

NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Basic Research (Session 1A)

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Background

Basic research is a broad domain that includes molecular, cellular, systems and behavioural neuroscience. Often research is conducted in non-human species in order to capitalise on invasive techniques, and better control environmental and developmental variables. Within the mental health space, basic research aims to understand the underlying neurobiological mechanisms that lead to psychiatric disorders. This can be via studies to understand fundamental aspects of brain function and development, using models to establish the plausibility of genetic and/or environmental risk factors, and assessing the viability of target compounds prior to Phase 1 clinical trials. The summation of these avenues of exploration is evident in the fact that most scientific breakthroughs of the past century were built on the groundwork of basic research.

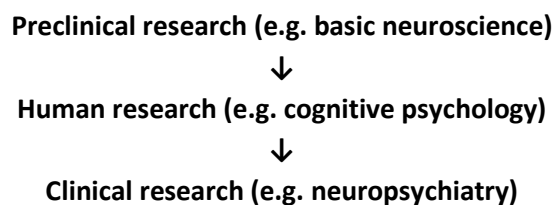
Traditionally, the role of basic research in mental health treatment has been, in essence, the Phase 0 of a clinical trial (i.e., the work preceding Phase 1 testing). Basic research underpins our ability to gain a deeper understanding of the neurobiology of psychiatric disorders and is essential to identifying novel avenues for treatment strategies

Key points for discussion

1. Prevention and better treatments require a detailed understanding of how the brain works, and how social factors and exposures (e.g. illicit drugs) impact the brain.
2. Neuroscience is one of the fastest growing areas of science. We need to harness this growth/potential to better understand mental disorders.
3. Technology will continue to provide new insights into the brain. Basic research is the initiator of technological innovations.
4. Facilitating shared career paths (to foster interactions between basic researchers and clinicians) will capitalise on established NHMRC Advanced Health Research and Translation Centres.
5. Improved industry involvement will help drive treatment strategies, but identifying avenues where basic research can inform these applications will be critical.
6. Better science communication to inform and educate consumers about basic research would establish an appreciation of research across all research domains.

(be they pharmacological, behavioural or preventative). For example, the discovery and understanding of the neurotransmitter dopamine, and subsequent Nobel prize to Arvid Carlsson and Paul Greengard in 2000, is basic research that underpins many of our current hypotheses and treatments in psychiatry (Iversen and Iversen 2007). Treatments such as Guanfacine for attention deficit and hyperactivity disorder (Arnsten and Jin 2012) and Ketamine for major depressive disorder (Krystal, Abdallah et al. 2019) were also based on years of basic research. In fact, the researchers credited with the use of Ketamine in depression highlight that *“its discovery emerged from the testing of a novel mechanistic hypothesis related to the pathophysiology of depression”* (Krystal, Abdallah et al. 2019). As these examples illustrate, the pipeline from the bench to the bedside takes many decades and relies on basic research to establish mechanistic hypotheses about brain health and disorders.

Given the broad portfolio of ‘basic research’, for the purposes of the NMHC workshop the authors have focused on their area of expertise, behavioural neuroscience. Specifically, understanding the molecular, cellular and systems neuroscience underlying complex behaviour in preclinical models. The basic pipeline we will discuss is as follows:

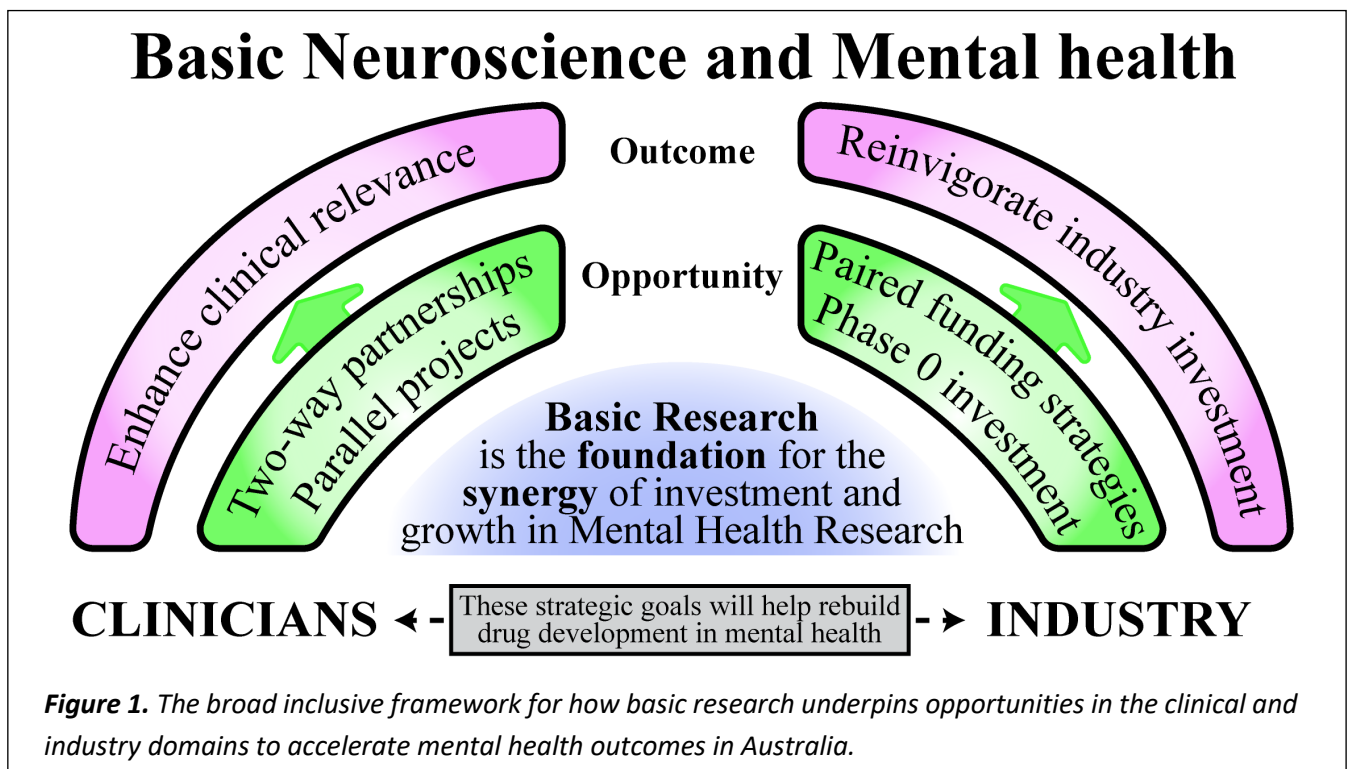


The strategic goals and recommendations we present are focussed on broad mental health outcomes and improving the transition along, and interaction between, each stage of this pipeline. Understanding behaviour and cognition is also of increased relevance to mental health research as most psychiatric conditions feature complex behavioural changes or symptoms, without robust diagnostic markers.

Within the field of mental health research our understanding of cognition and behaviour, as well as the available tools, are stronger than ever. Behaviour and cognition also represent a ‘common ground’ for communication and collaboration between basic researchers and clinicians. There have been several initiatives formed to drive mental health research in neuroscience, such as the National Institute of Mental Health’s (USA) Research Domain Criteria (Insel 2014), the MATRICS consensus (Marder 2006, Young, Powell et al. 2009) and CNTRICS initiative (Carter and Barch 2007, Moore, Geyer et al. 2013). These initiatives were designed to facilitate basic mental health research by focussing on dimensions of human behaviour (for example: attention, reward learning, memory) which span across diagnostic criteria. These initiative have not been without their critics. For example, the domain of executive functions reflect any cognitive process that relies on the prefrontal cortex, even though these processes may be fundamentally different anatomically, neurochemically and computationally. Criticisms aside, the goal of using basic research to drive mental health outcomes is valid and opportunities exist to improve upon these models in the Australian mental health sector to drive innovation and progress.

Neuroscience research is currently a hot spot for technical innovation. For example, viral strategies can be used to excite or inhibit specific brain circuits during behaviour. Various methods allow for either sustained manipulations (i.e., DREADDs; Urban and Roth 2015) or those requiring millisecond time scales (i.e., optogenetics; Kim, Adhikari et al. 2017). These techniques, in combination with sophisticated behavioural assays, are beginning to unravel the neurobiological processes underpinning brain function. Although this may seem a big step from developing novel treatment strategies, this is the bedrock that effective treatments are built on. Furthermore, the understanding of disease processes provide the potential for preventative

measures to be identified. Throughout this paper we will present areas of strategic focus that will prioritise better links between basic research, clinicians and industry (**Figure 1**).



These strategies build on the following three focus points:

1. Basic research is the foundation for improved clinical and/or industry led mental health outcomes across the mental health sector in Australia.
2. Increased collaboration and communication between basic researchers, clinicians and industry will generate mental health research synergies.
3. The flexible application of basic research discoveries, by not being limited to a specific diagnostic criteria, means the greatest benefits and innovations will include those that we do not foresee.

Gaps and uncertainties

We know little about how the brain works. Basic research allows us to tackle how the brain performs specific functions and where problems may arise. The influential Australian-born psychiatrist, Sir Aubrey Lewis put this bluntly - psychiatry suffers from "*too many theories balanced uncertainly on too few solid facts*". Therefore, it is vital that basic research continues to progress our understanding of fundamental brain function, alongside targeted mental health research. In order to facilitate this partnership, mental health needs to drive the agenda in basic neuroscience research.

Key gaps in basic research

1. We know very little about how a healthy brain works
2. Poor interaction between basic researchers and clinicians
3. Lack of industry involvement in Phase 0 research

A strength of basic research is that it is not restricted to an individual disorder. Clinical trials and studies are limited to testing the specific application or outcome for a target compound, and cannot determine potential alternative benefits or consequences as thoroughly. Without such a strict disease focus, discoveries from

basic research stand to benefit a far greater number of people and would, in practice, be a pre-emptive examination of a drug or preventative interventions 'repurposing' potential.

Preclinical and clinical research teams to facilitate translational research

Translational research can be interpreted from many different perspectives; from bench-to-bedside or cross-species research. For basic research, and likely complex psychiatric disorders, the more relevant is cross-species research, which reflects work in model systems alongside parallel human studies. Currently, there is a major gap between preclinical and clinical research, an impediment to the mental health research outcomes in Australia (Kesby, Eyles et al. 2018). Interacting with clinicians more closely would ensure our research questions remain relevant and targeted to the critical gaps that need addressing. Allowing basic and clinical researchers to identify more clinically-relevant outcomes with greater predictive validity i.e., results that generalise between species. The net effect would be a significant improvement in the experimental approach of translational mental health research and an increased capacity for large scale, multidisciplinary studies in Australia.

Better industry partnerships to increase support prior to clinical trials

The pharmaceutical industry has largely withdrawn from drug development and clinical trials in psychiatry. The main reason being the large expense to take a drug from Phase 1 through Phase 3 clinical trials (~USD\$340 million), and a low 10-15% success rate for target compounds (DiMasi, Grabowski et al. 2016). Basic research (i.e., Phase 0) is critical for the work preceding Phase 1 and requires better basic researcher and clinician partnerships, supplemented by industry involvement. Having basic neuroscientists working closely with industry partners provides an embedded consultancy network to promote better decision-making, on both sides. Furthermore, it is an order of magnitude cheaper to invest more thoroughly in Phase 0 studies so we can identify the strongest candidates before Phase 1 trials.

Challenges

There are currently many challenges and barriers facing researchers in Australia that are not unique to basic research. However, Australia's mental health research sector has been increasing its focus on 'impact' for new funding schemes (e.g., NHMRC Investigator Grants) and service priorities by those in policy, public health and health services. This focus is

understandable and reflects the end goal as there are huge unmet needs. We have a moral obligation to do anything we can to address these needs now. In this climate, long-term projects are harder to justify. However, it is a poor measure for valuing and appreciating the role of basic research in driving innovation and identifying novel approaches for clinical applications. A fundamental understanding of brain function is required prior to the applied research that produces these broader impact outcomes. The value of basic research is well respected in other health fields (e.g. cardiovascular, cancer and metabolic syndrome research etc.). But this is not always the case with respect to mental health. We must avoid setting up false dichotomies related to this issue – current mental health services are underfunded. Mental health research in general is underfunded. Instead of acting like hungry dogs fighting over a bone, we need to invest in (a) a bigger health spend, alongside (b) a bigger mental health research spend. We need a balanced portfolio in how we invest our research dollars. Within this allocation, basic science is the long-term investment strategy. In order to do this effectively, we must acknowledge and address the key barriers currently facing basic research. Here we will focus on two major challenges:

Key challenges in basic research

- 1. Short-sighted timeframes and goals.**
- 2. Poor incentives for translational research programs**

Short-sighted goals

Short-term fellowships and contracts for emerging scientists are *actively preventing* measured approaches to build better models and integrate with clinicians or industry. As such, basic research now suffers from pressures associated with short-sighted timeframes and goals – a key driver being the ‘publish or perish’ mantra. This is compounded by the fact that typically, cross-disciplinary mental health research, has a slower publication rate than many publication mediums (i.e., meta-analyses, systematic reviews etc.) or research in other fields (i.e., molecular screens of novel compounds). The consequence of this combination of factors is that basic research in mental health is falling victim to these external pressures, **preventing the necessary combinations of long-term strategies to understand complex disorders and high-risk projects to facilitate innovative advances**. Funding models have the potential to incentivise and encourage a more long-term translational focus. Without sufficient funding for discovery science, then the building blocks won’t be there for the ground-breaking changes needed in mental health.

Lack of translational research programs

Basic researchers are trained to test new hypotheses by conducting well designed and controlled studies, but often lack experience in clinical practice or in understanding the process of treatment approval and commercialisation. Despite the clear benefits of embedding these skills in basic research via targeted collaborations, these partnerships are often difficult to establish, involve time consuming learning curves and require careful balancing of each party’s needs. We need to overcome the barriers that stand in the way of such relationships and support/reward efforts to create cohesive teams.

It is critical that Australia’s mental health research strategy begins to focus on how we can facilitate better long-term prospects for basic research. We argue that this cannot be tackled by targeting basic research in isolation. But rather, by enhancing the capacity for basic research to impact and leverage cross-disciplinary and broadly focussed mental health research programs.

Opportunities

In **Figure 2** on page 6 we outline our vision.

Basic and clinician research teams

In order to capitalise on the expertise of basic and clinician researchers, there needs to be clinicians embedded in basic research laboratories/institutes and basic researchers spending time at hospitals with their clinical colleagues. This will establish a better understanding between disciplines (even vocabulary differs), which facilitates ongoing productive discussions to drive more informed research. Clinician feedback can help to maintain a focus on clinical outcomes and conversely, basic researchers can help clinician’s select behavioural assays (for example) that are more translationally aligned. Combined, this will improve our ability to produce clinically relevant animal models, and align both basic and clinical research to optimise the predictive validity of interventions in basic research.

Our recommendations are to increase support via longer-term fellowships for early-to-mid career basic researchers that require a significant proportion of their time is spent within clinician-led research teams. Similarly, we recommend the opposite be supported, clinician researchers who spend time undertaking basic research projects. These need to be long enough in length to allow for the decreased productivity associated with forging and establishing these partnerships, as well as designing studies and obtaining approvals. We believe there would be widespread support for this proposal as researchers in mental health are beginning to understand the necessity for multi-disciplinary skill sets and research.

Strategic platform for future basic research

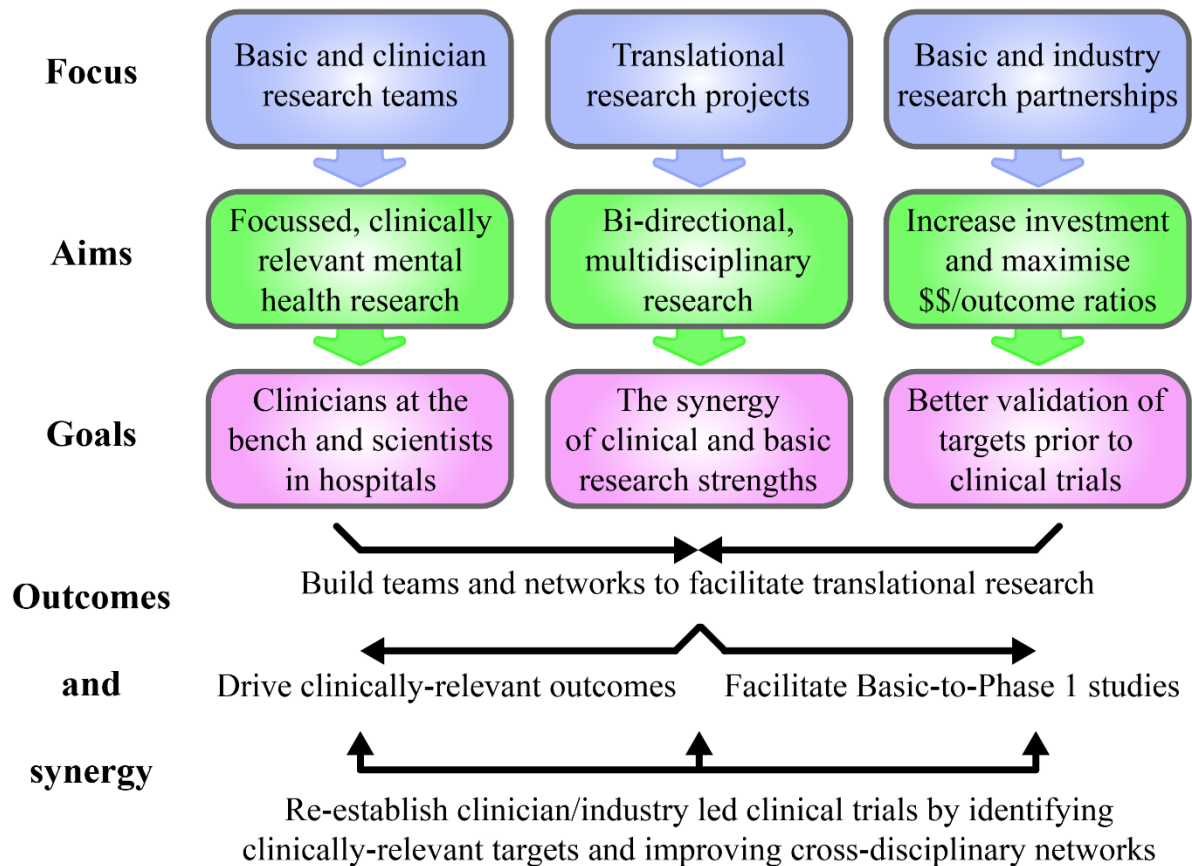


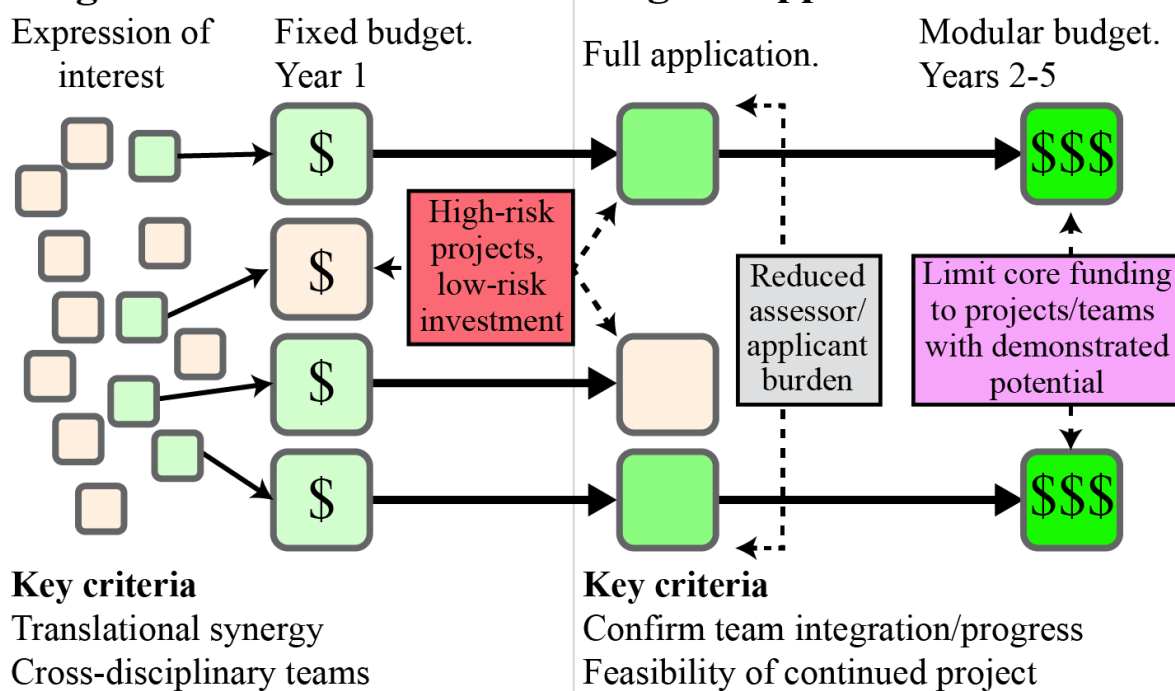
Figure 2. The primary strategic goals recommended to form better fundamental science integration in the Australian mental health sector. These inclusive strategies synergise with one another in order to invigorate a broad range of mental health outcomes.

Translational research projects

There is a growing push for research that reflects translational outcomes, in that it includes both basic research and clinical research. However, this work can take many years as experiments need to be conducted in multiple species/systems, and results can be difficult to analyse and compare. Furthermore, more diverse research means funding applications and manuscript submissions may be less cohesive and suffer from more scope for assessors/reviewers to criticise. This is due to the broad level of expertise required to understand all aspects of the research and the limitations of page/word limits when explaining both rodent and human experiments/protocols. Thus, there is a need for a scheme focussed solely on funding translational research projects or programs. This would remove these assessor issues and also promote collaboration between disciplines and across research categories.

Our recommendations are that modular, flexible funding be allocated solely to projects that bring together basic and clinician (or industry) researchers, of varying career stages. Supporting young scientists and clinicians, by nesting them with experienced mentors, will build long-term research capacity for Australia. The modular concept for funding would reduce assessor/applicant burdens, and allow for adaptive responses to unexpected outcomes as projects progress. It would also facilitate the inclusion of additional sectors as projects advance. It would be a strict requirement that there is evidence highlighting the parallel focus and

synergy of the research i.e., so that it is not merely basic and clinical research projects conducted alongside one another. The concept of seed funding could be more explicitly integrated into the funding mechanism to improve efficiency and outcomes (**Figure 3**). For example, the Wellcome Trust (London, UK) features seed grants with the intention of subsequent applications for larger grants. Initial one-year 'start-up' seed grants could be awarded after competitive review. After one year, successful projects are then eligible to apply for larger project funding extensions. This design aims to reduce the required capital and invest in 'sure things', as well as reducing assessment burden. Moreover, only the strongest projects that demonstrate progress, translational integration and outcomes would receive longer and larger funding extensions. These could be trialled initially as targeted calls for funding.



Translational synergy
Cross-disciplinary teams

Full application.

Modular budget.
Years 2-5

Limit core funding to projects/teams with demonstrated potential

Confirm team integration/progress
Feasibility of continued project

shared training in academic and industry environments (e.g., Boehringer Ingelheim Fonds, Germany). The success of these schemes demonstrate the feasibility and interest from industry for these opportunities.

Synergy and outcomes

There is untapped potential for synergistic outcomes from establishing the aforementioned collaborations. The unique approach and expertise of each group has the potential to change the direction of basic research in Australia to maximise impact, reduce cost and accelerate innovation. The strategic goals outlined above are self-perpetuating in that they each foster the development and productivity of each other.

- By establishing better links between basic researchers and clinicians there will be a greater opportunity for the identification of relevant and synergistic translational research projects.
- Supporting these projects will lead to long-term partnerships between basic researchers and clinicians which drive further intellectual investment in translational research. Similarly, these projects will help generate Phase 1 clinical trial targets and take advantage of industry partnerships.
- By establishing better translational research approaches, confidence in the predictive validity of potential treatment strategies will be improved.

By integrating research sectors more effectively, the opportunity for further gains also lie in general scientific communication. The general public, and consumers alike, need to understand the importance of mental health research in order for systemic change to occur nationally. A strong and cohesive message to the public regarding the importance of mental health research will help to amplify our calls for increased investment.

Conclusion

We need to build inter-disciplinary research capacity in the Australian mental health sector. We need to fund and support collaborations and upskill basic/clinical/industry in a shared space with an understanding of the language, priorities and knowledge from other parties. Together, we stand to accelerate improved mental health outcomes through synergistic innovation. The greatest benefit of these collaborations will be the innovations we don't expect, the new discovery that might have been missed or the creative idea triggered by bringing together people from different fields. It all starts with the creation of new knowledge, which is why we need to include basic research as a key stakeholder in the plan for improved mental health of Australians.

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