Neurological and Sense Disorders Taskforce Report

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A. AIM

1. This report details the analysis and recommendations of the Neurological and Sense Disorders Taskforce (NSTF). It reviews both global and local neurological and sense disorders (NSD) research landscapes and identifies Singapore's current strengths, challenges and potential areas of growth. The report recommends a single unifying theme in NSD research for the Open Fund Large Collaborative Grants (OF-LCGs). Lastly, the report proposes a ten-year research roadmap and articulates the resources required to achieve the desired outcomes of NSD research in Singapore.

B. BACKGROUND

2. Rising life expectancy and increased prevalence of neurodegenerative risk factors such as stroke, obesity and diabetes have contributed to rapid increases in the worldwide prevalence of NSD. The World Health Organization (WHO) predicts that by 2040, as many developed countries' population age, neurodegenerative diseases such as dementia and Parkinson's disease, will overtake cancer to become the second leading cause of death after cardiovascular diseases. The number of people in the world living with dementia is expected to rise significantly to 131.5M by 2050 from 46.8M in 2015[1]. While recent studies[2,3,4] found a declining incidence of dementia in high-income Western countries, it is still premature to determine if factors such as better management/treatment of obesity, diabetes and heart disease contribute to this trend.

3. Singapore mimics global trends in life expectancy and the prevalence of NSD. The prevalence of dementia[5] and Parkinson's disease[6,7] in Singapore is found to be comparable to Western countries. Singapore's population is also ageing rapidly. In 2000, 7.2% of Singaporeans were aged 65 years and above[8]. By 2030, this would soar to 20%[9] due to rising life expectancy and falling birth rates. 35.5% of the entire burden of disease and injury in Singapore was borne by the elderly, aged 65 years and above[10]. Of this, NSD contribute 15% of the disease burden in the elderly, making it the third top contributor of disease burden in this age group. Most strikingly, this study found that Neurological (dementias), Vision, Hearing (adult-onset) and Mental disorders, together, had the highest contribution (21%) to the disease burden in the entire population (**Figure 1a**). NSD is also characterised by a much higher proportion of Years Lived with Disability (YLD)

[1] World Alzheimer Report 2015.
[2] Martin Prince et al. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimer's Research & Therapy 2016; 8:23
[3] Sharon Begley. Dramatic decline in dementia seen among older adults in the US. The Stat News 2016.
[4] David S. Jones. Is Dementia in Decline? Historical Trends and Future Trajectories. NEJM Feb 2016; 374:507-509
[5] Source of data: Ministry of Health
[6] Tan LC et al. Incidence of Parkinson's disease in Singapore. Parkinsonism Relat Disord. Feb 2007; 13(1):40-3.
[7] Tan LC et al. Prevalence of Parkinson's disease in Singapore: Chinese vs Malays vs Indians. Neurology. Jun 2004; 62(11):1999-2004.
[8] Source: Census of Population 2000, Department of Statistics Singapore
[9] Source: National Population and Talent Division, Prime Minister's Office (2013)
[10] Source: Singapore Burden of Disease study 2010, Ministry of Health

compared to Years of Life Lost (YLL) due to premature mortality (**Figure 1b**). The top causes of NSD burden in terms of Disability-Adjusted Life Years (DALYs) is shown in **Table 1**. While adult onset hearing loss is ranked second highest, the NSTF has chosen not to prioritise this due to the lack of expertise within Singapore.

4. The higher proportion of YLD compared to YLL contributed by NSD is due to the fact that many NSD are age-related neurodegenerative diseases which are non-fatal, yet incurable and permanently incapacitating. Consequently, these age-related NSD usually cause high disease and economic burden throughout the patient's remaining lifetime. There is an urgent need to reduce the disease burden attributed to NSD and to invest more into NSD research to discover novel therapies for age-related NSD.

5. The need for more investments into NSD research, especially age-related NSD, is also supported by a 2014 simulation study by Duke-NUS Medical School that studied the activities of daily living (ADL) needs of Singaporeans aged 60 and above. This study concluded that the number of elderly Singaporeans with one or more ADL limitations would increase from 31,738 in 2010 to 82,968 by 2030. This would constitute 7% of the total population aged 60 and above[11].

6. It is important to note that NSD-related costs are not just limited to direct medical costs; the loss of productivity, social costs and indirect costs associated with caregivers should also be taken into consideration. Given the ageing population and shrinking work force, it is important to alleviate the burden caused by these disorders, through accessible acute medical services, enhanced primary prevention programmes, effective healthcare policies and interventions, application of technology and innovations, and more directed research on specific neurodegenerative disease areas.

7. While DALYs are a quantitative measure of disease burden, they only measure the time lost due to both premature mortality (YLL) and non-fatal conditions (YLD). The relative number of DALYs across different diseases does not fully reflect the exact burden of disease to the patient, caregivers and hospitals, and should not be the sole consideration in determining the severity of NSD disease burden to Singapore.

8. For the remainder of this report, the NSD field is categorised into the following sub-categories [12] : Neuroscience (encompassing neurodegenerative diseases), Neuropsychiatry (encompassing mental health) and Sense Disorders (encompassing eye diseases, hearing disorders and peripheral neuropathy).

[11] Thompson, et al. Projecting the number of older Singaporeans with Activity of Daily Living Limitations requiring human assistance through 2030. Annals Academy of Medicine Singapore 2014; 43:51-6

[12] The ambit of diseases under neuroscience (G00-G99 Diseases of the nervous system), neuropsychiatry (F00-F99 Mental and behavioural disorders) and sense disorders (H00- H95 Diseases of the eye and adnexa, Diseases of the ear and mastoid process) are categorised according to ICD-10 version 2016.

Figure 1: DALYs by diseases expressed as (a) percentage of total population, and (b) percentage of years of life lost due to premature mortality (YLL) and years lived with disability (YLD) in the total population

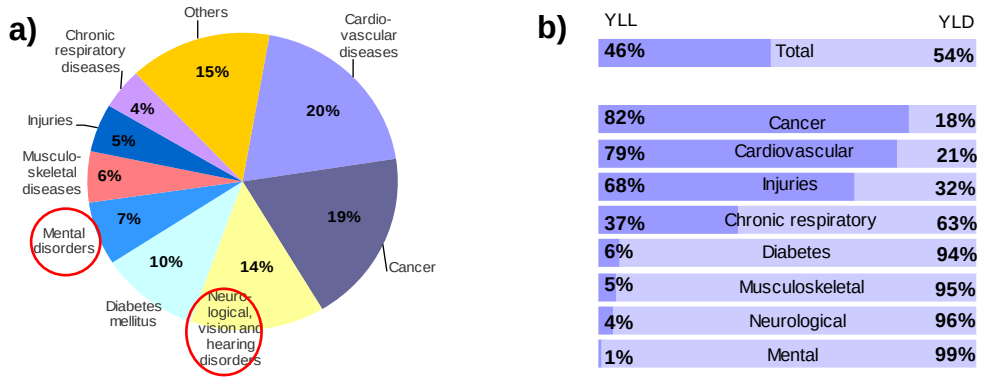

Table 1: Top 10 Causes of Neurological and Sense Disorders Burden (in DALYs)[13]

Rank	Specific Cause	DALYs
1	Alzheimer & other dementias	15,440
2	Adult onset hearing loss	11,797
3	Schizophrenia	10,860
4	Low vision and blindness due to Uncorrected refractive error	10,827
5	Anxiety and Depression	6,794
6	Autism & Asperger Syndrome	5,022
7	Low vision and blindness due to Cataract	2,632
8	Parkinson's disease	2,188
9	Migraine	2,142
10	Low vision and blindness due to AMD	1,768

C. CURRENT LOCAL NSD RESEARCH LANDSCAPE

9. Research Infrastructure. Singapore possesses a significant number of academic and research institutes that specialise in Neurological, Neuropsychiatry and/or Sense Disorders research. These include the Parkinson's disease and Movement Disorders Centre at the National Neuroscience Institute (NNI), the Singapore National Eye Centre (SNEC) and the Singapore Eye Research Institute (SERI), which serves as the research institute of SNEC, Duke-NUS Medical School, National University of Singapore (NUS), National University Health System (NUHS), the Neuroscience and Mental Health Research Programme at the Lee Kong Chian School of Medicine at Nanyang Technological University (NTU) and A*STAR research institutes.

10. Scientific Expertise. The local research talents have generated a significant number of high-impact publications and citations in NSD research. Singapore has a strong base of neuroscience researchers in NUS, NTU, A*STAR research institutes, SNEC/SERI and NNI. The publication track records (from 2006 to 2015) for SNEC/SERI and NNI are comparable to other renowned regional and global

[13] Source: Singapore Disease Burden Study 2010, MOH

institutes [14] . Singapore's eye research, specifically in ophthalmology and optometry, is ahead of its international competitors in terms of number of citations. Singapore is also one of the most prolific nations in ophthalmology publications and produced the most publications per capita[15] and ranked second globally in producing quality papers[16].

11. Talent. Singapore's investments in talent development programmes have enabled a growing pool of internationally competitive local talents in NSD research. World-class experts in NSD research originating from Singapore include Prof Wong Tien Yin, Prof Saw Seang-Mei, Prof Aung Tin and Prof Tan Eng King. Other exemplary local experts in NSD research include Prof Barry Halliwell, Prof Liu Jian Jun, Prof Guan Cuntai, Prof Soong Tuck Wah, Prof Chong Siow Ann, Prof David Matchar, Prof Balazs Gulyas, Prof Jodhbir Mehta and A/Prof Lim Kah Leong.

12. Local and International Collaborations. There are many ongoing local projects in Neuroscience, Neuropsychiatry and Sense Disorders. These include the Translational and Clinical Research (TCR) Flagship Programmes in Parkinson's disease, Schizophrenia and Eye Surgery and Innovative Technologies (EyeSITe). Local investigators are in collaborations with international NSD programmes which are crucial for establishing networks, strengthening expertise and enhancing the competitiveness of research efforts in Singapore.

D. INTERNATIONAL NSD RESEARCH LANDSCAPE

13. Global competition. Major investments have been made in the area of neuroimaging, neurostimulation, computational sciences, neurorobotics and deep brain stimulation, with the aim of developing new strategies for the prevention, diagnosis, and treatment of different neurological disorders. Most notably, the U.S. and Europe have been investing billions of dollars into neuroscience and neurotechnologies. Examples of key global initiatives and programmes in NSD research include the BRAIN initiative (US), Human Brain Project (Europe), Alzheimer's Disease Neuroimaging Initiaive (ADNI) (US), UK Biobank imaging study, Roadmap for Mental Health Research in Europe (ROAMER) (Europe) and NEI Audacious Goals Initiative (AGI) (US).

E. INDUSTRY INTEREST AND ECONOMIC OPPORTUNITIES

14. Economic Opportunities. Singapore has been successful in attracting private sector investments in NSD research. Multi-national companies (MNCs) such as GlaxoSmithKline (GSK) and ophthalmology companies such as Menicon, Essilor International and Santen Pharmaceutical have invested significantly in

[14] The 15 countries in the international comparison are: Australia, Canada, China, Finland, France, Germany, Hong Kong, Japan, Singapore, South Korea, Sweden, Switzerland, Taiwan, United Kingdom and United States. Source of data: SCOPUS-SCImago

[15] Guerin MB et al. Worldwide geographical distribution of ophthalmology publications. Int Ophthalmology Dec 2009; 29(6): 511-6

[16] Christophe Boudry et al. Trends and topics in eye disease research in PubMed from 2010 to 2014. PeerJ Jan 2016; 4:e1557

NSD research in Singapore. In addition, local investigators have forged many industrial collaborations with the MNCs to generate more value capture.

15. EDB and SPRING Singapore have been supporting local start-ups at different stages of growth through a variety of funding schemes[17]. Several successful start-ups have emerged from Singapore, including TauRx Therapeutics, Cellresearch Corp, Nextan and T.Ware Pte Ltd.

16. Another area with rapidly growing market interest is in the digital health space, with companies moving into this space with various thrusts in software solutions and patient monitoring. Of note, remote monitoring of patients for neurodegenerative diseases has attracted much interest, with Apple and Roche providing solutions to complement the regular doctor's visits. The use of digital technology in healthcare has immense potential to improve both economic and health outcomes by delivering health services more efficiently and effectively. The ability to collect and analyse real-time data would be useful in enhancing the current research and healthcare landscape. With Singapore's ageing population, this technology can be applied to NSD research and healthcare service delivery to further enhance these areas.

F. SELECTION OF RESEARCH FOCUS AREAS

17. In order to identify priority disease areas for the HBMS initiative to devote resources to fund key research areas in an "all the way" manner, the NSTF organised a workshop involving more than 80 researchers, clinicians and policymakers from various institutions to canvass suggestions and feedback from the NSD community. The NSTF adopted a consultative approach by further conducting an email survey to obtain inputs from the heads of research institutes and public healthcare institutions.

18. Four subpanels were established within the NSTF to conduct a deeper analysis of the identified priority areas, namely the: *Ageing related diseases and complications Subpanel*, *Neuropsychiatry Subpanel*, *Neurotechnology Subpanel* and *Sense Disorders Subpanel*.

19. Due to limited resources, it is important for Singapore to focus on niche areas with the greatest potential for success to maximise value capture. Considerations for prioritising NSD research areas include (i) local disease burden; (ii) impact to Singapore; (iii) industry interest and opportunities for Singapore; (iv) scientific expertise and research talent and (v) ongoing efforts in NSD research.

[17] SPRING Singapore offers equity investment schemes to start-ups such as (i) Business Angel Scheme, (ii) SPRING Startup Enterprise Development Scheme and (iii) Sector Specific Accelerator Programme, grants such as ACE Startups Grant, and funding for technology commercialisation viz Technology Enterprise Commercialisation Scheme.

20. With these considerations in mind and the discussions from the workshop and the NSTF meetings, the NSTF identified four promising disease areas, with neurotechnology functioning in a cross-cutting horizontal manner:

a. Neurodegenerative diseases (vascular dementia & Parkinson's disease);
b. Neurodegenerative eye diseases (AMD and glaucoma);
c. Mental health disorders (depression); and
d. Neurotechnology (cross-cutting horizontal platform for the above areas).

G. RECOMMENDED RESEARCH PRIORITY AREAS FOR OPEN FUND-LARGE COLLABORATIVE GRANT (OF-LCG)

21. For the OF-LCG call, the NSTF recommends a single priority theme: **Neurodegenerative diseases**, specifically focusing on the following sub-themes i) **vascular dementia & Parkinson's disease** and ii) **Neurodegenerative Eye diseases (AMD & Glaucoma)**.

22. In Singapore, chronic neurodegenerative conditions such as Parkinson's disease and other dementias, contributed 4.4% of total DALYs. Vision disorders including neurodegenerative eye diseases also contributed 4.4% of total DALYs. The NSTF recommends focusing on these two areas for the OF-LCG as they account for the highest disease burden amongst all NSDs:

a. **Vascular dementia & Parkinson's disease; and**
b. **Neurodegenerative Eye diseases (AMD and glaucoma)**.

Challenge statement for vascular dementia & Parkinson's disease
To reduce the disease burden and hospital readmission rates of vascular dementia and Parkinson's disease by 10-20% in ten years.

Challenge statement for Neurodegenerative Eye diseases (AMD and glaucoma)
To reduce the prevalence of age-related blindness and vision loss by 20% within ten years in the national population and reducing complication of eye diseases by 20% within ten years in the at-risk populations in Singapore.

Desired outcomes
A 10% reduction in the aggregate cost burden of Dementia and Parkinson's disease, which takes into consideration direct medical care costs, direct non-medical care costs, as well as losses to productivity would lead to an estimated societal cost savings of $40M per year for both conditions.

23. Given the ageing Singapore society and ageing being a major risk factor for neurodegenerative diseases, the NSTF proposes that research in the priority areas should focus on alleviating the national health care burden. This includes improving disease diagnosis, delaying disease progression and enhancing quality of life.

Elaboration of the proposed sub-themes for OF-LCG

24. Vascular dementia & Parkinson's disease. The number of Singaporeans aged 60 and above who suffer from dementia is projected to increase from 28,000 in 2014 to 80,000 by 2030[18]. Based on the Singapore Disease Burden Study 2010, the main causes of disease burden of NSDs are neurodegenerative diseases such as vascular dementia, Parkinson's disease and neurodegenerative eye diseases such as age-related macular degeneration (AMD) and glaucoma. It is also notable that there is higher prevalence of vascular dementia and Parkinson's disease in Singapore compared to other neurodegenerative diseases (e.g. Huntington's disease and spinal muscular dystrophy).

25. Local studies estimating the economic burden of neurodegenerative diseases found that the lifetime economic burden of Parkinson's disease is substantial[19], amounting to a lifetime cost of S$60,487 per patient[20]. The study also found that the top components of total lifetime cost were productivity losses, pharmacotherapy and homecare. These identified components constitute major considerations for cost reductions in future research and policy formulation.

26. In another economic burden study on the societal cost of dementia conducted by IMH[21], it was estimated that dementia cost Singapore S$1.4B every year. The total cost of dementia alone in 2013 was estimated at S$532M while the annual cost per person was estimated at S$10,245.

27. A health economic analysis to determine the impact of a 10% reduction in burden of Dementia and Parkinson's disease found that there was significant implications on societal cost savings. A 10% reduction in the aggregate cost burden of Dementia and Parkinson's disease, which takes into consideration direct medical care costs, direct non-medical care costs, as well as losses to productivity, would lead to an estimated reduction in total costs of $32M per year for dementia, $8.2M per year for Parkinson's disease, or a societal cost savings $40M per year for both conditions. Of note, this analysis highlights that an intervention of very modest effectiveness affecting a substantial segment of the population, as in the case for Dementia and Parkinson's disease, can translate into significant positive aggregate effects and cost savings.

28. We believe that there is a high likelihood for the impact of vascular dementia and Parkinson's disease research due to the large number of individuals at risk of suffering from these diseases in the next few decades, and the substantial unmet needs in these diseases. From the patients' perspective, a cure for neurodegenerative diseases is much desired. Alleviating the disease symptoms

[18] Source of data: https://www.duke-nus.edu.sg/news/singapore%E2%80%99s-largest-neuroscience-research-institute-launched-advance-care-disorders-stroke-and

[19] Zhao YJ et al. Economic burden of Parkinson's disease in Singapore. Eur J Neurol. Mar 2011; 18(3):519-26.

[20] Zhao YJ et al. Estimating the lifetime economic burden of Parkinson's disease in Singapore. Eur J Neurol. Feb 2013; 20(2):368-74.

[21] Abdin E et al. The societal cost of dementia in Singapore: Results from the WiSE study. J Alzheimers Dis 2016; 51(2):439-49

by improving their assisted daily mobility in a cost-effective manner is also important. Examples of specific unmet needs include:

a. Precise pathogenesis of vascular dementia and Parkinson's disease is not known;
b. Complexity and inaccessibility of the human brain;
c. Lack of non-human primate models (NHPM) to study brain functions and its associated pathologies;
d. No reliable diagnostic and predictive tests for neurodegenerative diseases;
e. Susceptibility factors such as genetics affecting neurodegenerative diseases are not understood;
f. Lack of established well-studied health and lifestyle factors that can prevent, delay the onset or slow down vascular dementia and Parkinson's disease;
g. No known cures or treatment that can cure or delay the onset of neurodegenerative diseases;
h. Lack of cost-effective pharmacotherapy methods and assisting equipment to deal with patients' incapacitated daily activities; and
i. There is a need for new approaches to prevent and treat neurodegenerative diseases, particularly vascular dementia and Parkinson's disease.

29. Given the higher prevalence of vascular dementia and Parkinson's disease, there is correspondingly greater industry interest in the development of new therapies for these diseases. The research opportunities for vascular dementia and Parkinson's disease are:

a. Understanding the mechanisms of age-related diseases;
b. Development of molecular and imaging biomarkers for early detection of disease and elucidation of key therapeutic targets for disease prevention & treatment;
c. Identification of epidemiological/ unique lifestyle factors that reduce disease risk or improve overall brain health;
d. Development and integration of neurotechnology platforms and tools for early diagnosis, intervention, patient monitoring and new devices for treatment of diseases;
e. Development of more effective pharmacotherapy treatment;
f. Leverage technology to assist patients' daily activities in a cost-effective manner;
g. Development of digital health technology to help patients manage the disease more efficiently and cost-effectively; and
h. Translation of knowledge into clinical intervention, public health planning & policy implementation.

30. Neurodegenerative eye diseases (AMD and glaucoma). Another priority sub-theme recommended by the NSTF is neurodegenerative eye diseases. Of the 285M people suffering from severe visual impairment and blindness, 65% of the visually impaired and 82% of the blind people are aged 50 years or older. Neurodegenerative eye diseases such as glaucoma and AMD are the major causes of blindness globally.[22] The local trend mimics the global trend of prevalence of neurodegenerative eye diseases and major causes of blindness[23]. The 2010 Singapore Burden of Disease Study found that among vision disorders, neurodegenerative eye diseases such as AMD and glaucoma contribute the greatest disease burden after uncorrected refractive error and cataract. However, unlike cataract and vision disorders due to uncorrected refractive error which could be managed and treated effectively, there is a lack of effective reversible treatment and unknown cures for AMD and glaucoma.

31. While age is a known major risk factor for these neurodegenerative eye diseases, there are still substantial unmet needs in these diseases. Examples of specific unmet needs include:

a. Precise pathogenesis is not known;
b. Lack of established well-studied susceptibility factors (e.g. genetics) and risk factors;
c. Lack of established well-studied health and lifestyle factors that can prevent or slow down the progression of AMD and glaucoma;
d. Preventive measures to prevent the onset of these diseases are not known;
e. No known cures or treatment that can cure or delay the onset of AMD and glaucoma;
f. There is a need for new approaches to prevent and treat neurodegenerative eye diseases, particularly AMD and glaucoma.

32. To develop new therapies for these neurodegenerative eye diseases, there is a need to research in the following methodologies:

a. Improve the understanding of basic mechanisms that contribute to AMD and glaucoma, and their progression;
b. Identify novel and innovative strategies to understand the etiology of these diseases;
c. Develop new treatments and reduce the impact of AMD and glaucoma;
d. Identification of epidemiological/ unique lifestyle factors that reduce disease risk or improve overall eye health;
e. Development and integration of neurotechnology platforms and tools for early diagnosis, intervention, patient monitoring and new devices for treatment of diseases; and

[22] Madeleine Zetterberg. Age-related eye disease and gender. Maturitas. Vol 83, Jan 2016; 19-26
[23] Source: Singapore Malay Eye Study, Singapore Indian Eye Study, Singapore Chinese Eye Study

f. Translation of knowledge into clinical intervention, public health planning & policy implementation.

H. TEN-YEAR ROADMAP FOR NEUROLOGICAL AND SENSE DISORDERS RESEARCH

(I) RESEARCH PRIORITY AREAS

33. In addition to the recommended neurodegenerative diseases (i.e. vascular dementia and Parkinson's disease) and neurodegenerative eye diseases (i.e. AMD and glaucoma) for OF-LCG, the NSTF recommends focusing on building capabilities in the mental health and neurotechnology fields, and addressing the major local public health problem of myopia and stroke over the next ten years. While local research in the mental health field has yet to achieve the same level of international recognition as Singapore's Parkinson's disease and eye research, mental health disorders such as depression are extremely debilitating to the individual and society at large. Hence, more needs to be done to strengthen Singapore's research capabilities in the mental health field. For neurotechnology, the NSTF recognises that advances here have the potential to revolutionise the prevention, diagnosis and treatment of many NSDs as it provides the means to assess and manipulate human consciousness, cognition, emotions and behaviours. Therefore, by focusing on these research priorities and building supportive R&D and healthcare ecosystem, Singapore would be able to tackle the economic and societal problems posed by NSD efficiently and effectively.

34. The long term vision of NSTF's research roadmap is to advance Singapore into a world leader in neurological and sense disorders research, with emphasis in neurodegenerative diseases. To achieve this vision, the NSTF has devised a ten-year research roadmap for developing the local research ecosystem.

Vision:
To advance Singapore into a world leader in neurological and sense disorders research (particularly in neurodegenerative diseases such as vascular dementia, Parkinson's disease, AMD and glaucoma) to create health and economic value for Singaporeans.

(I) Neurodegenerative Diseases (vascular dementia & Parkinson's disease)

35. Prevention, delay and treatment strategies for Neurodegenerative diseases. Compared to other diseases (e.g. diabetes and cancer), the development of preventive and therapeutic solutions for neurodegenerative diseases (particularly vascular dementia and Parkinson's disease) has moved slowly. New solutions will require investment in:

a. Brain Anatomy and Pathophysiology in Neurodegenerative diseases. Novel therapeutics can be developed only with improved understanding of

fundamental sciences. For instance, although AD and Parkinson's disease have distinct clinical symptoms and pathologies, they have shared characteristics (e.g. inflammation and apoptosis). Targeting critical pathological events may be effective in abating symptoms or slowing down their progression[24]. Research should also look into developing more precise and accurate diagnostic tools (e.g. biomarkers), and the delaying of onset of neurodegenerative diseases. In addition, advances in Deep Brain Stimulation (DBS) Therapy System require the identification of specific sites to be targeted. Therefore, identification and development of novel therapies is contingent on our understanding of brain anatomy and the pathophysiology of diseases;

b. Regenerative Medicine. Natural stem cells in the brain have the potential to regenerate the brain, but fail to do so in many diseases. Understanding age-related changes to neurogenesis is key to promote neurogenesis and neuroprotection. Grant agencies should continue to invest in embryonic stem cells, iPSCs and adult stem cells biology (neural stem cells), as well as research into enabling fields such as biomaterials, gene-editing (e.g. Clustered Regularly Interspaced Short Palindromic Repeats [CRISPR]/CRISPR-associated protein-9 nuclease [Cas9]) and gene therapy technologies. The NSTF also recommends investing into cell therapy facilities in Singapore, in anticipation of their eventual application in healthcare;

c. Neurotechnology strategies. Neurotechnology strategies, including neurostimulation, which modulates the nervous system's activity through electromagnetic approaches, is a potential alternative therapy for neurodegenerative diseases where traditional interventions have failed. Singapore should capitalise on our strength in engineering and biomedical research to build a pipeline of neurostimulation solutions, and strengthen interdisciplinary and cross institutional collaborations to achieve this;

d. Identification of disease modifying factors. There is a lack of studies to demonstrate that, over the long term, health or lifestyle factors can prevent or slow dementia or age-related cognitive decline. More definitive studies with animal models and long-term human studies are required before these studies may be translated into health guidelines and policies. With Singapore's growing food and nutrition research portfolio, there is scope for more research into the effects of nutrition in preventing and/or delaying the onset of neurodegenerative diseases;

e. Identification of biomarkers for early diagnosis and drug development. A major goal of clinical research in neurodegenerative diseases is to improve pre-symptomatic detection of neuronal dysfunction. Standard clinical diagnoses are based on relatively advanced symptoms which often do not consider the underlying biological variation. Hence, improvement in early detection by

[24] Rawan Tarawneh et al. Potential Future Neuroprotective Therapies for neurodegenerative disorders and stroke. Clin Geriatric Medi. Feb 2010; 26(1):125-147

identifying biomarkers for pre-symptomatic diagnosis would allow early intervention that could halt or delay disease progression. Additionally, biomarkers for stratification of disease subtypes and stages could lead to more targeted interventions. Biomarkers would also help verify diagnostic standards and define 'health/disease' threshold for local population.

36. Health and social care recommendations for patients with neurodegenerative diseases. Health and social care are important to improve the quality of life of patients with neurodegenerative diseases. Technological advances have greatly benefited how these patients are managed. There is scope to improve and/or implement on a larger scale the below:

a. Health service research (HSR) to determine the needs of patients with neurodegenerative diseases in Singapore;
b. Assistive technology for gait, fall prevention and rehabilitation;
c. Wearable implants or bio-implantables;
d. Home monitoring systems to provide off-site patient care and
e. Smart hospitals/home/community designs, which provides integrated patient services as well as real-time monitoring and alerts on patient's vital signs, health parameters, and behaviour.

(II) Neurodegenerative Eye Diseases (AMD and glaucoma)

37. Prevention, delay and treatment strategies for Neurodegenerative eye diseases. Similar to neurodegenerative diseases, neurodegenerative eye diseases such as age-related retinal diseases (e.g. AMD) and glaucoma currently have no known cures and prevention, intervention and management of the disease are currently the main approaches of combating the disease. New solutions will require investment in the following areas: (a) better understanding of the basic mechanisms of AMD and glaucoma and their progression (e.g. developing more precise diagnostic tools for early detection; delaying onset of AMD and glaucoma), (b) development of novel strategies/treatments to reduce progression and severity of AMD and glaucoma and (c) translation of basic research into clinical studies and commercialisation.

38. Health and social care recommendations for patients with AMD and glaucoma. To manage the acute and chronic conditions of patients suffering from neurodegenerative diseases, the NSTF recommends investing in health and social care to improve the quality and productivity of patients' lives. There is scope to improve and/or implement the following: (a) assistive devices and technologies, (b) wearable implants or bio-implantables and (c) rehabilitation technologies.

(III) Mental Health Research

39. There are multiple social, psychological and biological factors that influence the state of an individual's mental health. The likelihood of many common life

stressors such as loss of financial independence, bereavement, reduced mobility and increased physical problems are compounded by age. As such, these factors can result in poor mental health, depression and even suicide in elderly people. Hence, with Singapore's ageing population, there is an increasing need to address the issues of mental health.

40. Mental health disorders. There are a few mental health disorders such as Depression, Suicide, Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) that the NSTF have identified for further investment.

41. Prevention, delay and treatment strategies for mental health disorders. There is much scope to improve and implement the following:

a. Reducing stigma and promoting mental health. People suffering from mental health problems are among the most stigmatized and vulnerable members of society. One of the most significant implications of stigma is the delay or avoidance of seeking of treatment. In Singapore, the treatment gap for the various mental health problems including depression and suicide ranges from 60% of those with major depression to more than 90% for those with alcohol use disorders. Increased efforts to better understand the complexities surrounding stigma are needed. Efforts are needed to dispel myths about mental illness, increase mental health literacy and empower people with mental illness to seek appropriate help without delay. Using locally developed and culturally relevant instruments such as the Positive Mental Health instrument can serve as an effective way to measure positive mental health and its correlates among the multi-ethnic local population. Since mental disorders are associated with various determinants, this also necessitates a multi-pronged approach to prevention including initiatives to reduce risk factors, strengthen protective factors and result in positive mental health.

b. Identification of biomarkers for early diagnosis and drug development. There is no known biomarkers and cures for many mental health diseases such as depression, schizophrenia, ASD and ADHD. In addition, there is currently no pharmacotherapy for the core symptoms of ASD and various evidence-based 'remediative' therapies can help affected children gain skills but overall, early access to intervention is the most important determinant of better outcomes. However, the current clinical challenge of validating of the revised criteria of diagnosis affects access to the therapies services. Research into bio- or neuro-markers, through effective interdisciplinary collaborations (e.g. basic and cognitive scientists, geneticists together with clinicians such as paediatricians, psychiatrist, and psychologists) will aid in the discovery of objective biomarkers.

c. Neurotechnology treatment strategies. The use of neurotechnology for gaze tracking, brain imaging and cognitive rehabilitation could help uncover differentiating phenotypic or plasticity factors to improve diagnosis or advance intervention. Other important areas include the tracking and monitoring of the condition, for which trajectory factors are largely currently uncharted. The leverage of technology can facilitate such processes and improve knowledge as well as service delivery models for individuals and their caregivers. However, there is a dearth of trained therapists for such neurotechnology-based therapy in Singapore.

d. Epidemiological studies. Population based, epidemiological studies provide invaluable information about the prevalence of mental illnesses in Singapore and also risk factors, correlates, treatment gaps, service use and the associated cost of mental illnesses, all of which are pertinent to policymakers, planners, service providers and advocates. The findings from such studies have been instrumental in the development and implementation of the National Mental Health Blueprint and Community Mental Health Plan. Moving forward, it is imperative to ensure serial epidemiological surveys take place, enabling policymakers and service providers to not only evaluate the impact of the various initiatives, improve accessibility, organization and quality of services, but also help them to identify emerging needs/ threats and changes in patterns of mental health status and deal with them appropriately.

(IV) Neurotechnology

42. There is immense potential in the field of neurotechnology. The Singapore Institute for Neurotechnology – Advancing through Partnership of Scientists and Engineers (SiNAPSE) was established by NUS in 2012 to use advanced research partnerships between engineers and scientists to develop neurotechnologies that offer the breakthrough potential for scientific discovery, medical or defence needs and for commercialisation and economic benefit[25]. NNI also established a Centre of Excellence for Deep Brain Stimulation (DBS) [26] in April 2016 to advance treatment for patients with Parkinson's disease with DBS devices. NNI also developed the NeuroTechnology Innovation Programme (NTIP), which spearheads the development of a series of key technological platforms to accelerate their clinical development and translation into routine clinical practice. Singapore Bioimaging Consortium (SBIC) has a focused neuroscience programme that investigates the CNS-peripheral metabolic organ interplay. There are also advanced neuroimaging facilities across institutions in NTU Centre for Cognitive Brain Imaging, NUS and A*STAR.

[25] SiNAPSE's focus areas involve the brain and its cognitive and neurobiological mechanisms, modelling brain function and building mathematical and computational models, development of technologies for interfacing to brain and treating brain disorders, building brain inspired or neuromorphic computers and machines, and developing intellectual property that will result in product of value to industrial society.

[26] The Deep Brain Simulation (DBS) system is used to help control tremors and chronic movement disorders, like Parkinson's disease. Tiny electrodes are surgically implanted into specific parts of the brain and are connected via a subcutaneous wire to a neurostimulator, implanted under the skin near the clavicle.

43. In general, neurotechnology in Singapore is relatively isolated and disconnected although there are excellent talents in this area. Singapore can focus on high-end neurotechnologies and ride on the Smart Nation initiative. In particular, the NSTF recommends the following:

a. Priority neurotechnology areas to focus on. Neuro-imaging and analytics, brain and nerve stimulation, Brain-Computer interfaces (BCI), and clinical translation technologies are areas of growing industry interest where Singapore has ready talents and infrastructure in;

b. Pre-manufacturing Good Manufacturing Practice/Good Laboratory Practice (GMP/GLP) support. Enhancing infrastructure and regulatory support for pre-manufacturing (GMP/GLP) are critical for clinical translation technologies;

c. Common large database in clinical/imaging/behavioural data. We should synchronise aggregated clinical/imaging/ behavioural data through the development of a common database with aggregated clinical/imaging/ behavioral data and centralized platform/supporting team. This will also encourage more collaboration among neurotechnology researchers and clinician scientists in A*STAR, hospital, NNI and universities;

d. Neurotechnology expertise in regulatory bodies. With more innovative neurotechnology devices and services anticipated, it is necessary to have neurotechnology specialists in regulatory bodies to review and approve experimental medical devices expeditiously;

e. Training of interdisciplinary engineers and translational minded physicians. There is a shortage of qualified interdisciplinary engineers knowledgeable in neuroscience and neuroscientists who are technology-minded. Thus, the education curriculum could be reviewed and revamped to imbue neurotechnology elements. Training of interdisciplinary (biology/neuroscience and engineering) engineers is vital to support the development of neurotechnology research in Singapore. Fellowships and attachments could be created between hospitals and universities to allow exposure and training.

(V) Other diseases

44. Other than neurodegenerative diseases, there are other diseases which are important to Singapore due to their high disease burden and impact. The NSTF recognises that due to limited resources under the OF-LCG, research into these diseases could be funded from other funding sources. The NSTF recommends that more research investments could be devoted into myopia and stroke.

45. Myopia is a huge public health problem in Singapore and worldwide. Of note, the prevalence of myopia in Singapore is one of the highest in the world. This is of concern because adults with high myopia may have potentially blinding Pathologic Myopia (PM) pathology such as staphyloma (23%), chorio-retinal atrophic lesions (19.3%), lacquer cracks (1.8%), retinal haemorrhage (0.9%) and choroidal neovascularization (CNV) (0.9%). The prevalence of PM is likely to increase drastically in older adults over the next few decades in Singapore, largely contributed by the generational effect/cohort effect[27]. An estimated 83% of 40-50 year olds will be myopic in 30 years' time, including 15% with high myopia. The PM changes are likely to increase in prevalence with increasing age and refractive error, which may lead to visual impairment and loss of productivity, in turn posing a major socio-economic burden.

46. The cause of myopia is not fully understood, although both genetic and environmental factors are postulated to be related to myopia. High myopia and related PM follows early-onset myopia in childhood. PM may be potentially preventable if early environmental behavioural changes such as more outdoor time are encouraged in school children.

47. Stroke was one of the top five causes of death in Singapore from 2013 to 2015[28]. It was the third top contributor of disease burden (in DALYs) across all age groups[29]. In elderly aged 65 years and above, stroke was the major contributor of the burden of disease. In view of the ageing population in Singapore and the increasing burden and costs related to the disease, it is paramount that novel therapies for stroke be developed. **The NSTF notes that the Cardiovascular Diseases Taskforce (CVDTF) has already recommended stroke as one of its research priorities and hence will just highlight some of the areas which NSTF feels strongly about that should be improved/developed.** These include (a) stroke prevention and management, (b) robust animal models for stroke research, (c) greater participation in clinical stroke studies and trials, (d) health services and systems research in stroke, (e) improvements in national databases and platforms (eg: improving the Singapore stroke registry) and (f) more collaborations and partnerships in stroke research.

(II) ROADBLOCKS AND RECOMMENDATIONS

48. The NSTF has identified the following key roadblocks and gaps:

a. Lack of mechanisms and coordination to translate research outcomes into health and economic outcomes;

[27] Generational or cohort effect is whereby the prevalence of myopia in young adults (83%) is much higher than middle-aged and elderly adults (about 30% in 40-80 year olds) in Singapore. The pattern of high myopia and subsequent development of PM in young adults may be different in older adults as there are generational differences contributed by the different schooling systems recently compared to a few decades ago.
[28] Source: Singapore Ministry of Health (MOH).
[29] Source: Singapore Disease Burden Study, MOH (2010).

b. Insufficient public engagement to increase support for NSD research and to improve brain health and mental health literacy;
c. Regulatory, ethical and legislative roadblocks that impede approval of medical devices and use of patient data and tissue samples;
d. Insufficient coordination and collaboration within the local research community and interaction with international initiatives;
e. Lack of national brain and neuroimaging database and national platforms that can provide neuroimaging, high-throughput 'omics', health informatics support;
f. Insufficient manpower trained in the application of cross-disciplinary solutions such as neurotechnology, artificial intelligence, research-trained optometrists and digital health, lack of assurance of sustainability for pre-existing non-clinician researcher talent pool in the areas of mental health research, and lack of clarity on career progression for clinician-scientists;
g. Uncoordinated and insufficient engagements with the private industry that are currently on an ad-hoc basis and undermine the reaping of economic benefits from NSD research.

Recommendations to Address the Gaps

49. To address these roadblocks and gaps, the NSTF suggests the following recommendations:

50. Recommendation 1: Provide a clear framework for the translation of research outcomes into health and economic benefits. To maximise returns from research investments, it is crucial to evaluate the cost-effectiveness of project proposals. Patient-oriented outcomes, with more immediate health outcomes that can be measured, should be encouraged. Early engagement with MOH and HSA, in the pre-clinical stages would help to expedite regulatory processes. In addition, engagement among researchers, clinicians and the private industry players should ideally start early in order to forge closer collaborations, increase value capture and help to differentiate researchers' innovations.

51. Like many countries, Singapore lacks enablers to translate research outcomes into economic outcomes, such as technology teams with domain knowledge and industry network, industry partners with experience in licensing from academia, and commercialisation-minded researchers. To accelerate the translation of research outcomes into economic outcomes, more development should be focused in the following areas:

a. Effective and well-executed technology/IP development process. The development of an effective and well-executed technology/IP process within the research institute will generate a compelling technology/proof-of-concept (POC) case together with associated documentation;

b. A capable, dedicated and proactive technology commercialisation group. The establishment of a capable technology commercialisation group would help to complete licensing deals on behalf of researchers. This is similar to the role of Exploit Technologies Pte Ltd in A*STAR. The NSTF notes that the National Health Innovation Centre (NHIC) was established in 2014 to support the translation and commercialisation of healthcare innovations. An increased awareness of NHIC among the research community will allow NHIC to adopt a more coordinated commercialisation approach to all research performers;

c. Public-private partnerships. Execution of technology/IP development processes will be more effective through partnerships with industry players experienced in co-developing or licensing technology from academia; or establishments of start-ups by the institute's technology commercialisation team, and/or partnerships with the public or private incubator frameworks.

52. Recommendation 2: Increase public engagement. Public engagement may be enhanced by encouraging researchers to communicate the importance of NSD research and to share significant research discoveries and innovations on public platforms. This would allow public recognition of scientific achievements and provide accountability for the use of public funds for research. In addition, this may lead to increased participation in clinical trials. There is also a need to improve brain and mental health literacy in Singapore to encourage early help-seeking behaviour and to reduce the stigma associated with mental health disorders. Increased public confidence and buy-in would in turn aid in the speed and effectiveness of implementing policies and practices.

53. Recommendation 3: Resolve regulatory, ethical and legislative barriers. Healthcare institutions could obtain consent for the use of cell and tissue specimens from patients at the point of diagnosis or treatment so as to circumvent the patient data protection issues. Relationships with policymakers and the regulators have to be built to progress our shared agenda in translational and clinical research. Outreach to relevant government entities such as Smart Nation Programme Office could help to lay the ground for integration of experimental neurotechnologies with Smart Nation and other data sources/platforms.

54. Recommendation 4: Establish national infrastructure platforms and services. Researchers in Singapore will benefit from the setting up of a national brain bank comprising anonymised tissue samples for research. A range of tissue resources, such as post-mortem brain tissue should be made available for research. This will provide a valuable resource to support neurological research in Singapore. The neuroscience researchers would also benefit from the development of non-human primate models for neuroscience research. In addition, researchers require access to state-of-the-art technology to carry out cutting-edge research and generate scientific discoveries that transform the knowledge base.

55. Thus, we should deliver national infrastructure that increases access to cutting-edge technologies in a cost-effective way. An online platform of all cutting-edge infrastructure/equipment across all institutions could be developed, and a shared services agreement could be instituted for all research performers to have access to these sophisticated equipment and technology. This will reduce duplication of resources and enhance the usage of expensive cutting-edge technology for the benefit of all researchers.

56. Recommendation 5: Improve coordination and collaboration of research efforts. The development of a network to allow researchers to find and communicate easily would allow better coordination of research efforts in the local ecosystem. The development of a joint virtual platform by NNI e.g. One SG-Neuro, comprising all the neuroscience and neuropsychiatry researchers in Singapore, could serve as a starting point for this connected network. A consortium on neurodegenerative diseases (specifically in vascular dementia, Parkinson's disease and their neuropsychatric conditions, and neurodegenerative eye diseases) could be established with the best scientists from the public and private sectors. To encourage and establish international collaborations, opportunities should also be provided for local researchers to participate in global programmes.

57. Recommendation 6: Establish clear pathways for career development and groom manpower trained in interdisciplinary skills, and develop the minimum research capabilities required for mental health research. It is important that we continue to prioritise investments in skills to develop and foster innovative and creative researchers. In addition to strengthening the research base, future research leaders should be supported at critical stages in their careers, provided with clear pathways for career development and access to appropriate support networks and mentorship. Systematic mentorship processes and succession planning practices should be established among research and healthcare institutions to groom more clinician-scientists. In addition, more manpower should be equipped with interdisciplinary skills (e.g. medical bioinformatics, data analytics and neuroimaging) in regulatory, research and clinical settings.

I. CONCLUSION

58. In summary, Singapore has the potential to be an international leader in AMD, glaucoma, vascular dementia and Parkinson's disease in the next 5 years. Hence, the NSTF recommends a common theme focusing on neurodegenerative diseases encompassing vascular dementia & Parkinson's disease and neurodegenerative eye diseases (AMD and glaucoma) for the OF-LCG. Under the longer-term research roadmap, the NSTF proposes to focus on additional themes, including mental health disorders (depression), neurotechnology and myopia.

Annex – Composition of the Neurological and Sense Disorders Taskforce

S/N	Name	Designation
1	Prof Tan Eng King *(Chair)*	Director, National Neuroscience Research Institute Singapore Director, Research, National Neuroscience Institute (NNI)
2	Prof Wong Tien Yin	Medical Director, Singapore National Eye Centre
3	Prof Chong Siow Ann	Vice Chairman, Medical Board (Research), Institute of Mental Health
4	Prof Barry Halliwell	Senior Advisor to the President, National University of Singapore (NUS) Professor, Dept of Biochemistry, Yong Loo Lin School of Medicine (YLL SoM), NUS
5	Prof David Matchar	Director, Health Services and Systems Research Programme, Duke-NUS Graduate Medical School (Duke-NUS)
6	Prof Balazs Gulyas	Scientific Director, Neuroscience & Mental Health Research Programme, Lee Kong Chian School of Medicine, Nanyang Technological University (NTU)
7	Prof Soong Tuck Wah	Head, Dept of Physiology, YLL SoM, NUS
8	Prof Liu Jian Jun	Deputy Director (Research Programmes), Senior Group Leader (Human Genetics), Genome Institute of Singapore, Agency for Science, Technology and Research (A*STAR) Adjunct Associate Professor, Saw Swee Hock School of Public Health, NUS
9	Prof Guan Cuntai	Principal Scientist & Head, Dept of Neural & Biomedical Technology, Institute for Infocomm Research (I2R), A*STAR Co-Director, Rehabilitation Research Institute of Singapore
10	A/Prof Lim Kah Leong	Deputy Director, Research, NNI Associate Professor, Dept of Physiology, YLL SoM, NUS
11	A/Prof Lee Tih-Shih	Associate Professor, Neuroscience & Behavioural Disorders Programme, Duke-NUS Associate Professor, Psychiatry and Behavioural Sciences, Duke University
12	Prof Gene Yeo	Professor, University California, San Diego Adjunct Professor, Department of Physiology, YLL SoM, NUS