitudes are shaped by ignorance and misinformation. A national research program will have the information and credibility to support major community awareness campaigns, to turn around these views.

Other stakeholders will be crucial to the success of our proposal. Funders take many forms, but ultimately large scale recurrent funding will have to be mainly a government responsibility. Governments do not tend to be proactive but prefer to respond to community demand. We propose that this demand be initiated by community organisations, possibly philanthropic trusts such as the Myer Foundation.

Research Proposals

It has been proposed that the network should have a thematic and strategic approach to discovery of molecular pathways involved in schizophrenia and bipolar disorder, and that this should be integrated into a larger set of research themes that allow translation of fundamental research into better outcomes for people with psychotic illness.

Our challenge is to articulate a common theme that can be applied to all levels of research and has enough specificity to offer a driving principle to discovery. The proposal currently before us is that we build the Network research around the role of genes as risk factors for psychotic illness.

Why genes? To date, no other descriptive and predictive hypothesis for psychosis has been advanced. This is not to say that there are not many ideas regarding the causes of psychosis, but that many of them involve hypotheses that are difficult to test in a range of experimental paradigms. By focussing on genes, we are able to envisage a range of cellular and molecular studies, studies on postmortem brain tissue, studies using animal models including transgenics, epidemiological studies, brain imaging studies and potential drug development studies

Are we really certain as to which genes may be involved in the etiology of psychosis? No! But one of the more exciting developments in schizophrenia research in the past couple of years has been the success of microarray approaches using postmortem human tissue and transgenic animal models, and from the identification by positional cloning of several candidate genes from genetic linkage studies. Of great interest has been the convergence of these two approaches where it now appears that genes involved in synaptic communication, especially presynaptic communication, are critically involved as either genetic risk factors or as causal or consequential changes in brain tissue.

Susceptibility genes for psychosis have been identified by positional cloning of candidate genetic loci. This has led to the following genes being implicated in schizophrenia: neuregulin-1 (NRG-1), dysbindin (DTNBP-1), G72 (a novel primate gene) and its interacting protein D-aminoacid oxidase (DAAO) and the calcineurin gamma subunit (PPP3CC).

A number of potential genes have been proposed by direct candidate selection including: regulator of G-protein signalling-4 (RGS-4), proline dehydrogenase (PRODH), metabotropic glutamate receptor-3 (GRM-3) and catechol-O-methyltransferase (COMT). In addition, two genes that were identified as marking a cytogenetic breakpoint in a Scottish schizophrenia pedigree have also been implicated (Disrupted In Schizophrenia-1 and –2: DISC-1 & DISC-2). Equivalent susceptibility genes have not yet been published for bipolar disorder although several groups have strong candidates identified through linkage studies and positional cloning approaches.

These results make testable hypotheses that can be validated or refuted and can lead to other research questions being formulated. It is the concept of success in the areas of genes and molecules rather than the specific research results to date that are most important. Indeed, it is likely that even today, many of the currently claimed 'genes' will not be validated, but more importantly these claims are now testable.

CELLULAR AND MOLECULAR NEUROSCIENCE PROGRAM

Description of proposals

Major advances in treatment have rarely occurred without understanding the pathophysiology of a disease. Adequate descriptions of the cellular, subcellular and molecular abnormalities do not exist for the psychotic disorders. This lack of knowledge limits research at all levels because the relevance of candidate susceptibility genes cannot readily be

assessed, animal models cannot be validated, functional imaging studies cannot be precisely targeted biochemically, and specific molecular targets for drug design are lacking. The breadth of this field demands that molecular or functional targets be specified for productive applied research. Specific susceptibility genes serve that role and permit the application of transgenic animal models to the study of psychosis. The Cellular and Molecular Neuroscience program will carry out two types of studies: one type investigating human postmortem brain tissue and the other type developing and investigating animals that have been genetically designed to 'model' an aspect of psychotic disorder (animal models).

The neuroscience centres proposed for inclusion are: Mental Health Research Institute Victoria (MHRIV); The Howard Florey Institute; Brain Sciences, University of New South Wales; Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD) and its NSW affiliated research centres (located at the Universities of Sydney, Wollongong, Newcastle, and Garvan Institute of Medical Research); The Prince of Wales Medical Research Institute; Hunter Medical Research Institute; Queensland Brain Institute; Queensland Institute of Medical Research; Queensland Centre for Mental Health Research; Centre for Molecular Neurobiology, Griffith University; Flinders University; Centre for Clinical Research in Neuropsychiatry, University of Western Australia.

■ **Human postmortem brain tissue studies**

It is essential to carry out research directly on human brain tissue because only humans develop schizophrenia or bipolar disorder. This research is fundamental to achieving a full phenotypic description of the diseases which is necessary for valid selection of animal models.

Decisions about animal model design are best informed by human postmortem studies. Although collection of appropriate postmortem tissue has been occurring for some years, both in Australia and internationally, funding of research using human postmortem tissue has been inadequate. Glial morphology and substructure have been virtually ignored. Little or no postmortem tissue research that is informed by the discovery of candidate susceptibility genes has been carried out.

This state of affairs exists despite a number of exciting lines of postmortem human tissue research indicating abnormalities in specific receptor systems and disease specific morphological changes in cerebral cortex. For example, world-leading research at the MHRIV has implicated dysfunction of a specific subtype of muscarinic receptor in schizophrenia, and glial cell abnormality in bipolar disorder. A number of major findings in schizophrenia concerning abnormalities of the dendritic trees of cortical neurons, and their synapse-carrying spines, have been made by the Yale University Neurobiology Program. These changes were not observed in bipolar disorder. Discoveries such as these provide a firm scientific foundation for a collaborative research program on human postmortem brain tissue in Australia.

We propose that the collaborative research program on human postmortem brain tissue determine protein and mRNA levels for each of the susceptibility genes in schizophrenia, using high-throughput technologies (proteomic and microarray-based) to create large databases for protein and gene expression for future investigation of other pathways, in addition to building on existing lines of research.

■ **Studies of human cell lines**

A variety of cells can be derived from biopsy of patients and healthy controls. Biopsies can be made in well characterised patients without some of the problems associated with postmortem tissue and variable cause of death. Human cells available within the group include lymphoblastoid cell lines, fibroblasts, and stem cell lines derived from the olfactory neuroepithelium. These cells can be examined for gene and protein expression and be used to identify candidate genes for human genetic studies. These cell lines can also be stimulated with drugs, growth factors or other means to identify altered growth states or to determine changes in protein and mRNA levels on a global basis or for each of the susceptibility genes using proteomic and microarray-based methods. Candidate genes identified in these studies can

then be verified for their expression in postmortem tissues.

We propose treated cellular preparation studies (with susceptibility gene product ligands; psychotogenic and antipsychotic agents) to determine changes in protein and mRNA levels for each of the susceptibility genes, using high-throughput technologies (proteomic- and microarray-based) to create large databases for protein and gene expression for future investigation of other pathways.

■ **Animal treatment studies**

Studies of the effects of treatment of animals, mainly rodents, with psychotogenic and anti-psychotic agents can be used to determine changes in protein and mRNA levels using high-throughput proteomic- and microarray-based approaches. These experiments complement the human postmortem and cell line studies and lead to the creation of large databases of protein and gene expression for future investigation of other pathways. Future experiments can be directed to similar approaches using animals with altered expression (eg knockout) of identified susceptibility genes or treatment of animals with novel ligands that may inhibit or enhance the actions of susceptibility gene products.

We propose treated animal studies (with susceptibility gene product ligands; psychotogenic and antipsychotic agents) to determine changes in protein and mRNA levels for each of the susceptibility genes, using high-throughput technologies (proteomic- and microarray-based) to create large databases for protein and gene expression for future investigation of other pathways.

■ **Transgenic and other animal models**

Relatively few transgenic animal models of psychosis have been proposed, largely because until recently, very few candidate genes had been identified. However, the NMDA receptor R1 subunit knockdown model of Mohn et al. has been an important advance as this model supported both the synaptic transmission hypothesis and resulted in mice with behavioural traits that were reversed by anti-psychotic medications. As susceptibility genes have been identified, pre-existing knockout mice have also been used to provide supportive data; for example, neuregulin knockout hypomorphs have been used to support the discovery of neuregulin as a schizophrenia susceptibility gene.

Schizophrenia and bipolar disorder are certainly the result of interactions between genes and the developmental environment. Probably multiple gene pathways are involved. Animal models that investigate possible environmental risk factors include prenatal infection, prenatal hypoxia, prenatal hypovitaminosis D, and exposure to cannabinoids during brain maturation. Such models are open to interrogation via behavioural, structural and microarray-based approaches. Candidate gene-environment interactions can be explored using a combination of transgenic and environmental models.

As they become available, we propose transgenic studies (including transgenes, knockout's, conditional knockout's, knockdown's, etc) be used to determine the function of susceptibility genes, and compare the resulting animal phenotypes with the findings from postmortem tissue from patients with psychosis.

BUDGET: Cellular and Molecular Neuroscience Program

PROJECT	STAFFING	PA COST
Human postmortem brain tissue studies		
• Microarray and proteomic approaches	2 staff and consumables	200,000
• *in situ* and immunohistochemical validation	2 staff and consumables	200,000
• Morphological description	2 staff and consumables	200,000
Studies of human cell lines		
• Microarray and proteomic approaches	1 staff and consumables	100,000
• *in situ* and immunohistochemical validation	1 staff and consumables	100,000

PROJECT	STAFFING	PA COST
Animal treatment studies		
• Microarray and proteomic approaches	2 staff and consumables	200,000
• *in situ* and immunohistochemical validation	2 staff and consumables	200,000
Transgenic animal studies		
• Microarray and proteomic approaches	2 staff and consumables	200,000
• *in situ* and immunohistochemical validation	2 staff and consumables	200,000
• Develop collaborative behavioural network	2 staff and consumables	200,000
• Anatomical and biochemical studies	2 staff and consumables	200,000
• Electrophysiological studies	2 staff and consumables	200,000
Expansion of infrastructure for supply of specimens		
• Human brain tissue collection, storage and processing		100,000
• Human cell lines collection, storage and processing		75,000
Development of new models based on candidates plus existing lines		
• Molecular work for constructs	0.5 staff	50,000
• Generation of knockout subcontracted to Ozgene	subcontract	50,000
• Breeding and distribution	maintenance costs	25,000
TOTAL	**22.5 staff plus costs**	**2,500,000**

HIGH FIELD MAGNETIC RESONANCE PROGRAM

Description of proposals

Over the last decade, advances in the development and application of magnetic resonance (MR) technology have provided unprecedented opportunities for conducting non-invasive *in vivo* investigations of human brain structure and metabolism. Conventional field strength MR imaging systems (~ 1.5 Tesla), such as those installed in most hospital radiology departments, provide reasonable spatial and temporal image resolution of neuroanatomical structures and the opportunity to perform limited spectroscopy and functional studies. However, in order to obtain ultra high resolution images that might be compared with *in vitro* cellular data, either a substantial increase in signal-to-noise or imaging time are required. High Field MRI offers the additional signal to noise required to achieve a spatial resolution of 200 micron (currently at 4T), and the potential for further improvement with new parallel imaging technology (phased arrays). Similarly, MR signals associated with brain metabolites are typically small, but the ability to detect these increases approximately linearly with field strength.

The MRI literature on schizophrenia has often provided conflicting results. This is perhaps not surprising given the *ad hoc* manner in which many of these experiments have been conducted, and the small sample sizes typically studied. Often, researchers have applied novel MR measures without formulating *a priori* hypotheses informed by *in vitro* cellular data or other convergent evidence. The lesson to be learned is that simply having an MRI system proximal to a patient population does not guarantee results.

Recently, there has been considerable interest in using genetic information to interrogate MRI data. Success has already been achieved in terms of identifying genetic influences upon brain development and function in healthy adolescents and adults. A genetic predisposition to psychosis has been demonstrated to produce reliable differences in fMRI measures, in the absence of similar differences on behavioural measures, attesting to the sensitivity of the MRI technique. The use of genetic information has the potential to ground MRI research into psychosis in a more formal neuroscience framework. Specific hypotheses concerning candidate genes and their relationships with brain structure and metabolism may be developed and tested *in vivo*, in both cross-sectional and

longitudinal designs. One of the most recent developments in MRI involves the development of novel contrast agents, that are based on molecular pathways specific to particular genes. The High Field MRI group would draw on the findings of the genotyping group and the expertise of the Drug Development Program (see later) to develop such agents and then visualise where in the brain they accumulate.

An important use of the technology, especially in the application of spectroscopy, is to identify neuropharmacological mechanisms or biomarkers of drug interventions *in vivo*. While contrast agents that target specific molecular pathways are in development, it will be some time before they might be used in human trials. Another application of MRI is in psychopharmacological investigations. This involves the use of conventional fMRI to demonstrate pharmacological modulation of brain function during the performance of cognitive tasks. To date, the modulatory effects of available dopaminergic, cholinergic and gamma-aminobutyric acid (GABA)-ergic drugs have been studied. It is expected that the formulation of specific research questions will depend heavily upon collaborative efforts between other neuroscientists/groups within our network and the high field MRI researchers.

We propose to add funding to two or three Collaborative High Field MRI Research Centres, as a separate initiative to the clinical neuroimaging of the large samples proposed in the Genetic Epidemiology Program (see next section). This high field MRI initiative is essential because it is the only way to bridge the scale of measurement gap between *in vivo* imaging and *in vitro* cellular research. Also, it is necessary because MR spectroscopy is far superior at high resolution. Although high field MRI is relatively less well developed in Australia compared with the United States, it represents a critical link in our translational research model, and because of the paucity of collaborative multi-site high field MRI studies into schizophrenia and bipolar disorder in the United States, is a highly competitive and desirable proposal.

It is intended that identical protocols be developed, established and conducted at each centre, with regular assessments using phantoms for quality assurance. This will provide essential data concerning replicability of results, a problematic area for MRI studies of psychosis, and the potential of pooling data to achieve sufficient sample sizes. The high field MRI centres proposed for inclusion are: Centre for Magnetic Resonance, University of Queensland (4 Tesla); The Prince of Wales Medical Research Institute MRI centre (3T); and, Brain Research Institute, Austin Hospital, Melbourne (3T).

Budget: High Field Magnetic Resonance Program

The following costs are calculated on a per site basis.	**COST**
Hardware*	
• Coils (assuming 1 broadband or 1H phased array coil per site)	$75, 000
• MR-compatible fMRI devices	$15, 000
Imaging studies	
100 scan sessions per annum	
• (1 scan session = ~$800, including contrast agent etc)	$80, 000
Staff	
• 2 staff and consumables (half time radiographer & full time physicist/ computer scientist)	$200, 000
Per site total	$370, 000
TOTAL = annual per site total x 3	**$1.11 million**

**The first year hardware budget will be used recurrently to support larger imaging studies.*

GENETIC EPIDEMIOLOGY PROGRAM

Description of proposals

Genetic epidemiology is the study of the genetic determinants of specific characteristics of individuals (phenotypes) in a population. Defining relevant phenotypes for the psychotic disorders is not straightforward. Unlike diseases caused by a single gene, psychotic disorders involve multiple gene variants that interact with one another, and the environment, to produce disease. Most people who carry these gene variants do not meet the diagnostic criteria for psychotic disorder (though many may be diagnosed with persistent, adolescent-onset, non-psychotic psychiatric disorder). That is, the gene variants involved do not determine the presence or absence of psychosis but rather, the degree of susceptibility or risk for developing disease. These gene variants are normal, abundantly distributed in the general population. Vulnerability to psychosis is proportional to the number of susceptibility gene variants carried and their individual effect sizes. In individuals carrying susceptibility gene variants who do not develop disorder (for example, in some family members), a number of personality, neuropsychological, and brain mapping differences can be measured that reflect genetic predisposition to psychotic disorder. Compared to diagnosis, susceptibility gene variants more directly determine these individual differences.

Many decades of studying the pattern of aggregation of diagnosable psychotic disorder in families has demonstrated that these disorders have strong genetic backgrounds - at least 80% of the risk for these disorders being due to genetic factors. With the molecular genetics revolution, gene mapping of DNA extracted from peripheral white blood cells collected in family studies has demonstrated 'linkage' or co-inheritance of specific chromosomal regions (identified with a known reference 'marker' gene) and psychotic disorder. For more than ten years a number of international groups (at least two of which include Australian researchers) have carried out linkage analysis on families with multiple members affected by psychotic disorder. Linkage analysis focuses on the chromosomal position of a susceptibility gene. Although this approach is powerful for gene variants of large effect, it is less likely to detect gene variants involved in psychotic disorder that are individually of small effect. An alternative approach, the association method, tests whether a particular allele of a marker, a specific genotype, or a haplotype is enriched in (or statistically associated with) affected individuals compared with unaffected controls. Association studies enable the direct investigation of candidate gene variants of small effect, although relatively large sample sizes (at least 1000 in non-related subjects) are required. Whilst assisting family collection processes for linkage studies in Australia, we propose to resource a large association study involving the comparison of first presentation patients with their siblings, and a general population sample. In addition to cross-sectional assessment of these subject groups, a longitudinal assessment component will be supported. Of particular interest will be the emergence of illness in the siblings of patients, which will provide the opportunity to correlate genotypic and phenotypic markers with the occurrence of subsequent illness. This work will inform a third project in the Genetic Epidemiology Program, namely the development of a risk assessment battery for use in children and adolescents to predict risk of psychotic illness.

In relation to these projects, there are two preliminary issues to address. First, as pointed out in the Jablensky et al. submission (see Appendix 1), *"restriction of the phenotype used in genetic analyses [and, by extension, other measures of psychopathology or even treatment] to the clinical diagnosis of schizophrenia [or, for that matter, other psychoses and bipolar disorder] . . . may not be the most appropriate phenotype."* Thus, supplementing diagnostic classification with other measures of brain structure and function is believed necessary to identify "endophenotypes"[1], thereby facilitating the search for susceptibility genes and shedding light on processes of pathogenesis. Second, if primary prevention is to become a realistic possibility, a means for identifying high-risk individuals before the onset of the prodrome needs to be found. Furthermore, the identification of high-risk children and adolescents would enable a prospective study to be undertaken (with genetic analyses, measures of brain structure and function, and assessments of environmental exposure).

Family history is currently the only reliable means of identifying risk (and such studies are in progress in several overseas centres), but the majority of cases of schizophrenia do not have a family history.

It is possible that these two potential starting points, traditional diagnosis and high-risk, can converge around the concept of the endophenotype. If a risk-screening instrument applicable to large populations of young people can be devised and validated against the neurocognitive measures used to define putative endophenotypes (and other risk indices), with the cohort thus screened positive followed-up through the period of highest risk for psychosis onset, then the two strategies would complement each other.

- ***Within family case-control study: cross-sectional assessments***

It is proposed to recruit 1,600 nuclear families across multiple centres. Each family will comprise a proband, at least one sibling and two parents. Diagnoses of the probands will be schizophrenia (N=800) and bipolar disorder (N=800). These samples will be assessed diagnostically, neurocognitively, genetically, electrophysiologically and by MRI measurement, and on a battery of personality and endophenotypic characteristics (eg, neurological soft signs, minor physical anomalies).

The clinical probands will be invited to participate in the Novel Therapeutics, Psychosocial Intervention and Rehabilitation Program, thereby allowing assessment of treatment response and outcome. A general population sample (N=800) will be recruited for selected components of the study (risk factors for psychosis and genetic analyses). The reader is referred to Appendix 1 for the methodological details of core aspects of this study. We acknowledge the work Professor Assen Jablensky and his colleagues in drafting the core study. As we propose to incorporate Professor Jablensky's methodology into the collaborative network, we are indebted to him and his team and thank him for allowing his proposal to be included in this document. Appendix 2 details the background to the genetic analysis supporting this program. Appendix 3 details the supplementary cognitive assessments proposed for this program.

- ***Within family case-control study: longitudinal follow-up of siblings***

Probands under the age of 26 years (clinical cases diagnosed as either schizophrenia or bipolar disorder) will be recruited shortly after their first presentation to a mental health service for treatment. Based on the assumption that the probands will be the first member of their sibship to develop a psychotic illness, we can expect that ten percent of the sibling sample recruited will develop a psychotic illness, and many of these cases will emerge within a few years of the proband's illness. Hence the regular assessment of the siblings longitudinally will map out the evolution of the onset of psychotic illness as well as enable comparison of those siblings who develop illness with those that do not, on a range of assessments of risk. In addition, this study will provide valuable information to base the design of a risk assessment battery for use in school-aged children and adolescents.

- ***Development of a screening instrument for the identification of young people at risk***

It is not yet feasible to conduct a population-based longitudinal study of children and adolescents at high risk for schizophrenia and related disorders. Instead it is proposed to develop a screening instrument for the identification of young people at risk and determine the prevalence of risk factors in a population of year 4-5 (9-10-year old) children and year 9-10 (14-15-year old) adolescents. The reader is referred to Appendix 4 for details of the methodology proposed for this project. The development of the screening instrument is anticipated to take three to five years. Thereafter this instrument will be able to be applied to the selection of a sample of school aged children at high risk of developing psychotic disorder for longitudinal assessment and follow-up. (The budget for this future longitudinal study has not been determined).

Supporting the Genetic Epidemiology Program, clinical research centres proposed for inclusion are: Perth, Melbourne, Sydney, Newcastle, Brisbane. The genetic analysis centres proposed for inclusion are: Perth, Melbourne, Sydney,

Newcastle, Brisbane. The neurocognitive assessment centres proposed for inclusion are: Perth, Melbourne, Sydney, Newcastle, Brisbane. The clinical neuroimaging centres proposed for inclusion are: Perth, Melbourne, Sydney, Newcastle, Brisbane. The methods developed by The Brain Resource Company (Director: Dr Evian Gordon) and the Melbourne Neuropsychiatric Centre (Director: Prof Chris Pantelis) offer models upon which to base across centre imaging data aggregation. The centralised genotyping processing laboratories of the Queensland Institute of Medical Research (Director: Prof Nick Martin) provide a world-leading example of genetic analysis procedures for the Program.

[1] *An endophenotype is a set of measurable characteristics on the pathway between genotype and disease.*

BUDGET: Genetic Epidemiology Program

The overall budget estimate of $4.45M is based on the annual budget ($4.2M) for the cross-sectional study (Years 1 - 4) plus the average annual budget for the screening instrument development ($0.705M/3).

● Within family case-control study: cross-sectional assessments (Annually, Years 1-4)

CLINICAL ASSESSMENTS	
Screening of potential probands:	
5 sites x 116 per site x $25 contribution to clinical staff/GPs	$14,500
DIAGNOSTIC AND NEUROCOGNITIVE ASSESSMENTS	
5 sites x 360 assessments X 4 hours @ $30 per hour	$216,000
(Assessments per site over 4 years: 40 schizophrenia probands, 80 parents, 40 siblings; 40 bipolar probands, 80 parents, 40 siblings; 40 from the general population)	
NEUROBIOLOGICAL ASSESSMENTS (STRUCTURAL/FUNCTIONAL MRI, PPI, MMN)	
5 sites x 360 assessments (as above) x $1,500 per person	$2,700,000
GENETIC STUDIES	
Blood collection, storage, transport, preparation	
5 sites x 360 subjects @ $40 per person	$72,000
GENETIC ANALYSES	
5 sites x 360 subjects @ $400 per person	$720,000
EQUIPMENT AND CONSUMABLES	
5 sites x $10,000	$50,000
PERSONNEL	
Main Project Officer at each site	
5 sites x $55,000 (PSP3)	$275,000
Central project staff (Genetic analyses, software development, database management and analysis)	
3 x $55,000 (PSP3)	$165,000
Annual Total (Years 1-4)	**$4,212,500**

● Within family case-control study: longitudinal follow-up of siblings

FIRST FOLLOW-UP (ANNUALLY, YEARS 4-7)	
5 sites x 160 subjects (probands and siblings)	
Diagnostic and Neurocognitive assessments	**$96,000**
Neurobiological assessments	**$1,200,000**
SECOND FOLLOW-UP (ANNUALLY, YEARS 8-10)	
5 sites x 160 subjects (probands and siblings)	
Assessments as for first follow-up	**$1,296,000**

● Development of a screening instrument for the identification of children at risk

Indicative total budget over 3 years (see Appendix 4)	**$705,380**

● 10-Year Budget	Costs
CROSS-SECTIONAL STUDY (YEARS 1-4)	
4 Years x $4,212,500	$16,850,000
FIRST FOLLOW-UP (YEARS 4-7)	
4 Years x $1,296,000	$5,184,000
SECOND FOLLOW-UP (YEARS 7-10)	
4 Years x $1,296,000	$5,184,000
DEVELOPMENT OF SCREENING INSTRUMENTS	$650,000
Key Project Staff (Years 5-10)	
Regional staff: 6 years x 5 sites x PSP3 ($55,000)	$1,650,000
Central staff: 6 years x 3 staff x PSP3 ($55,000)	$990,000
CONSUMABLES AND EQUIPMENT (YEARS 5-10)	
6 years x 5 sites x $10,000	$300,000
Subtotal (10-year budget)	**$30,808,000**
Allow 15% inflation	$4,621,200
TOTAL	**$35,429,200**

DRUG DEVELOPMENT PROGRAM

Description of proposals

Information from other aspects of the program will lead to the identification of genes that are up or down regulated in particular psychotic conditions. The primary target of the drug development program will be those genes that are up-regulated, and the strategy will be to develop chemical antagonists of these targets. Rather than focus on one specific target, this part of the proposal will illustrate the general principles and infrastructure that will be created as part of the overall collaborative psychosis research network proposal. Similar principles will apply to specific individual targets that will be identified in the course of the program. Although the Drug Development Program will be coordinated with activities in the other levels of research, unlike other levels of research it will be mainly led by one centre, and conducted principally at the University of Queensland in the Institute for Molecular Bioscience (IMB) and the School of Biomedical Sciences. The inclusion of only one centre arises from the paucity of academic centres with drug design research infrastructure in Australia. We propose to direct seeding funding toward this gap in research infrastructure that particularly affects drug development for the psychotic disorders. We aim to provide this funding from the outset to ensure that our collaborative network has a firm foothold in this critical research link in translating basic research into better therapeutic outcomes for patients in the clinic. Importantly, the University of Queensland and the Queensland Institute of Medical Research have jointly established the Queensland Preclinical Drug Development Facility, which will enable further development of lead compounds discovered in this program.

The drug development pathway involves target validation, lead discovery and lead development. Once a protein target is identified lead compounds are traditionally identified either by screening against a large library of compounds or natural products extracts, or via rational drug design. We will adopt the latter approach and will use two rational strategies for identifying lead compounds. First, in a structure-based design approach the three-dimensional structure of the target protein will be determined and lead molecules designed based on this structure. If the target protein has an identifiable ligand, then structural analysis of the ligand can be used to further guide rational drug design. Second a linked-fragment approach will be applied.

The structure-based drug design approach will require the determination of the three-dimensional structures of target proteins. X-ray crystallography will be used for those proteins for which high

quality diffracting crystal can be obtained, and magnetic resonance (MR) spectroscopy will be used where this is not possible and the protein size is smaller than approximately 35 kDa. Facilities for both technologies are available in the IMB and are available for this program. Once the structures have been determined active sites will be identified and potential drug ligands that bind and block that site will be designed. X-ray and/or NMR will be used to verify the nature of the interaction and further optimise the lead molecules.

The linked-fragment approach will be based on the SAR-by-NMR method recently developed at Abbott labs. It involves rapid screening a small library of simple molecular fragments, or building blocks, for binding to the target protein, identification of two such binding interactions that are proximate to each other and then chemically linking the two fragments. It has the advantage that it is relatively easy to find weak binding leads, and by joining two weak binders together and simultaneously capturing both binding interactions it is possible to gain a substantial thermodynamic leverage of binding affinity. For example, two leads that bind with relatively modest millimolar to micromolar affinity may be joined to produce a linked fragment with nanomolar affinity. This approach is much more efficient than attempting to optimize the affinity of a weak binding lead and has created much excitement in the pharmaceutical industry as a new approach to lead discovery strategy. Because of the need for a dedicated high field NMR spectrometer for screening (>$1million capital cost) it would normally not be applicable in an academic setting. However, such a robotic instrument has recently been installed at the IMB at UQ and up to 10% of available instrument time is available for this program. An appointee funded under this proposal is required to manage the screening operations and design the linked fragments.

We propose to direct seeding funding towards the early stage of the drug discovery process and this will be used to leverage funds for further development. In particular, we anticipate that leads identified in this discovery program will be further developed in partnership with biotechnology or pharmaceutical companies. Three postdoctoral-level positions will be required to drive the discovery program.

• Target identification/validation/expression
The appointee will interact closely with clinical members of the program and will assist in the identification of target genes and associated proteins. This person will develop protocols for recombinant expression of the target proteins for subsequent structural and screening studies. Both aspects require tens of milligrams of highly purified proteins. The IMB houses a protein expression facility having all of the required infrastructure. Access to this infrastructure will be available to this appointee on a cost-recovery basis if conducted as a collaboration with the ARC Centre for Functional and Applied Genomics within IMB. This arrangement will result in substantial leverage of Drug Development Program funds.

• SAR-by-NMR screening
This appointee will develop and optimise the fragment library, run the screening protocols and design linked-fragment leads based on the initial binding hits. Once again, the required high field NMR facilities are available via a proposed collaboration with the IMB.

• Structural biology
This appointee will have skills in X-ray crystallography and/or NMR spectroscopy and will determine high-resolution structures of target proteins. The X-ray and NMR facilities at UQ are arguably the best in Australia for structural biology and will be available to this program.

BUDGET: Drug Development Program

TARGET IDENTIFICATION/VALIDATION/EXPRESSION	
One staff and consumables	$100,000
SAR-BY-NMR SCREENING One staff and consumables	$100,000
STRUCTURAL BIOLOGY One staff and consumables	$100,000
TOTAL ANNUAL BUDGET	**$300,000**

NOVEL THERAPEUTICS, PSYCHOSOCIAL INTERVENTION AND REHABILITATION PROGRAM

Description of proposals

Research consistently indicates that treatment outcomes in schizophrenia and related disorders are suboptimal. For example, a recent follow up study of first onset patients found consistent recovery in less than 15% of patients at 5 years after the onset of symptoms.

Whilst antipsychotic medications, including more recently developed agents, are successful in the alleviation of positive symptoms in a significant number of patients, they have limited effects on negative and cognitive symptoms, do not abolish the occurrence of relapse, and the degree of long term psychosocial recovery of many patients remains quite poor. Even when patients are able to return to life roles, they often remain symptomatic and with impaired quality of life.

We propose to establish a collaborative network of clinical trials centres (CTC) to support two inter-related research programs on novel therapeutics, and psychosocial intervention and rehabilitation.

NOVEL THERAPEUTICS

Interventions to enhance outcomes in psychotic disorders should be carefully linked to the type of discovery projects to be undertaken within this overall research proposal. These are targeted at the discovery and development of new and innovative biological compounds. This may arise from a variety of the research streams but the most promising possibility will be the generation of agents based on the identification and characterization of specific genotypes in groups or sub-groups of patients. There will be a direct need for the testing of these agents through a series of phase I, II and III clinical trials.

In addition, the process of phenotype and genotype definition possible in the case control association study will present the possibility of the identification of potential pharmaco-genetic studies using established agents in specifically defined subpopulations.

PSYCHOSOCIAL INTERVENTIONS AND REHABILITATION

In addition to the testing of novel biological agents, there is a pressing need for the development and evaluation of established and new psychosocial interventions. There is available research evidence for the efficacy of a number of well defined psychosocial interventions in schizophrenia.

For example, the Schizophrenia Patient Outcomes Research Team (PORT) made 9 treatment recommendations relating to specific individual and group treatments (including behavioural and cognitive skills training), family treatments, vocational rehabilitation and service systems (Lehman & Steinwachs, 1998). However, much less is known about which psychosocial interventions are helpful, since some treatments have not been adequately evaluated (Lehman & Steinwachs, 1998). Little systematic research points to the superiority of one strategy over others across all outcome measures (Huxley et al 2000).

A rational basis for matching particular approaches to the individual remains to be identified (Huxley & Baldessarini 2002). The efficacy and effectiveness in different settings, and the content, duration, and optimal mode of delivery of the different treatment elements are not well elucidated. In addition, the implementation of recognized psychosocial interventions in routine clinical practice is rare both internationally and in Australia, owing to complex and as yet unresolved barriers to their uptake (Thornicroft and Susser 2001). Thus in Victoria, the recent report of the Auditor General highlights the relative lack of psychosocial interventions, including services for carers and families (information, education, consultation, training and support) (Auditor General, 2002).

Specific training of staff in these evidence-based interventions is required, but alone is insufficient to achieve sustained implementation. Service development and organisational change have been increasingly identified in the literature as a necessary additional component (e.g. Torrey, Drake & Dixon, 2001). However, research has neglected this component (Corrigan et al, 2001) and therefore little is known about what strategies are effective in

promoting sustainable change and whether these changes can be replicated in different settings. Further, Thornicroft and Susser (2001) note the need to research the admixture of two strands in the community care of patients with schizophrenia: the delivery of mental health services by community teams and the use of psychotherapeutic interventions.

In addition to the real world evaluation of these established interventions, there is considerable scope for the development, evaluation and distribution of new psychosocial treatment tools, especially targeting areas of unmet need. Examples of this might include interventions to address social isolation, in-vivo skills training and consumer and peer support initiatives to rebuild social relationships and meaningful occupation.

COLLABORATIVE CLINICAL TRIAL CENTRES (CTC)

We propose to support the development and implementation of a collaborative network of clinical trial centres (CTC) with the goal of facilitating and conducting a variety of clinical trial activities in psychotic disorders in Australia. This will include:

1. Coordinating the conduct of clinical trials of novel agents generated within the cellular and molecular neuroscience and drug development programs: this may involve the conduct of trials at CTC sites as well as the recruitment and coordination of other sites.

2. Coordinating the conduct of clinical trials of other novel therapeutic agents proposed by network members and requiring the recruitment of subjects across multiple sites.

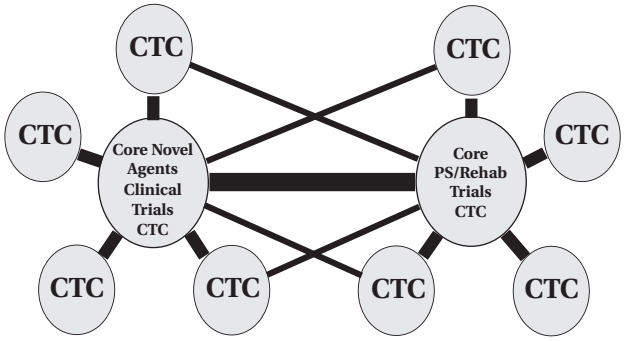
3. The provision of a central coordinating agency for the conduct of industry sponsored non-network trials.

4. The development and implementation of large quasi-experimental studies of established but poorly disseminated psychosocial interventions (including individual and group cognitive behavioural interventions, and family interventions).

5. The development and implementation of randomised controlled trials to test the efficacy of new psychosocial treatments and rehabilitation strategies.

A CTC will be funded in each region, which will be required to develop a core set of resources and expertise. This will be supported by two national lead sites each of which will provide a coordinating role in one of either trials of novel agents or psychosocial/rehabilitation: that is, there will be one 'novel agents' and one 'psychosocial/rehabilitation' lead site nationally.

Individual CTCs may either focus on one of the two trial areas or develop expertise in both, liaising with the national lead centres. It is anticipated that separate CTCs in the two different streams may be more viable in states with larger more concentrated populations although the composition of CTCs is likely to be primarily determined by local expertise.



The two lead sites in each domain will have responsibility for the overall coordination of the network activities. In addition there will be the requirement for the lead sites to develop and maintain specific expertise in data management, data analysis, the maintenance of infrastructure for central trial randomization activities and liaison with TGA in regards to CTC submissions. Depending on the circumstances for each trial, the novel agents lead site may also be required to liaise with appropriate companies for the provision of adequately blinded trial medications. The lead sites will also provide central coordination of various training and monitoring activities, and of the distribution of resources.

Each CTC will support the development and provision of training and expertise in other local centres for a range of activities including:

- use of clinical rating scales
- maintenance of inter-rater reliability
- training of site clinical trial coordinators

• data monitoring
• reporting and recording of adverse events
• coordination of ethics committee submissions

In addition, each psychosocial/rehabilitation CTC will be responsible for the development of intervention manuals and the training of personnel at local centres in the procedures required for trials of psychosocial and rehabilitative interventions.

The clinical research centres proposed for consideration as lead CTCs are: Melbourne (novel therapeutics and rehabilitation), Newcastle (psychosocial intervention and rehabilitation) and Brisbane (psychosocial intervention).

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BUDGET: Novel Therapeutics, Psychosocial Intervention and Rehabilitation Program

Lead CTC 1		
Senior Project Officer	$80,000	
Data Manager	$65,000	
Data management and office resources	$30,000	
		$175,000
Lead CTC 2		
Senior Project Officer	$80,000	
Data Manager	$65,000	
Data management and office resources	$30,000	
		$175,000
CTC		
Project Officer	$70,000	
Educational and Information resources	$20,000	
	$90,000 x 7	$630,000
	Total	**$980,000**

RESEARCH INTO PRACTICE PROGRAM

Description of proposal

There is a substantial delay between therapeutic discovery and its incorporation into clinical practice. The translational research pathway is completed by ensuring full and rapid uptake of existing and new treatments in the clinic. Processes to achieve this step now come under the rubric of Research into Practice, and include clinician and manager education and training.

The Cancer Council of Australia has applied these processes in the management of cancer by drafting best practice treatment protocols for early detection and optimal staged care.

We propose to adopt these procedures in relation to the management of psychotic disorders. Nationally coordinated development of evidence based treatment protocols for dissemination and implementation in services participating in our network will be initiated.

The selection of clinical research centres for inclusion in this program will be made by competitive tendering.

BUDGET: Research Into Practice Program

National coordinator (CNC level nurse appointment)	$65,000
Writing group expenses	$20,000
Printing and multimedia training materials	$30,000
Travel expenses involved in monitoring implementation of protocols in participating services	$35,000
TOTAL	**$150,000**

COLLABORATIVE SENIOR RESEARCH FELLOWSHIP PROGRAM

Description of proposal

A network that is multi-levelled, multi-disciplinary, and nationally distributed will require considerable collaborative 'glue' to keep it together. It is considered essential that some of this glue take the form of 'flesh and blood'.

It is proposed that about 10% of the total budget be used to fund a number of highly competitive senior research fellowships.

Senior research fellowships will secure the network's future scientific leadership of collaborative researchers into psychotic disorders, and recruit researchers most likely to attract competitive funding.

We propose that two or three full-time fellowships be funded in the first instance, but in time this program should support six fellowships.

BUDGET: Collaborative Senior Research Fellowship Program

Senior Research Fellowship 1 (including on costs)	$75,000
Research support	$75,000
Senior Research Fellowship 2 (including on costs)	$75,000
Research support	$75,000
Senior Research Fellowship 3 (including on costs)	$75,000
Research support	$75,000
Senior Research Fellowship 4 (including on costs)	$75,000
Research support	$75,000
Senior Research Fellowship 5 (including on costs)	$75,000
Research support	$75,000
Senior Research Fellowship 6 (including on costs)	$75,000
Research support	$75,000
Assuming two of the Fellowships are appointed at professorial level, add	$70,000
Assuming one of the Fellows is a clinician, add clinical loading	$20,000
Total	**$990,000**

Promotion and Development

As described in the "Aims and Strategic Issues" section, our research proposals are currently unlikely to attract NHMRC funding and the success of our network will depend on consumer and community support. In recognition of the importance of these issues, we propose to support consumer development, community awareness, and marketing and promotion functions.

Consumer development

Patients have been stigmatised, and their disorders and needs misunderstood, on a scale unequalled with any other medical disease. This discrimination operates not only directly against the consumer but indirectly through poor resource allocation to psychosis research.

The general public's negative perception of people with psychotic illness is considered to contribute to the structural barriers in obtaining research funding.

We propose to engage the patients and their families and carers as the key stakeholders in our research program and to ensure they have direct consultative input into all levels of our work. In particular, we will support a consumer development program aiming to both offer them greater opportunities for creative expression, and to promote a positive view of consumers as valuable members of society. This will be done by supporting local arts and crafts workshops, and annual regional arts and crafts exhibitions, building towards a national arts and craft show and prestigious national creative arts prize. This program will form a central part of a national awareness and anti-stigma campaign.

Community awareness

There are a number of organisations and government programs dedicated to reducing discrimination against people with psychotic disorder. Generally these organisations do not focus on discrimination at the level of research funding. As community engagement in our research network is considered crucial to its chances of obtaining funding, we propose to develop strategic alliances with organisations involved in advocacy on behalf of people with psychotic disorder to increase community awareness about the value of research.

We will provide such organisations with the latest scientific evidence pertaining to psychotic disorder and strategically fund their work that is focussed on promoting research and its resourcing.

Marketing and promotion

Although some research institutes do not attempt to raise money directly from the public, most now do. In association with consumer development and community awareness activities, we propose to support a marketing and promotion function. This has been successfully carried out in relation to psychotic disorder in New South Wales by NISAD, and we propose to model our marketing and promotion on NISAD's program.

A key element in NISAD's success has been the engagement of a number of high-profile members of the community to champion the cause of research. We propose to adopt a similar strategy and have already approached a number of people, including Alan Fels, the ex-chairman of the Australian Consumer Complaints Commission, and Pru Goward, the current Federal Sex Discrimination Commissioner.

BUDGET: Promotion and Development Program

CONSUMER DEVELOPMENT		
Support for annual creative arts workshops in each state, two in NSW and Victoria ($2500 x 8)		$20,000
Co-sponsorship of annual creative arts show in each state ($10,000 x 6)		$60,000
Co-sponsorship of annual national creative arts show		$25,000
National creative arts prize and competition		$10,000
Publicity to promote the creative arts program		$10,000
Start-up costs for art calendar and creative arts website		$15,000
Half-time arts program coordinator		$30,000
	Subtotal	**$170,000**
COMMUNITY AWARENESS		
Half-time liaison officer		$30,000
Product activity funding		$30,000
	Subtotal	**$60,000**
MARKETING AND PROMOTION*		
Promotions officer		$70,000
Promotions activity funding		$50,000
	Subtotal	**$120,000**
	TOTAL	**$350,000**

**Marketing and promotion will be self-funded within two years of start-up.*

Scientific Management and Governance

Up to the present the project has been managed by Professor Stanley Catts, University of Queensland. A $60,000 grant-in-aid (September 2002) provided by the Myer Foundation is administered by the University of Queensland. Professor Catts established a broad scientific consultative process drawing on the contributions of 83 scientists (see Appendix 6).

At the Scientists Meeting in Sydney on 26 March 2004 it was unanimously decided to appoint Professor Catts as the Chair of a newly formed Scientific Steering Committee (Appendix 5), comprised of co-ordinating authors of writing groups which had drafted the first versions of the research proposals upon which this submission is based.

Although a minimalist management and organisational approach was endorsed by the Scientists Meeting for the short term, implementation of the network proposal will require that a formal organisational structure be established. At the Scientists Meeting the preferred organisational structure was left an open question, options to be considered when the level of funding is known.

Currently the organisational structure that most resembles the national collaborative psychosis research network proposed is that of the Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD). A number of approaches to establishing the long-term organisational structure for the national network were discussed at the Scientists Meeting. One alternative was to create a new independent organisation with a management structure for the national network modelled on NISAD. Another alternative was to incorporate the national network within the existing NISAD organisation, providing obvious cost savings. If the national network was developed as an independent organisation modelled on the NISAD structure it would have the configuration described overleaf.

1. Type of organisation: A not-for-profit public company limited by guarantee; registered as a charity; and, approved by the Australian Taxation office to receive tax deductible donations. An auditor will be appointed.

2. Board of Directors: A Board of Directors will be appointed by the voting members of the organisation. Some Directors will act as stakeholder representatives, but most will be appointed in the service of specified organisational functions. All Directors will have extensive experience in professional directorial or chief executive roles, or have specific expertise relating to a Board objective.

Two committees will report directly to the Board:

a) The Scientific Management Committee (SMC)
Members will be Directors of funded participating research centres or their nominees. The Chairperson will be a member of the Board of Directors. The purpose of the SMC is to provide across-centre coordination; review of research proposals drafted by the Research Council (RC, see below); address intellectual property matters; identify strategic research directions; monitor performance of research groups and their projects; and advise the RC and the Board about all of these matters.

b) The Research Council (RC)
Members will be leaders of the research groups. The Chairperson will be a member of the Board of Directors. The purpose of the RC is to generate research proposals; integrate research projects into programs; identify technical problems delaying or preventing progress; trouble shoot all aspects of the research work; field human resources issues pertaining to researchers; and advise the SMC and the Board about all these matters.

3. Management Structure:
a) Business Manager: A business manager, supported by an administrative officer and a promotions officer, will be appointed by the Board. The business manager will: 1) be responsible for the financial, promotional and development functions of the Network, 2) chair a range of committees (Marketing and Promotion, Consumer Development, Audit and Finance, Policy and Procedure, and General Administration), and 3) report directly to the Board.

b) Research Manager: A research manager, supported by the administrative officer and clerical staff, will be appointed by the board. The research manager will: 1) be responsible for overseeing the coordination and competitive tendering of the research activities of the network and the central reporting of groups within the network, 2) assist the SMC and RC to carry out their role, and 3) report directly to the Board.

4. Approach to administrating research funds:
Research work will be competitively tendered, and funding paid to the successful Centre. Apart from the research fellowships, research salaries will be administered by participating Centres.

5. Network spokesperson:
This role will be shared by the Chairpersons of the Board, SMC and the RC, in a coordinated fashion.

6. Budget:
Please note that the proposed budget (see next page) includes the cost of the scientific meeting and management processes. That is, the budget does not simply reflect an administative burden.

BUDGET: Scientific Management and Governance

Excludes capital items

1. Board	
Quarterly face-to-face meetings (assuming 15 Directors)	
[biannual face-to-face; biannual video conferences]	$28,000
2. Scientific Management Committee	
Quarterly conferences (assuming 15 members)	
[biannual face-to-face; biannual video conferences]	$28,000
3. Research Council	
Quarterly video conferences (assuming 20 members)	$12,000
4. Annual Scientific Strategic Meeting	
(60 attendees)	
[$800 x 60 + $4,000]	$52,000
5. Management	
Business Manager (with accounting qualifications)	$90,000
Research Manager	$90,000
Travel/ Car allowance x 2	$40,000
Administrative Officer	$45,000
Receptionist/clerical	$35,000
Auditor	$10,000
6. Office:	
Rent	$40,000
Overheads	$40,000
GRAND TOTAL:	**$510,000**

General Budgetary Considerations

The annual budget for the seven research programs fully implemented is estimated to be $10.47 million (this excludes non-research functions) as listed below:

1. Cellular and molecular neuroscience
($2.5 million)
2. High field magnetic resonance
($1.1 million)
3. Genetic epidemiology
($4.45 million)
4. Drug development
($300,000)
5. Novel therapeutics, psychosocial intervention and rehabilitation
($980,000)
6. Research into practice
($150,000)
7. Collaborative senior research fellowships
($990,000)

The annual budget for the non-research functions fully implemented is estimated to be $860,000 as listed below.

8. Promotion and development
($350,000)
9. Scientific management and governance
($510,000)

Therefore, when fully implemented the total annual budget of APRN will be $11.33 million. Over time, some research programs will require less funding whilst other will receive more. Staged implementation is proposed so that in the first tri-ennium an effective annual budget could range from $1 million to $5 million, the level being determined by available funding. If $1 million annually were available to fund research, only two programs seem appropriate to be considered: either the collaborative senior research fellowships program or the high field magnetic resonance program. If $5 million per annum were available, the genetic epidemiology program could be commenced at a restricted number of sites in parallel with partial implementation of one or two other programs.

It is assumed that APRN will initially be unable to attract competitive funding. Its successful establishment will require strong stakeholder support. The limited sponsorship of a small number of widely respected philanthropic trusts may be instrumental in eliciting broader stakeholder and community support, and in offering critical leverage in seeking recurrent government funding.

The Myer Foundation may wish to consider taking the lead role in building a consortia of trusts, committing a grant as leverage to encourage other trusts to make similar commitments. In turn, this larger pool of funding could be used as greater leverage on government to commit recurrent funding.

Outcomes and Significance

In the last decade billions of dollars were invested in the Human Genome Project and The Decade of the Brain initiative. As a result, breathtaking advances in the neurosciences, genetics and brain imaging technologies have occurred. For the first time in human history complex brain diseases such as schizophrenia and bipolar disorder can now be understood and potentially prevented.

Several $100 million are spent each year on psychosis research in the United States. So how will funding psychosis research in Australia by an additional $10 million per annum make any real difference?

First, with relatively modest funding psychosis researchers in Australia add significantly to the scientific knowledge about these disorders. As more money has been spent on this research, this contribution that Australian scientists make grows faster than the funding does. That is, research investment in Australia attracts higher yields than investment elsewhere.

Second, because research in the United States is fiercely competitive, the multi-site multidisciplinary collaborative research program proposed herein would be almost impossible to implement in that country. There, bringing together schizophrenia researchers and bipolar researchers to collaborate would be seen as highly unusual.

Third, specialised neuroscience and neuroimaging facilities in the United States are not usually co-located with clinical services, particularly mental health services, as is often the case in Australia. Proximity of research and clinical facilities is also necessary to carry out the programs of research proposed herein.

Fourth, to our knowledge there is no plan to initiate a large-scale translational research project in the field of psychotic disorder in the United States. Indeed, we believe our proposal for a national psychosis research network that is primarily designed to do a full range of translational research is the first of its kind in the world. Our strategic and coordinated approach to program implementation offers a unique chance of not only increasing basic knowledge about psychotic disorders but translating this knowledge directly into therapeutic outcomes.

The statistics used to convey the size of the social, economic and public health problem represented by the psychotic disorders never seem to quite communicate the human misery these diseases inflict on the individual sufferer. Last week a patient with schizophrenia told me that she was "the origin of all sin", something she had been for more than ten years. She said that she was responsible for everything that was bad in the world and that she could no longer tolerate the profound despair and hopelessness she felt. She said she was looking "for an exit" meaning she wanted to die. She had not come to the hospital for treatment but instead with the hope that we would put her out of her misery by euthanasia.

The patient had not had a moment's relief from the way she felt in more than a decade. The tragedy for me as a clinician is that the treatments I could offer most likely would not be very effective. Research is the only way to defeat these dreadful illnesses. Now that the scientific tools for conquering them are available, we must apply them in the best way to produce results.

Patients with psychotic disorder will not ask us to do this for them – it is up to us to make sure that there is no delay in finding the means to prevent or cure these diseases. If anyone you loved had schizophrenia, you would want a cure.

Appendices

APPENDIX 1

GENETIC BASIS OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: A COLLABORATIVE LINKAGE AND CASE-CONTROL STUDY

Chief Investigators

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INTRODUCTION
We seek support for a collaborative, consortium-type program of genetic-epidemiological research into schizophrenia which should result in a major national and international resource including a detailed phenotypic characterisation and a DNA collection from over 800 nuclear families (> 3000 individuals) with one or more members affected by schizophrenia. This resource will be highly informative for genetic research, enabling both association (case-control) studies of currently indexed candidate genes and advanced versions of linkage analysis to identify novel candidate regions and genes. It should also enable future applications of state-of-the-art genomic and proteomic technologies to clone susceptibility genes and determine their function in the pathogenesis of schizophrenia.

Background: advances in the understanding of complex diseases. New concepts and technologies generated by the Human Genome Project are having a far-ranging impact on the biomedical research agenda. While uncovering the genetic basis of the majority of the monogenic diseases presents no longer major conceptual difficulties but is rather a matter of time and funding, the genetics of the so-called common, or complex diseases (including diseases such as hypertension, diabetes, asthma, arthritis, and many of the psychiatric disorders) raises far greater challenges. Their aetiology involves multiple genes of small to moderate effect, allelic heterogeneity (different combinations of genes causing the disease in different populations or even pedigrees), incomplete or variable expression in affected or at-risk individuals, and interactions with non-genetic, environmental exposures ranging from intrauterine insults to psychosocial and lifestyle factors. Current approaches to the study of common disorders invest heavily into: (i) large clinical and DNA samples to overcome the weak "signal-to-noise" ratio of the underlying genes; (ii) refined characterisation of the disease phenotype, often resulting in the splitting of a broad clinical entity into component phenotypes; and (iii) multidisciplinary efforts to identify pathogenetic pathways leading from genotype to phenotype. Such research is already producing important results, anticipating the advent of novel effective treatments and prevention.

Schizophrenia as a priority target of this proposal. Schizophrenia affects approximately 1% of the population worldwide (1500-2000 new cases per year in Australia – Jablensky et al., 1999) and accounts for 2.3% of the total burden of disease in the established market economies and for 0.8 percent in the demographically developing regions. In OECD countries, the direct costs of schizophrenia amount to 1.4% - 2.8% of national health care expenditure and up to 20% of the direct costs of all mental disorders. More effective treatment and, ultimately, prevention of schizophrenia, will become possible when its neurobiology and causes are fully understood. Mapping and isolating genes that increase the risk of schizophrenia (or protect from schizophrenia) is a crucial step towards this goal.

Schizophrenia shares all of the features of complex diseases (Lander & Schork, 1994). Results of family, twin and adoption studies converge on heritability estimates at around 80%. Research into its genetic basis in the last two decades has been based on genetic linkage studies of multiply affected pedigrees, affected sib-pairs, and case-control association studies. Although a number of tentative findings pointing to multiple chromosome regions that may harbour susceptibility genes have been published, few findings have been replicated on independent samples and no single gene or chromosomal region has yet been definitively identified as conferring risk of schizophrenia. The limiting factors on the power of such studies to detect predisposing genes include sample size, ethnic heterogeneity, and the restriction of the phenotype used in genetic analyses to the clinical diagnosis of schizophrenia. Although current clinical classification based on ICD-10 or DSM-IV criteria is reliable, it may not be the most appropriate phenotype for genetic studies (Ginsburg et al., 1996). Abnormal behaviour and clinical symptoms, such as hallucinations and delusions, result from complex interactions of biological and environmental factors and are likely to be too far "down-

stream" from the immediate action of the predisposing genes. Supplementing the clinical assessment with objective measures of "modular" phenotypes indexing intermediate levels of brain function and structure, such as cognitive processing, brain anatomy, and neurophysiological responses, is likely to increase the power to detect specific gene effects. Current research, including our own data (Hallmayer et al., 2003), supports the view that specific patterns of neurocognitive dysfunction are correlated with clinical schizophrenia and may represent "endophenotypes" of the disorder, facilitating the search for susceptibility genes.

Prior work underlying this proposal. A "testbed" for the concepts, hypotheses and procedures in the project is provided by the studies on heterogeneity and correlated phenotypes in schizophrenia in Perth (supported by NHMRC grants), in which over 150 nuclear families (over 500 individuals) comprising probands, family members and controls were evaluated for clinical symptomatology, neurocognitive performance on tests of attention, memory, speed of information processing and IQ; personality traits; neurophysiological indicators (P50, P300, MMN and saccadic eye movements); and structural MRI. These multiple measurements were integrated into composite, multivariate quantitative phenotypes using grade of membership and latent class analysis. Results indicate that the neurocognitive and personality trait patterns aggregate into at least two distinct clinical subtypes of schizophrenia: subtype I, characterised by significant cognitive deficit, neurodevelopmental insults (maternal obstetric complications) and clinical features of behavioural disorganisation; and subtype II, characterised by attenuated cognitive disorder and prominent paranoid symptoms. Genetic linkage analysis, using neurocognitive and personality measures as a quantitative trait supplementing clinical diagnosis, resulted in lod scores greater than 3.0 on chromosome 6p and 8p (for subtype I) and on chromosome 10p and 10q for subtype II (Hallmayer et al., 2003). This is the first study demonstrating different genetic bases for cognitive subtypes of schizophrenia.

Aims and scope of the proposed research. The project aims at ascertaining, across several sites Australia-wide, a large number (> 800) of nuclear (two-generation) families that will achieve the power of analysis required for the reliable identification of susceptibility genes. The project will implement a "correlated phenotypes" strategy that was developed and extensively tested in NHMRC-funded research conducted by the Perth-based investigators in the last 7 years. This research produced a methodology of supplementing the clinical phenotype with composite measures of neurocognitive functions (attention, memory, executive control, speed of information processing, general ability) and personality traits (schizotypy, novelty seeking, harm avoidance). Distinct patterns of neurocognitive performance, neurophysiology and personality traits were found to characterise subgroups of patients with schizophrenia, and similar patterns were present in about 50% of their symptom-free first-degree relatives. By using such correlated phenotypes to supplement clinical diagnosis, we have been able to demonstrate significant genetic linkage (lod scores in excess of 3.0) to regions on chromosomes 6p, 8p, 10p and 10q, i.e. sites which have also been reported by other investigators as potentially linked with schizophrenia and containing promising candidate genes. We estimate that by generalising this approach to a larger sample of families, and by combining linkage and association (linkage disequilibrium) approaches, we can achieve > 90% power of reliably identifying and validating susceptibility genes in schizophrenia. The essence of the proposed work plan for 3 years consists of:

• Recruitment of >800 nuclear families, each including a proband with schizophrenia, two parents (at least one of them unaffected); at least one sibling (affected or unaffected); and collection of blood samples from all participants.

• Comprehensive clinical characterisation of the probands and the rest of the family members for current and past psychopathology.

• Neurocognitive assessment of the >800 proband-sib pairs and identification of multivariate patterns of test performance and deficits as phenotypes allowing clustering the participants into discrete subtypes. A smaller (N = 200) sample of unrelated, healthy community controls will also be assessed to provide additional normative data on the neurocognitive traits.

• Fine-mapping (FM) genotyping of all families, using panels of microsatellite markers and single nucleotide polymorphisms (SNP), in the candidate regions on chromosomes 6p, 8p, 10p and 10q which have shown the highest lod scores in the original Western Australian sample of families.

• Applying (a) parametric and non-parametric linkage analysis; (b) linkage disequilibrium case-control analysis, focusing on identity-by-descent (IBD) allele sharing and utilising transmission disequilibrium tests (TDT) where the parents provide internal controls.

• Depending on the results of these last stages (i.e. successful identification of highly plausible candidate genes), we will consider applying for further funding to initiate gene expression and functional studies leading to complete characterisation and validation of susceptibility genes.

Expected outcomes. Large-scale studies of this kind have not been done until now. Within a given outlay of resources, the model of collaboration we are proposing is a highly cost-effective way of developing a research resource of

national and international significance that will be a major step towards align schizophrenia research with the advances in the study of other complex diseases. Therefore, it is in the long-term public interest to create in Australia a high-quality research database on schizophrenia, and to lay down groundwork for future theoretical and practical applications, including intellectual property and commercialisation prospects.

PLANNED TECHNIQUES AND METHODOLOGIES

We envisage participation of five catchment areas across Australia (Brisbane, Hobart, Newcastle, Perth and Sydney), with a total population of 4,107,000. Each area has a network of clinical services providing assessment and treatment of patients with psychotic disorders.

Case definition and inclusion/exclusion criteria for probands through whom nuclear families will be ascertained. "Affected"case: (i) a proband meeting both ICD-10 and/ DSM-IV criteria for schizophrenia (see Table 1); (ii) age 15 – 54; (iii) length of illness since first treatment contact not less than 6 months and not exceeding 10 years; (iv) no evidence of organic brain disease or injury; no evidence of substance abuse of a degree and duration that may explain the psychotic symptoms; (v) having two parents and at least one sibling potentially available for recruitment. The criterion of ≥6 months since first contact is chosen to reduce the rate of false-positive and false-negative diagnoses (the rate of diagnostic error drops sharply after 6 months of symptom duration). The limit of 10 years length of illness will reduce the confounding of the phenotype by risk factors, such as chronic substance use, effects of medication, or psychosocial adversity(Tsuang et al., 1995).

Table 1: Inclusion / exclusion criteria

DSM-IV	ICD-10
Two or more of the following, each present during a 1-month period: • Delusions; hallucinations; disorganised speech; grossly disorganised or catatonic behaviour; negative symptoms (affective flattening, alogia or avolition) • Social or occupational dysfunction •Continuous signs of disturbance persist for at least 6 months. **Exclusions:** • Schizoaffective and mood disorder • Symptoms not explained by substance or general medical condition • Pervasive developmental disorder	At least one of the following present for at least 1 month: • Thought echo, insertion, withdrawal, broadcasting; delusions of control, influence or passivity; hallucinatory voices giving a running commentary; persistent delusions, culturally inappropriate; Or at least two of the following: • Persistent hallucinations in any modality; neologisms, incoherence or irrelevant speech; catatonic behaviour; negative symptoms (apathy, paucity of speech, emotional blunting) **Exclusions:** Mood disorder Symptoms not attributable to organic brain disease or drug-related intoxication, dependence, withdrawal

Sampling design. A sampling protocol will be established, based on genetic epidemiological case-control considerations. There will be two groups of controls: (i) internal (family) controls – the biological parents with whom the proband shares 100% of genetic background; (ii) a smaller group (N = 200) of external, unrelated controls recruited from the same community and group-matched with the probands on age, sex and education. The sets of probands with their parents as internal controls will constitute genetically informative triads for allelic association studies and transmission disequilibrium tests (TDT). The latter are the genetic equivalent of the randomised trial, since each of the 2 alleles in a parent has an equal chance of being transmitted to the offspring (Clayton & McKeigue, 2001). External controls (not to be included in the genetic analysis) will provide normative neurocognitive data within the age-specific performance range of the probands. The set of triads as defined above will provide the robust core of the study sample, ensuring more than adequate power for conclusive data analyses. Over and above the number of such proband-parents triads, we will recruit and assess on the neurocognitive measures at least one sibling. The assessment of siblings is critical to the identification of heritable neurocognitive phenotypes and can boost dramatically the power of the analysis (Dolan et al., 1999).

Power estimates and needed sample size. In order to detect linkage disequilibrium between genotypes and schizophrenia, we will employ family-based association and case-control analyses, using the transmission disequilibrium test (TDT). The basic concept of the TDT is that marker alleles have a high probability of being transmitted to affected offspring (Spielman et al., 1993). TDT is a test of both linkage and linkage disequilibrium and measures distortion of the inheritance of alleles from parents to an affected offspring, i.e. whether the frequency of transmission of alleles from heterozygous parents to their affected children deviates from the expected 50% frequency when there is no linkage. Since TDT is robust to nonrandom mating, it can be extended to families with more than one affected child. In the instance of not obtaining blood samples from some of the parents, we will also employ a design using unaffected sibs as controls. Power was calculated using the TDT power calculator (Chen and Deng, 2001) and formulas

provided in Risch and Teng (1998). Excerpts from the power analysis are shown in Table 2.

Table 2: Power estimates with 2 alternative configurations of affected families

Full sample	N	Power	Pop Freq	f1	f2	f3	f1/f3	f2/f3	D
Trios (2 parents + affected child)	800	1.00	0.1	0.050	0.025	0.006	8	4	0.01
		1.00	0.1	0.025	0.025	0.006	4	4	0.01
		0.89	0.1	0.033	0.017	0.008	4	2	0.01
		1.00	0.3	0.044	0.011	0.003	16	4	0.01
		1.00	0.3	0.028	0.014	0.003	8	4	0.01
		1.00	0.3	0.016	0.016	0.004	4	4	0.01
2 parents + child	600	1.00	0.1	0.050	0.025	0.006	8	4	0.01
1 parent + sibs	200	1.00	0.1	0.025	0.025	0.006	4	4	0.01
		0.78	0.1	0.033	0.017	0.008	4	2	0.01
		1.00	0.3	0.028	0.014	0.003	8	4	0.01
		0.99	0.3	0.024	0.012	0.006	4	2	0.01
		0.99	0.5	0.018	0.009	0.004	4	2	0.01

The disease frequency in the population is assumed to be 0.01. Power is calculated for: (a) a sample size of 800 triads, each comprising an affected proband and 2 parents; and (b) a combination of triads (N=600) and sets of relatives (N=200), each consisting of proband, one parent and one sibling. Similar calculations are presented for a subset of the total sample, selected on a hypothetical phenotype expressed in 30% of probands. The calculations indicate that nearly 100% power to detect a susceptibility gene using TDT will be achieved with either 800 complete parental trads, or with a mixed sample containing 600 parental trads and 200 sets of a single parent plus one sib (in addition to the affected proband). Adequate power will also be available to detect the genetic basis of correlated phenotypes expressed by 30% of the subjects or less.

Sample size, recruitment targets and caseloads. Conservative estimates, based on the Australian National Survey of low-prevalence (psychotic) disorders (Jablensky et al., 1999; 2000), of the likely number of cases per year suggest that: (a) if schizophrenia makes up ~ 70% of all the cases of psychoses, there will be at least 530 potential recruits per year; (b) if 10% have no sibs and no parents, the figure drops to 477 per year; (c) if the refusal rate is 25%, the annual intake could be about 360 per year. This indicates that the target sample size can be reached and even exceeded within 3 years. Table 3 details the target recruitment numbers and projected caseloads per centre over the total duration of the project. The final sample size will be greater since the 150 nuclear families (> 450 subjects), already assessed in Perth, will be added to the analysis.

Table 3: Population of catchment areas and target recruitment

Centre	Total population ('000s)	Recruitment targets for 3 years			
		N affected probands	N parents	N sibs	Total N of subjects
Brisbane	841	150	300	150	600
Hobart	470	100	200	100	400
Newcastle	540	200	400	200	800
Perth	591	150	300	150	600
Sydney	1665	200	400	200	800
TOTAL	**4107**	**800**	**1600**	**800**	**3200**

Case detection, recruitment & retention strategy. Cases will be detected at service entry points, such as community mental health clinics, inpatient units, outpatient departments of hospitals and general practices. A systematic approach will be adopted, involving administration of two "first-line" instruments: (a) Psychosis Screener (a modified version of the screener used in the Australian National Survey, sensitivity 0.67, specificity 0.84), administered by a case worker (15 min); (b) Family ascertainment: the NIMH Family Interview for Genetic Studies (FIGS), administered by a research assistant (45 min), will provide an overview of the structure, composition and morbidity of the entire pedigree, of which the ascertained family with affected proband is part. An informed consent form and information sheet will be given to those meeting the inclusion / exclusion criteria. To improve retention rates, participants will be offered a small fee for their participation, and periodic contact will be maintained via phone calls and a newsletter.

Diagnostic assessment and clinical description. The following assessment instruments will be administered within 2

weeks of recruitment: (1) the WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN, WHO, 1995); (2) the WHO Psychiatric and Personal History Schedule, modified to include the Queensland Inventory of Risk Factors; and (3) assessment of temperament and personality traits using the Temperament and Character Inventory (TCI, Cloninger et al., 1994); and the Schizotypal Personality Questionnaire (SPQ, Raine, 1991). ICD-10 and DSM-IV diagnoses will be generated by computerised diagnostic algorithms linked to the SCAN and checked for validity by senior clinicians reviewing all data. At least 10% of all SCAN interviews at each site will be videorecorded for diagnostic reliability assessment. Site investigators will gather from the services follow-up data on short-term course and outcome and on pharmacological treatments, as additional clinical descriptors and potential covariates in the analysis of neuropsychological and electrophysiological data.

Neurocognitive assessment. Neurocognitive deficits are likely to be more closely related to neurobiological processes that lie at the core of schizophrenia than are the clinical symptoms used in diagnosis. The selection of sets of specific tasks for the neurocognitive assessment battery was guided by several validity criteria that are in addition to the standard requirements for reliability, sensitivity and lack of significant floor / ceiling constraints. These criteria included: (i) mediation of the performance on the selected tasks by partially different brain systems; (ii) suitability for a fine-grained description of component neurocognitive processes; (iii) relationship of the task to functional networks or subdivisions recently identified by PET of fMRI studies; (iv) evidence of heritability, according to the literature and our own data. As a result of such selection, all patients, relatives and controls will be offered a battery of tasks targeting selected functions (Table 4) and administered in two sessions of 1hour each.

Table 4: Neurocognitive assessment battery

Cognitive function	**Task / paradigm**
Sustained attention	Continuous Performance Task, Identical Pairs (CPT-IP)
Divided attention	Dual Task paradigm
Spatial working memory	Visual Patterns Test
Working memory capacity	Digit span
Planning	Tower of Hanoi task
Sequencing	Trails B
Verbal fluency	Phonemic and semantic verbal fluency tasks
Inhibition of a prepotent response	Hayling Sentence Completion Test; Visual Delayed Response task
Choice reaction time	Posner paradigm (visual targets)
Episodic memory and recall intrusions	Rey's Auditory Verbal Learning Task (RAVLT)
Premorbid general ability (IQ)	National Adult Reading Test (NART)
Current general ability (IQ)	WAIS-R
Motor speed	Finger tapping task
Laterality / handedness	Edinburgh Handedness Inventory

Constructing composite quantitative traits. The integration of multi-domain neuroscience measurements into quantitative traits for genetic analysis is an important objective. We have extensive experience with methods derived from latent class (LCA) models, in particular the grade of membership (GoM) methodology, through a collaboration with M. Woodbury and E. Corder at Duke University (Manton et al, 1994; Jablensky & Woodbury, 1995). This methodology is particularly well suited since it allows the determination of a multivariate profile of characteristics for a group, and the degree to which each individual is described by that profile. Each individual is assigned to several analytically derived "pure types", and the degree to which an individual expresses any given pure type is quantified by a coefficient (probability) of membership (Woodbury et al., 1978). The method has been successfully used to map the IDDM11 locus in diabetes (Corder et al., 2001). In a recent analysis of the current WA database on families with schizophrenia (Hallmayer et al., 2003) we used GoM coefficients as genetic scores of a composite neurocognitive trait. In this project, we will use GoM, as well as alternative methods for integrating multiple measurements, e.g. those based on canonical correlation and canonical discriminant analysis (Morrison, 1976).

DNA collection and storage. Blood samples (30 ml) will be obtained from all family members at the time of interview. Frozen blood samples will be shipped to the Neurogenetics Laboratory in Perth where DNA will be extracted. The amount of DNA we routinely obtain from 20 ml of blood is sufficient for at least 10 000 genotypes.

BUDGET Table 5. Budget estimates for the total cost of the project

Research staff / job description	
Case finding, recruitment, assessment	10 FTE x PSP2 ($50,000 p.a.) = $500,000 x 3 years = $1,500,000
Genetic analysis	1 x PSP 5 ($75,000 p.a.) = $75,000 x 2 years = $150,000
Lab technician	1 x PSP 2 ($50,000 p.a.) = $50,000 x 3 years = $150,000
Central database management for the project	1 x PSP3 ($55,000 p.a.) = $55,000 x 3 years = $165,000
TOTAL research staff over 3 years	**$1,965,000**

Direct research costs

Clinic staff / GP fee for screening patients	$20 per proband screened and referred x 800 = $16,000
Reimbursement of travel to families	$50 per family x 800 = $40,000
Genotyping (AGRF) ~50 markers per subject	$250 per subject x 3,200 = $800,000
TOTAL direct research costs over 3 years	**$856,000**
TOTAL project budget over 3 years	**$2,821,000**

Significance and relevance of the program. There are compelling socioeconomic, scientific and mental health policy reasons for proposing a major national research effort targeting schizophrenia. There is growing interest worldwide in establishing very large DNA databases linked to data on clinical outcomes in common diseases such as cancer, IHD or asthma, as platforms for the application of genetic, genomic and computational research strategies and high-throughput technologies to unravel the molecular aetiology of complex morbidity. Psychiatric disorders must not be left out of this development. The advantage of the proposed research strategy is in the implementation of a design that will maximise the chances that genes conferring susceptibility to schizophrenia will be detected and isolated using the database generated by the project. It is in the long-term public interest to create in Australia a high quality research database on schizophrenia that would allow us to resolve within the next a number of critical issues in the genetic epidemiology of the disorder, thus laying down the groundwork for future expression and functional studies.

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APPENDIX 2

GENETIC ANALYSIS

There are a number of approaches to recruiting samples for identifying susceptibility genes for complex diseases such as schizophrenia (SZ) and bipolar disorder (BPD). The first is to recruit one or a small number of very large pedigrees containing many people affected with the disease of interest. This approach has led to gene discovery in diseases such as Huntington's chorea, and Alzheimer's disease however, this has not been fruitful to date in psychiatric disorders such as SZ or BPD. Secondly, given the rarity of large dense pedigrees for these disorders, research groups have focused on recruiting very large numbers of sibpair pedigrees (i.e. families with two or more siblings affected with illness). Results of these studies have implicated a modest number of chromosomal regions across the genome as candidates for more detailed "fine mapping" studies aimed at isolating the causal genes.

Thirdly, research groups conduct more refined mapping studies of candidate regions and hypothesised candidate genes using single nucleotide polymorphism (SNP)-based association studies (looking for association between disease and a particular allele). There are two types of these studies: (a) Family-based association methods, based on the Transmission Disequilibrium Test (TDT) model, can avoid false positive findings due to ethnicity-based case-control marker allele frequency differences, since these methods employ internal family controls in the form of alleles which are not transmitted to the affected child and which are controls for those alleles transmitted to the affected child; (b) however, the advantages of case-control designs are being increasingly recognized. For adult-onset diseases, case-control studies can most easily achieve the very large sample sizes (thousands) required to detect the small genetic effects expected in complex diseases. Samples collected from specific ethnic groups can be studied while allowing for genetic substructure with methods such as "genomic control" which detects associated loci as outliers against a background of smaller case-control allele frequency differences, or "structured association" which divides cases and controls into subgroups based on allele frequencies at neutral loci prior to association analysis. A number of single and multilocus linkage disequilibrium-mapping methods for case-control data have recently been described, and the integration of association and linkage analyses represents a particularly promising approach. Some of these rapidly-evolving methods can be applied to enhance the power of case-control analyses.

Budget:

(1) Sample recruitment and blood sample processing: Funding is needed to recruit and diagnostically ascertain the samples, and to transform cell lines and to extract DNA in preparation for genetic analyses.

Cohort: 1000 patients, 1000 controls
Example: Clinical recruitment and diagnosis: 6 RAs x 55,000/RA = $330,000
2000 individuals x $30/individual for cell line construction and DNA extraction = $60,000

(2) Genetic analysis: The two most attractive options are: to screen using SNPs (a) the best-ranked candidate regions for SZ and BPD prioritised by support from meta-analyses and recent genome scans, and conduct high resolution fine-mapping. Single-marker, haplotype-based and structured association (if required) LD analyses of a number of genes in the region would follow, with genes prioritised on prior evidence, potential biological relevance, and available SNP information. Since haplotype structure is variable, between 5 and 10 SNPs per gene would be chosen based on prior evidence, allele frequencies, and position in the gene; (b) candidate genes: we would type 5-10 SNPs per gene according to prior evidence, allele frequencies, and gene position. Additionally, we could consider a third option, using DNA pooling to conduct a genome-wide association scan for each disorder.

Cohort: 1000 patients, 1000 controls:
Example one: One candidate gene:
10 SNPs x 2000 individuals x $0.30/SNP = $6000; 10 SZ genes + 10 BPD genes = $120,000

Example two: 1 candidate SZ region + 1 candidate BPD region:
50 initial screen SNPs + 50 fine mapping SNPs x 2 = 200 SNPs x 2000 x $0.30/SNP = $120,000

Example three: 100,000 SNPs for genome wide association scan (using DNA pooling) = 2 pools x 100,000 SNPs x $4 = $800,000

APPENDIX 3

Supplementary details of the Neurocognitive Assessment drafted for the Genetic Epidemiology Program. Please refer to Appendix 1, Table 4.

Cognitive Neuroscience: Cognitive deficits are likely to be more closely related to neurobiological processes that lie at the core of schizophrenia than are the clinical symptoms used in diagnosis. In this section we outline the cognitive deficits that have been implicated in schizophrenia, and a set of instruments and procedures for measuring these cognitive deficits behaviourally and their neurobiological basis. Domains of cognition that are most consistently affected in schizophrenia are working memory and inhibition, context processing, learning and memory, and speed of processing.

Cognitive Assessments: The selection of specific tasks for the cognitive assessment battery has been guided by several criteria in addition to the standard requirements for reliability, sensitivity and lack of significant floor / ceiling constraints, including : (i) coverage of the domains of cognition affected in schizophrenia, (ii) evidence of specificity in comparison to bipolar patients, (iii) use of standardized neuropsychological tasks supplemented by tasks that have been refined and validated over decades of research by experimental psychology (iv) suitable for investigation using a combination of structural and functional neuroimaging measures; (v) evidence of heritability and (vi) potential to be investigated using animal models. As a result of such selection, all patients and case controls will be offered a battery of tasks targeting selected functions (Table 4A) and administered in two sessions of 1 hour each.

Table 4A: Cognitive assessment battery

COGNITIVE FUNCTION	TASK /PARADIGM
Working memory	Visual working memory: spatial span task Verbal working memory: Digit span (forwards and backwards) and letter number sequencing
Inhibition	Motor inhibition: Stop signal task (or Go/NoGo task); Cognitive inhibition: Haylings sentence completion task Interference control: Stroop task
Context processing	Modifed A-X Continuous Performance Task (AX-CPT)
Verbal memory and learning	California Verbal Learning Test – Second edition (CVLT-II): shortened form
Speed of Information Processing	Inspection Time task
Premorbid general ability (IQ)	Weschler Test of Adult Reading (WTAR)
Current general ability (IQ)	Weschler Abbreviated Scale of Intelligence (WASI): either 2 or 4 subtest form
Laterality / handedness	Edinburgh (or Annett) Handedness Inventory

Neurobiological assessments: Three methodologies are to be employed to investigate the neurobiology of cognitive deficits in schizophrenia: MRI derived measures of regional grey-matter volume loss indicative of neuroanatomical abnormalities, functional MRI derived measures of regional areas of activation and electrophysiological measures of brain function. The selection of assessment procedures has been guided by (i) data on separable functional roles of regional areas showing grey matter volume loss prior to the first episode of psychosis (ii) functional brain measures of cognitive domains affected in schizophrenia (iii) evidence of specificity relative to patients with bipolar illness and (iv) evidence of heritability. Twenty percent of the cohort will be selected into the neurobiological component of assessment protocol from those sites with suitable facilities (Table 4B) in two sessions, an MRI session of one hour duration and an electrophysiological session of two hours duration:

Table 4B: Neurobiological Assessments

NEUROBIOLOGICAL MEASURE	METHOD
Regional grey matter volumes	High resolution structural MR images with voxel based morpho metric analysis
Functional integrity of right inferior frontal gyrus during motor inhibition	Event-related fMRI investigation of motor inhibition (Stop signal task or Go/NoGo task)
Functional integrity of anterior cingulate during interference control	Event-related fMRI investigation of Stroop task

Pre-pulse inhibition	Inhibition of blink reflex to startling sounds by weak auditory pre-pulse
Auditory context processing	Mismatch negativity (MMN) to low and high probability deviant sounds

Table 4C: Implementation costs:

ITEM	COST PER SITE
Neuropsychological tests	$6000
PCs for running computerized tasks	$2500
Costs of software development (CPT-AX, IT task, Stroop etc)	$5000
Total per site	**$9500**

Table 4D: Costs per participant*

ITEM	COST PER PARTICIPANT
Record Sheets for Neuropsychological tests	$30
Research Assistant for Cognitive Assessments (@ approx $30 per hour) plus scoring, verification and data entry	$240
MRI sessions on 1.5T scanner	$600
ERP consumables	$50
Research assistant for volumetric analysis inc attendance at scanner session	$600
Research assistant for analysis of fMR images	$300
Research assistant for recording and analysis of electrophysiological sessions	$200
Total per site for Cognitive Assessment per participant	**$270**
Total per site for Neurobiological Assessment per participant	**$1,750**

**Does not include recruitment costs, re-imbursement of participants and other infrastructure*

APPENDIX 4

DEVELOPMENT OF A MEANS TO IDENTIFY CHILDREN AND ADOLESCENTS AT HIGH RISK OF SCHIZOPHRENIA AND RELATED DISORDERS

BACKGROUND

The focus of early intervention for schizophrenia and related disorders has been pushed back from first episode psychosis to the identification of 'ultra-high risk' or 'prodromal' individuals presenting to clinical services. Can it be pushed back further to the identification of symptomatic adolescents at 'ultra-high risk' *prior* to them reaching the usual threshold for specialist referral (ie, pre-prodromal)? This is the subject of a current research project (Yung et al). Can it be pushed back even further to prepubertal children who display the risk factors for psychosis described in studies of the childhood antecedents of schizophrenia?

The further we move backwards on the developmental path from established diagnoses of schizophrenia in adolescence or early adulthood, the more we lose in diagnostic specificity and the more likely we are to identify individuals with vulnerabilities to a range of neuropsychiatric disorders. But is this necessarily a 'bad thing'? Schizophrenia and many other psychiatric syndromes overlap with each other in symptomatology. Likewise, there are no clear boundaries between schizophrenia, schizophrenia spectrum disorders, certain other neuropsychiatric disorders (eg, bipolar disorder) and healthy individuals in terms of neurocognitive functions, neurodevelopmental anomalies, psychophysiological indices, structural and functional brain changes and genetic factors. Neither are treatments diagnostically specific. In other words, schizophrenia and other neuropsychiatric disorders, as defined in current nosological systems, have not been validated by any conventional criteria, notwithstanding more than a century of effort. Perhaps it is time for a new approach, to step back from diagnosis as the first point of reference in the search for aetiology and pathogenesis, and instead begin with putative risk factors in a population, study their biological and functional correlates, and measure the clinical outcomes. That is, take a 'bottom-up' approach rather than a 'top-down' approach. Being outside the conventional way of doing things, this is a potentially high-risk strategy.

Growing epidemiological, genetic and clinical neurobiological evidence indicates that neurodevelopmental abnormalities are antecedents of schizophrenia. Similar evidence, although less extensive than that reported for schizophrenia, indicates that neurodevelopmental abnormalities are also antecedents of other neuropsychiatric disorders including affective psychosis, other psychoses, conduct or personality disorders, substance abuse and learning disorders. Efforts to identify the antecedents of psychosis have mainly been directed to schizophrenia, however, and fall into three main categories: high-risk, follow-back and follow-up studies. Most *high-risk* studies define risk status on genetic grounds, selecting offspring of parents with schizophrenia and following the cohort through adulthood and the period of risk of onset of psychosis. The *follow-back* strategy involves the use of contemporaneous records (eg, school reports, childhood home movies, medical records) to examine the childhood characteristics of individuals who have developed a psychotic illness later in life. Variants of this strategy include parental recall of childhood antecedents after the development of psychosis in their offspring and the retrospective analysis of information collected on population cohorts of military recruits who subsequently developed schizophrenia. The *follow-up* strategy entails prospective evaluations of children seen initially in child health clinics, children identified by population screening methods, or birth cohorts.

Schizophrenia risk factors and/or antecedents have been identified in the following broad categories: family history, maternal malnutrition, season of birth, urban birth, migrant/minority status, perinatal complications, neurodevelopmental deficits, family dysfunction, and social or behavioural maladjustment.

Neurodevelopmental dysmaturation

Neurodevelopmental immaturity (impaired motor skills and coordination, lower verbal IQ, visuospatial problems), attention deficits, and abnormalities in interpersonal relations (social ineptness and aggressive behaviour in males, social isolation and withdrawal in females) were identified 20 years ago among the childhood antecedents of schizophrenia. Since that time the literature has expanded on these themes and the early research of Fish on 'pandysmaturation' has set the scene for subsequent work that has adopted a broader concept of neurointegrative dysfunction in schizophrenia - neurodevelopmental dysmaturation.

Impaired intellectual functioning in preschizophrenic children is well established. An inverse relationship has been reported between IQ and risk for schizophrenia, and a similar but weaker relationship between low IQ and risk for affective psychoses. In addition, deficits in particular functions have also been identified in preschizophrenic or high-risk children and adolescents, including impaired verbal and mechanical skills, poor organisational abilities, speech problems, impaired verbal memory and attention, impaired working memory, and other perceptual and cognitive deficits. However, the non-specificity of these particular deficits is illustrated by the evidence for premorbid language delay in adult onset affective disorder and speech defects in childhood affective disorder. Impairments in intellectual function are reflected in lower educational achievement at school in premorbid individuals or children at

high risk for schizophrenia, particularly males, who are more likely to repeat a grade. Again, the non-specificity of lower educational achievement is reflected in the finding of low childhood premorbid education test scores in adult-onset affective disorder and the higher rates with which adults with schizophrenia, other psychoses and non-psychotic disorders have been in a class inappropriate for their age in school.

Impaired neuromotor development in premorbid and high-risk groups for schizophrenia is also a consistent research finding, including delay in the achievement of motor milestones and abnormal motor signs, particularly in motor coordination. Delayed motor development is reflected in the impaired performance of children premorbid for schizophrenia in tasks requiring good fine and gross motor coordination such as handicrafts and sport. However, delayed motor development has also been identified in children who develop childhood affective disorder and adult affective disorder. In addition, perceptual-motor disturbance has been reported in children who later develop affective disorders, personality disorders and other psychopathology.

Neurological 'soft' signs in established schizophrenia can be interpreted as a further manifestation of neurodevelopmental abnormality in this disorder. The rate of abnormal neurological signs in schizophrenia may be as high as 50-65%. Abnormalities can be in the areas of sensory integration, sequencing of complex motor actions, and motor coordination. Although these signs are relatively common in schizophrenia, they also occur with lesser frequency in other conditions such as bipolar disorder and substance abuse. Neurological 'soft' signs in schizophrenia have variously been related to premorbid asociality, neuropsychological performance, negative symptoms, disorganisation symptoms, earlier age of onset, treatment responsiveness, poor outcome, obstetric complications (males), ventricular enlargement and family history in females. The neurological abnormalities identified in adults with psychoses are similar to those identified in premorbid and high-risk populations.

Electrophysiological indices of neurocognitive impairment in schizophrenia have also been well established such as P300, mismatch negativity (MMN) and sensorimotor gating (PPI). These indices have been shown to be closely associated with abnormal brain maturation, as well as early onset of psychotic illness (particularly in males), cognitive deficits, negative symptoms, reduced responsiveness to antipsychotic drug treatment and poor prognosis. Saccadic intrusions into smooth pursuit eye movement (SPEM) have also been well described in schizophrenic patients, their first degree relatives and those at genetic risk of schizophrenia.

Poor premorbid social adjustment

Several studies of premorbid functioning among high-risk groups have identified social maladjustment and behaviour problems. Antecedents to schizophrenia in males include poorly socialised aggressive conduct, feelings of isolation, vulnerability and rejection, and poor peer relationships; in females antecedents include shyness, passivity and seclusiveness. Male children who later develop schizophrenia have also been described as disagreeable, negativistic, egocentric and antisocial, and females as quiet, introverted, passive and emotionally unstable. By adolescence males were described as irritable, aggressive and defiant of authority, while females showed increased shyness and introversion. Other differences reported include: overreactivity in males and withdrawal in females; and loneliness, rejection, inappropriate behaviour and discipline problems in males, with nervousness and passivity in females. Findings unrelated to gender include various behaviour problems, impaired social functioning and, at a more fine-grained level, preference for solitary play and social anxiety, and socialising only in small groups and having less than two friends. These behaviours are not specific for schizophrenia, however. A relationship has been identified between premorbid adjustment and risk of both schizophrenia and bipolar disorder, although the relationship is stronger for schizophrenia. A delay in the acquisition of social skills has also been reported in relation to affective psychosis, premorbid behavioural problems have been found in affective disorder and personality disorder, and premorbid social maladjustment has been identified in relation to neuroses.

Family dysfunction and psychosis

Aside from the work on 'expressed emotion' in relation to relapse of schizophrenia, empirical studies are sparse in this area. In the high-risk literature, inconsistent parenting, overinvolvement, and hostility towards the child have predicted schizophrenia spectrum outcomes. Among adolescents, those whose families showed high levels of communication deviance (lack of a shared focus in communication) and a negative affective style (negative, critical, intrusive, guilt inducing attitudes) developed schizophrenia spectrum disorders. Communication deviance, expressed hostility, and overinvolvement characterised families in which offspring developed schizophrenia. Recently a Finnish adoptive study found an interaction between genetic risk for schizophrenia and family characteristics of 'critical/conflictual' behaviours, 'constricted' emotional style and 'boundary problems.'

Summary

A number of antecedents and risk factors for schizophrenia have been identified, but they are not specific to this disorder and underlie a broader spectrum of neuropsychiatric morbidity, including affective psychoses, other psychoses, conduct or personality disorders, substance abuse and, probably, learning difficulties. Neurodevelopmental

dysmaturation appears to be an antecedent of a number of major neuropsychiatric disorders having their onset in adolescence or early adulthood, of which schizophrenia is the most frequently studied and apparently the one in which neurodevelopmental dysmaturation is the most prominent. Consideration should be given to the possibility of a hierarchy of disorders from some 'neuroses,' through various developmental conduct or behavioural syndromes and learning difficulties, to certain affective disorders, the psychoses and schizophrenia, reflecting increases in degree and complexity of neurodevelopmental dysmaturation.

The brain may have a limited number of pathophysiological pathways that lead from neurodevelopmental disturbance to a variety of outcomes or some combination of outcomes. In a proportion of individuals, attention, cognition and motor control may improve with time so that they 'normalise'. A strategy to increase the power to detect individuals at risk of schizophrenia and other major neuropsychiatric disorders may therefore be to identify those individuals most likely to experience persistent neurodevelopmental and cognitive abnormalities. Deteriorating social adjustment may be another marker of risk. Thus, a population screening strategy that identifies children with evidence of neurodevelopmental dysmaturation and provides some measure of poor (or declining) functioning may increase the power to detect children who go on to develop a range of early onset severe neuropsychiatric disorders, including schizophrenia and related disorders.

PROPOSAL

The eventual aim of this proposal is to **screen** a population of year 4-5 children (aged 9-10 years) and year 9-10 adolescents (age 14-15 years), select a sample with evidence of neurodevelopmental dysmaturation and related risk factors for schizophrenia and a random sample of children of the same age, and then undertake a cohort study with regular contacts and periodic reassessments through the years of maximum risk of onset of psychosis. Subsequent to selection, participants would be assessed, directly and through informants or school records, on a variety of instruments to measure: family history, perinatal complications, developmental milestones, social adjustment, educational performance, family functioning, motor coordination, neurological soft signs, minor physical anomalies, neurocognitive functioning and psychological symptoms. Electrophysiological studies may be performed on representative subsamples to measure P300, MMN, PPI and SPEM. At later reassessments blood would be taken from participants and two first degree relatives for genetic studies, and functional brain imaging studies would be performed on representative subsamples. The periodic reassessments would occur every two years and include clinical interviews and other measures as may be deemed appropriate.

Alternatively, a **screener** – if reliable and valid – could be used in existing longitudinal samples (eg, Longitudinal Study of Australian Children), clinical samples, family studies and other settings.

The feasibility of the above hinges on the screening instrument. Currently there is no known, reliable and valid screening test for neurodevelopmental dysmaturation and related risk factors for schizophrenia. This problem must be solved before consideration can be given to undertaking a longitudinal study.

Accordingly, funding is currently sought for the following: -

Aims

1. To develop a screening instrument for the identification of neurodevelopmental dysmaturation and related risk factors for schizophrenia in children and adolescents.
2. To determine the prevalence of neurodevelopmental dysmaturation and related risk factors for schizophrenia in children and adolescents using the above instrument.

METHOD

OVERVIEW

Year 1:

1. Review the literature on childhood and adolescent assessment instruments that may be capable of identifying neurodevelopmental dysmaturation in light of the published literature on antecedents and risk factors for schizophrenia.
2. Construct provisional rating scalef for parents and teachers and for adolescents that are likely to identify neurodevelopmental dysmaturation and related risk factors for schizophrenia (and which includes a broad cross-section of items, including approximately twice as many items as that desired for the final scale).
3. Test the rating scale for feasibility of administration by parents, teachers and adolescents.

Year 2:

4. Administer the provisional rating scales to a representative sample of families with a 9-10 year old child and to adolescents aged 14-15 years. Undertake a preliminary examination of the psychometric properties of the items

in the provisional rating scales, including item and distributional characteristics, parent-parent concordance, parent-teacher concordance, test-retest reliability and internal characteristics of the provisional subscales.

5. Invite a stratified sample of these families to participate in a more detailed assessment using objective measures of neurodevelopmental dysmaturation and related risk factors for schizophrenia, including family history of psychiatric disorder, developmental milestones, social adjustment, educational performance, motor coordination, neurological soft signs, minor physical anomalies, self-reported psychosis-like symptoms, parent and teacher rated psychological symptoms, neurocognitive functioning and electrophysiological measures (P300, MMN, PPI, SPEM).

Year 3:

6. Determine the validity of the rating scales against the detailed measures, use this information to derive an abbreviated screening questionnaire, and report on the prevalence of neurodevelopmental dysmaturation in the original sample.

Subjects

1. Potential participants to be screened will be all children in years 4-5 (aged 9-10 years) and adolescents in years 9-10 (aged 14-15 years) at a set of representative schools in each of 4 centres to achieve a total sample of 2,000 participants, together with their approximately 3,500 parents/guardians and 64 teachers (children in years 4-5 only).
2. Exclusion criteria will be cerebral palsy, identified mental retardation and full-time presence in special education classes.
3. Approximately 600 participants will be selected for Stage 2 (the validation study), using a stratified selection procedure, with oversampling of those likely to experience higher levels of neurodevelopmental dysmaturation (see Table 1).

Table 1. Indicative Budget

BUDGET ITEM		YEAR 1	YEAR 2	YEAR 3
Personnel Costs (including 20% 'on costs')				
Project Officer (& Centre A) (HEW 7, Step 1)		$60,500	$62,500	$64,500
Research Assistant – Centre B (HEW 6, Step 1)			$55,000	
Research Assistant – Centre C (HEW 6, Step 1)			$55,000	
Research Assistant – Centre D (HEW 6, Step 1)			$55,000	
Casual Clerical/Data Management Support (HEW 5, Step 1) (1,000 hours in Year 2, and 500 hours in Year 3 @$30 per hour)			$30,000	$15,000
Casual Medical Officer (Stage 2: 544 assessments x 30 min. + 10 min. = 364 hours @$70 per hour)			$25,480	
Casual Neuropsychologists (Stage 2: 544 assessments x 90 min. + 30min. = 1,088 hours @$45 per hour)			$48,960	
	Sub-Total	**$60,500**	**$331,940**	**$79,500**
Maintenance Costs				
Stage 1:				
Printing, Postage, Reminders, etc (Stage 1) @$3.00 per participant x 6,400 participants			$9,600	
Return Postage and Voucher Return @$1.70 x 2,400 + 1,800			$7,140	
Administrative allowance to schools for distribution of letters and screening questionnaires and completion of teacher ratings (@ $15 per student x 3,200 students)			$48,000	
Reimbursement to Parents – in the form of Cinema Vouchers upon questionnaire return (@ $10 per parent x 1,200 + 900 questionnaires)			$21,000	
Stage 2:				
Printing, Postage, etc (Stage 2)			$500	
Reimbursement to Participants - @$50 for full (5 hour) assessment x 544 participants			$27,200	
(The majority of Stage 2 contacts will be by telephone)				
Equipment & Software Contribution/Support				
$30,000 x 4 Centres		$120,000		
	Sub-Total	**$120,000**	**$113,440**	**$0**
(Grand Total: $705,380)	**Total**	**$180,500**	**$445,380**	**$79,500**

APPENDIX 5

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