Neuroscience and Biobehavioral Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Commentary

What do experts think we should do to achieve brain health?

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ARTICLE INFO

Article history:
Received 6 December 2013
Received in revised form 28 March 2014
Accepted 2 April 2014

Keywords:
Expert ideas in neuroscience, innovation, technology and brain health
Neuropsychiatric disorders

The aim of this commentary is to discuss how we could achieve brain health for a flourishing society within the next decade. This will require integration and expertise from a number of different areas, including neuroscience, innovation and technology. Experts from these fields have contributed their ideas which are presented in Table 2.

There is not a single more important problem than understanding the brain in health and disease. Mental ill health is the single largest cause of disability in the UK (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_123993.pdf, No health without mental health; Fineberg et al., 2013). In addition to the distress and disability to the individual, mental health disorders are also extremely expensive to society and governments. For example, the wider costs of mental illness in England are estimated at £105.2 billion each year with two common neuropsychiatric disorders, depression and dementia, costing approximately £23.8 billion and £17 billion in total annual costs, respectively. Indeed, recently neuroscience and mental health policy have emphasised the importance of early detection and early effective treatment for people who develop a mental health problem (Collins et al., 2011; Insel et al., 2012; Beddington et al., 2008; Sahakian et al., 2010). One reason for this is that these problems are both common and are associated with large costs of disability. For example, 16% of adults in Britain have a common mental disorder, such as depression, at any one time (Jenkins et al., 2008). In England in 2007, lost earnings due to depression amounted to £5.8 billion and lower productivity accounts for a further £1.7–£2.8 billion. There are currently 800,000 people with dementia in the UK (http://www.alzheimers.org.uk/). Due to an increase in the ageing population, institutionalized care costs for dementia is expected to rise. The rise in numbers of people cared for in institutions will increase from 224,000 in 1998 to 365,000 in 2031. There is a growing acknowledgement that as mental health disorders become chronic and relapsing they may impact on the lifecourse and become difficult, if not impossible to treat. The same is true for addiction where the behaviour of the drug addict has become habitual and compulsive. It will be essential to initiate any treatments early if they are to be successful. For example, treatments for people with substance abuse will need to begin before the transition to habitual, compulsive behaviour seen in addiction, with its accompanying underlying neural changes.

The Foresight Project on Mental Capital and Wellbeing emphasized biomarkers for prevention, early detection and early effective treatment to enhance mental capital and wellbeing (Beddington et al., 2008). Biomarkers include cognitive, neuroimaging, genetic, cerebrospinal fluid and blood based measures. In the Prime Minister David Cameron's outstanding speech on dementia, given in March 2012, he remarked on the importance of early detection and early treatment stating that, "Only around 40 per cent of those with dementia know they have it." He also noted that, "You can help people live independently for longer or even put the brakes on their decline". Early detection is cost-effective for the National Health Service (NHS). Each patient with Alzheimer's disease who receives early assessment and treatment saves society £7741, compared to no early assessment and treatment. Of this, £3600 is in direct healthcare costs (Getsios et al., 2012).

Cholinesterase inhibitors (e.g. donepezil) are currently available and approved by the National Institute for Clinical Excellence (NICE) for the treatment of patients within the mild and moderate stages of Alzheimer's disease. Recent evidence has indicated that

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http://dx.doi.org/10.1016/j.neubiorev.2014.04.002

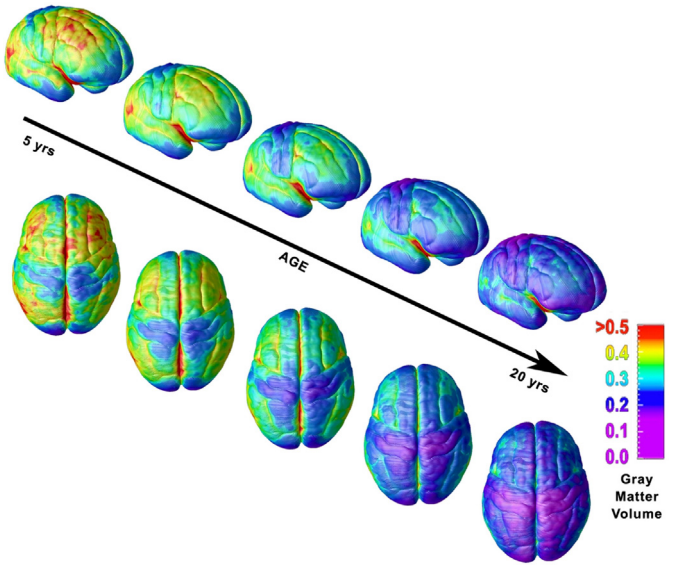

Fig. 1. Neuroimages of normal brain development from 5 to 20 years of age. Our brains are still in development through adolescence and young adulthood. Permission for use of this image was provided by Jay N Giedd MD, Chief, Brain Imaging Section, Child Psychiatry Branch, National Institute of Mental Health. This research work was conducted at the National Institute of Mental Health, NIH, USA. *Source*: Provided by Jay N Giedd.

this class of drugs may also prove beneficially in the more advanced, severe stage of the disease (Howard et al., 2012). This symptomatic treatment improves attention and concentration (Eagger et al., 1991; Sahakian et al., 1993) but other novel symptomatic treatments are needed which address the memory problems subserved by neural networks which critically include the hippocampal formation. Recent cognitive enhancing drugs which target symptoms (such as episodic memory) rather than diagnostic categories (e.g. Alzheimer's disease or schizophrenia) represent a novel approach to drug development which is likely to be successful since it is instantiated in a neurobiological approach. Highly important is the recent development of neuroprotective drugs (e.g. Solanezumab, Lilly), now in phase three clinical trials, for the treatment of patients with Alzheimer's disease. These drugs will actually halt the disease process, rather than treat symptoms only. It is therefore essential that people with mild cognitive impairment who are just developing Alzheimer's disease are detected so that they can be treated while they still maintain a good quality of life and their cognition, wellbeing and functionality at work and at home are still intact. They must receive effective neuroprotective treatment before there is extensive neuropathological damage to their brains.

Psychiatric disorders are disorders of cognition. Many psychiatric disorders are of neurodevelopmental origin with an onset or prodromal stage in childhood or adolescence. Indeed, mental disorders disproportionately affect the young, with 75% of illness having an onset before 24 years of age (Kessler et al., 2012). The cognitive manifestations of mental health disorders include distorted attentional biases, aberrant learning, memory impairments, dysfunctional reward systems and lack of top down cognitive control by prefrontal cortex. In recent years, studies based at the National Institute of Mental Health (NIH, USA) have shown that our brains are still in development into late adolescence and early young adulthood (Fig. 1; Gogtay et al., 2004). It is perhaps not surprising, therefore, that many neuropsychiatric disorders have symptoms of impaired top down cognitive control by prefrontal cortex over behaviour. The brain, particularly, the prefrontal cortex is still developing late into adolescence and therefore especially vulnerable to environmental insults and stressors. Indeed, early psychological stress combined with genetic risk can lead to a negative cognitive view of the world in adolescents which is consistent with biomarkers seen in depression (Owens et al., 2012) and this way of thinking may predispose to depression. It is not only for depression that top down cognitive control is important but also for a range of neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD) and schizophrenia. ADHD is a highly heritable and disabling condition characterised by core cognitive and behavioural symptoms of impulsivity, hyperactivity and/or inattention. ADHD affects 5–6% of children worldwide and is the most prevalent neuropsychiatric disorder of childhood. ADHD has important implications for education provision, long-term social outcomes and economic impact (Chamberlain and Sahakian, 2006; Chamberlain et al., 2007a,b). For example, long-term studies indicate that if not treated effectively, it is associated with poorer long-term outcomes, including educational dropout, job dismissal, increased accident rates, criminal activities and substance abuse and other mental illness. Over 50% of people with childhood ADHD still have symptoms as adults. In addition to problems in cognitive control, ADHD children have deficits in working memory. Working memory is a core cognitive function that is used for any higher level 'executive' task such as planning or problem solving. It allows us to manipulate information and material in our mind while we need it and then to discard it out of our working or 'online' space when it is no longer needed. Working memory is important for at least four reasons. First, it has a strong relationship to fluid or creative intelligence and also to crystallized intelligence or intelligence quotient (IQ). Second, correlation studies support a close relationship between working memory and science achievement. Third, working memory measures at the start of formal education is a more powerful predictor of subsequent academic success than IQ (Alloway and Alloway, 2010). Finally, working memory is impaired in a number of neuropsychiatric disorders, including ADHD and schizophrenia. Therefore, improving working memory with pharmacological, psychological or cognitive treatments could have a big impact on functionality and wellbeing. A shift to novel drug development for the treatment of neurobiologically based specific symptoms, such as working memory dysfunction or impulsivity, rather than diagnostic categories, such as schizophrenia and ADHD, will be crucial. An effective treatment for impulsivity could be used for ADHD, mania and substance abuse (Insel et al., 2012; Sahakian et al., 2010).

Cognitive enhancing drugs, such as methylphenidate or modafinil, can improve performance of healthy people as well as those with ADHD or schizophrenia (http://royalsociety.org/policy/projects/human-enhancement/workshop-report/; Lynch et al., 2013). In studies using positron emission tomography (PET), methylphenidate has also been shown to increase efficiency in the brain network activated during performance of a working memory task by healthy people (Mehta et al., 2000). This increased efficiency includes areas of prefrontal cortex known to be involved in higher level 'executive tasks'. Modafinil not only improves performance on a working memory task in healthy people, but also enhances task-related motivation (Muller et al., 2013). That is, people find doing the task more enjoyable. Therefore, drugs, such as modafinil, may promote motivation for completing tasks that people have been putting off doing, for example studying for exams, preparing long documents or dissertations. Modafinil may also promote task-related motivation in patient groups with apathy or negative symptoms, such as schizophrenia (Scoriels et al., 2012). These cognitive enhancing drugs act by affecting chemicals in the brain that modulate cognition and behaviour. Another of these drugs is atomoxetine, which relatively selectively increases the chemical in the brain noradrenaline.

Atomoxetine improves cognitive control in both healthy people and those with ADHD (Chamberlain et al., 2007a,b, 2010).

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Table 1
Important tools in neuroscience and mental health.

Technique	Method and potential	Reference
Modelling		
iPS cell-derived models	Induced pluripotent stem cells are an emerging tool for modelling disease. These cells can recapitulate the disease process in the cells of individual patients, and could also act as a screening mechanism for therapeutic strategies. In this way, iPS technologies will be important in personalised medicine.	Inoue, H., Yamanaka, S., 2011. Clin. Pharmacol. Ther., 89, (5) pp. 55–61
Genetic techniques		
New-generation antibodies	Monoclonal antibodies are a class of therapeutic molecule that have revolutionised the treatment of oncology since their introduction in the 1980s. However, due to their size they are not able to pass the blood brain barrier and have therefore had little impact in neuropsychology. Recently new generation antibodies, such as fragments and bispecifics, have begun to be developed that promise to finally open the door to this game changing class of drugs for diseases such as Alzheimer's and Multiple Sclerosis.	Buss, N.A., Henderson, S.J., McFarlane, M., Shenton, J.M., de Haan, L., 2012. Monoclonal antibody therapeutics: history and future. *Curr. Opin. Pharmacol.*, 12(5) pp. 615–622
Gene therapy	Viral based gene transfer systems are a useful tool in both research and gene therapy. Treatments for central nervous system disorders could be treated with viral vector approaches, such as in Huntington's and Parkinson's disease. New techniques for gene editing such as zinc finger nucleases, TALENs and CRISPRS are emerging with great potential for treating congenital diseases.	Coune, P.G., Schneider, B.L., Aebischer, P., 2012. *Cold Spring Harb. Perspect Med*., 2, (4) doi: 10.1101/cshperspect.a009431 Palpant, N.J., Dudzinski, D. 2013. Zinc finger nucleases: looking toward translation. *Gene Ther.*, 20(2) pp. 121–127
Engineered receptors	Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are engineered receptors, which are activated by otherwise inert, small, drug-like molecules. DREADDs are currently used by many labs to remotely and non-invasively control neuronal signalling. Although safe and effective viral vectors for delivery of engineered receptors into humans still need to be refined, DREADDs may one day provide an alternative treatment option for neuropsychiatric disorders.	Ferguson, S.M., Neumaier, J.F., 2012. Grateful DREADDs: Engineered Receptors Reveal How Neural Circuits Regulate Behavior. Neuropsychopharm. Rev., 37, pp. 296–297
Stem cell therapy	Stem cells in regenerative medicine are a rapidly growing field. The first successful clinical trials for stem cell implants in disease have now occurred, such as the Pilot Investigation of Stem Cells in Stroke. The first trial to transplant induced pluripotent stem cells into humans to treat macular degeneration are now underway and may soon be starting for spinal cord injury.	Sinden, J.D., Muir, K.W., 2012. Stem cells in stroke treatment: the promise and the challenges. *Int. J. Stroke*., 7(5) pp. 426–434 Cyranoski, D., 2013. Stem cells cruise to clinic. *Nature*, 494, pp. 413 Nakamura, M., Okano, H., 2013. Cell transplantation therapies for spinal cord injury focusing on induced pluripotent stem cells. *Cell Res.* 23, pp.70–80
Optogenetics	Optogenetics has been used to study the neurotransmitter systems in the brain and understand the circuits involved in healthy brain and in animal models of disorders, such as in autism, depression and addiction. Optogenetics can also be used alongside stem cell studies, such as for Parkinson's disease, to investigate whether the implanted stem cells that are altered to express a light sensitive protein can release dopamine.	Tye, K.M, Deisseroth, K., 2012. Optogenetic investigation of neural circuits underlying brain disease in animal models. *Nat. Rev. Neurosci*. 13(4) pp. 251–266 Tønnesen, J., Parish, C.L., Sørensen, A.T., Andersson, A., Lundberg, C., Deisseroth, K., et al., 2011. Functional integration of grafted neural stem cell-derived dopaminergic neurons monitored by optogenetics in an *in vitro* Parkinson model. *PLoS ONE* 6(3) pp. e17560
Imaging		
Diffusion spectrum imaging (DSI)	The development of DSI within the MRI field can measure diffusion directions from individual axonal tracts, allowing for mapping individual nerve fibres. This technique will be an important driving force for advancing connectome mapping.	Wedeen, V.J., Hagmann, P., Tseng, W.Y., Reese, T.G., Weisskoff, R.M., 2005. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn. Reson. Med.* 54(6) pp. 1377–1386
Magnetic resonance imaging (MRI)	With 7 Tesla MRI equipment in use and these machines advancing up the Tesla scale, this technology can allow metabolic processes to be studied at an individual neuron level. This could have great potential in developing and monitoring successful treatments. fMRI has now been used by researchers to decode activity from the visual cortex and reconstruct this into video sequences.	Nishimoto, S., Vu, A.T., Naselaris, T., Benjamini, Y., Yu, B., Gallant, J.L., 2011. Reconstructing visual experiences from brain activity evoked by natural movies. *Curr. Biol.* 21(19) pp. 1641–1646
Positron emission tomography (PET)	PET is a widely used technique for measuring activity relating to brain function, offering a method for early, non-invasive detection of disease. The development of novel radioligands could be important in diagnosing disease, such as Alzheimer's disease.	Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., 2012. Early clinical PET imaging results with the novel PHF-Tau eadioligand [F-18]-T807. *J. Alzheimers Dis.*, Doi: 10.3233/JAD-122059
'Omics'		
Connectomics	Connectomics will combine a number of techniques for studying connectivity within the brain. Understanding these connections could revolutionise our understanding of how the brain functions and the areas affected in 'connectopathies' including disorders such as autism, schizophrenia and Alzheimer's disease.	NIH, 2012. Human Connectome Project http://www.humanconnectome.org/ [date accessed: 04/09/2012] Sporns, O., Tononi, G., Kotter, R., 2005. The human connectome: a structural description of the human brain. *PLoS Comput. Biol.* 1(4) e42
Genomics and Proteomics	Rapidly progressing genomic and proteomic techniques offer huge potential for understanding brain disorders. These are essential for understanding the changes in gene and protein expression that underlie the disease symptoms. However, due to the great power of these techniques they will be of greatest use when data processing techniques catch up.	ENCODE Project Consortium, 2012. An integrated encyclopedia of DNA elements in the human genome. Nature 489, 57–74. Geschwind, D.H., Konopka, G., 2009. Neuroscience in the era of functional genomics and systems biology. Nature 461(7266) pp. 908–915

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Table 1 (*Continued*).

Technique	Method and potential	Reference
Pharmacogenomics	With rapid advances in genetic screening, iPS cell modelling and novel therapeutic developments, the potential for pharmacogenomics may finally be realised. Effective treatments could be tailored to groups or the individual reducing numbers of nonresponders to treatment plans.	McMahon, F.J., Insel, T.R., 2012. Pharmacogenomics and personalized medicine in neuropsychiatry. *Neuron* 74(5) pp. 773–776
Neurotechnology		
Bioinformatics	With so many neuroscience techniques gathering large amounts of data, it is the storing, processing and analysis of these sets that is of vital importance to all fields. The harnessing and mining of these large-scale data sets is progressing quickly but many other techniques are still waiting on bioinformatic advances, such as machine learning, to realise their power. Methods for network analysis offer the promise of integrating data from different scales, which will be essential for connectomics, genomics and linking pathways in the brain to function and disease.	Geschwind, D.H., Konopka, G., 2009. Neuroscience in the era of functional genomics and systems biology. *Nature* 461(7266) pp. 908–915
Brain–machine interface	Brain–machine interfaces (BMIs) link the electronic signals in the brain to a computational device, decode them and then translate them into a command for a robotic device. Such technology has existed for decades but recent advances in electrophysiological techniques has permitted the simultaneous recording of over 2000 neurons, thus permitting the decoding of far more sophisticated behaviours. This approach is now being developed to not only control robotic prosthesis but also restore function to otherwise paralysed muscles.	Welberg, L., 2012. Brain–machine interfaces: restoring movement in a paralysed hand. *Nat. Rev. Neurosci.* 13, pp. 360–361
Mobile health	The mobile phone is becoming one of the greatest tools in medical research. Existing apps already permit the live monitoring of patients following treatment and with the development of every more sensitive and miniaturised sensors it is foreseeable that the smart phone of the future will be able to monitor everything from a person's oxygen consumption to neural activity.	Luxton, D.D., McCann, R.A., Bush, N.E., Mishkind, M.C., Reger, G.M., 2011. mHealth for mental health: Integrating smartphone technology in behavioral healthcare. *Professional Psychol. Res. Pract.* 42(6) pp. 505–512

The most important advance will be the integration of many of these technologies.
Source: Jacqueline P Robbins, BSc, MRes, King's College London and Martin Ducker, BSc, MPhil in Biosciences Enterprise, University of Cambridge.

Neuroimaging studies using pharmacological fMRI has shown that the site of action of atomoxetine critically involves the right inferior frontal gyrus (Chamberlain et al., 2009). This brain area has been shown to be important for cognitive control and stopping impulsive actions. Impulsive actions include such behaviours as a child charging out into the street to retrieve a football rather than stopping by the edge of the road to check whether a car is coming or continuing to push another child in the lunch queue when the teacher has asked the child to stop. Novel pharmacological, psychological and cognitive treatments are in development. We can check their efficacy by observing changes in behaviour but also by detecting changes in the brain via neuroimaging techniques. For example, a meta analysis of cognitive training in people with schizophrenia has shown improvements in cognition and also psycho-social functioning with a moderate effect size (Wykes et al., 2011). These benefits of cognitive training are important particularly as they impact on the functionality of these patients. Studies of the brains of healthy people during cognitive training of working memory has shown both changes in brain activation and also in dopamine receptors (Klingberg, 2010; Olesen et al., 2004; McNab et al., 2009). These important studies illustrate the neurobiological basis to improvements in cognitive function following training. Cognitive training using games which run on iPads or mobile phones will be an important new development to make training exciting and fun. The use of 'serious' games in people with schizophrenia and in the healthy to improve forms of memory or to help promote social cognition and social interaction in children with autism or Asperger's syndrome would be exciting new innovations.

Realizing the future potential of neuroscience over the next 10 years will require a conceptual shift to focussing on good brain health. In the same way that we look after our bodies through healthy eating, exercise and monitoring and detecting physical illness onset through health check ups and screening, individuals need to be as attentive to their minds and wellbeing. Using current and new technology, such as mobile phones, the internet, the cloud will be essential for detecting and monitoring of wellbeing and brain health. The same approach in terms of healthy diet, quality sleep and exercise is important for developing resilience in the face of stress and as promotive factors for good brain ageing.

Education and new learning are known to enhance cognitive reserve and learning and exercise have been shown to increase neurogenesis in the brain in important areas such as the hippocampus, an area key to memory and known to deteriorate in Alzheimer's disease (Olson et al., 2006; Eadie et al., 2005; Gould et al., 1999; Orrell and Sahakian, 1995).

Cognitive function is associated with better wellbeing (Beddington et al., 2008). Science, technology, higher levels of cognitive ability and education are related to increased prosperity, such as gross domestic product (The Royal Society, 2010; Rindermann, 2008). Importantly, investment in mental health has provided substantial economic benefit in the past and should continue to do so in the future (Health Economics Research Group, Office of Health Economics, RAND Europe, 2008).

Working on good brain health is something that should start with the nutrition and wellbeing of the mother prior to birth. Early environment has been shown to be crucial to good development. At school, children should be taught about the factors that affect good brain health, such as healthy diet, exercise and learning for promoters and substance abuse and chronic and severe stress, for detractors.

It is especially important to develop resilience in those early years. Since 75% of mental health illnesses start before 24 years of age, it is crucial to detect the development of these illnesses so they can be treated early and effectively (Kessler et al., 2012). Over the next 10 years, there will be significant advances in understanding the neural basis of resilience. To date, the majority of research effort has focussed on treatment of patients with chronic and relapsing mental health disorders. There is a great need to

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Table 2
The future of neuroscience over the next 10 years: what experts think can and should be done and how it can be achieved.

Question 1: What do you think is a significant and important problem in neuroscience which could be answered/determined within the next 10 years? (i.e. An important and tractable problem/issue which could be successfully solved within 10 years).
Question 2. What do you think is needed that could facilitate that happening?—Other than the obvious answer of money.

Name: Bruce Altevogt
Affiliation:
Director, Forum on Neuroscience and Nervous System Disorders
Senior Program Officer, Institute of Medicine, US National Academy of Sciences, Washington, USA
Answer 1:
While there are numerous challenges facing the neurosciences and developing effective interventions, pharmaceutical and behavioral, for individuals with neurological and psychiatric disorders, I feel one that will have a significant impact over the next 10 years and beyond is investing in interdisciplinary training. Not only do we need to support programs that force collaborations between multiple academic fields, e.g. "traditional" neuroscience, computational biology, systems biology, mathematics, etc., but we also need to improve interactions between the various sectors. Current trainees do not get exposed to what it takes for a small molecule to be brought to market or a psychotherapy to be evaluated and validated. Therefore at the basic research level there is a huge gap created when trying to translate findings to the clinic. Improving the understanding of what it takes to take a finding from the bench to bedside, will get everyone sharing the same language and focused on the same ultimate end goal. This will help close the gap in the knowledge around the basic fundamental biology, and what knowledge is needed to support translation.
Answer 2:
Facilitating this will not require a tremendous fiscal investment. Instead it will require a culture shift in academia that too often shunts industry away from its training programs due to perceived conflicts of interest. Graduate and post doc training programs should include opportunities for courses focused on drug discovery as well as providing opportunities to do rotations in industry labs. True public–private partnerships need to be established at the onset of training.

Name: Edward T Bullmore
Affiliation:
Vice-President, Experimental Medicine, and Head, Clinical Unit Cambridge, Pharmaceutical R&D, GlaxoSmithKline
Answer 1:
Brain network organization – I think the question of how brain networks are organized – the principles that guide formation of brain networks a.k.a. connectomes at micro and macro scales—is an important question that is likely to become substantially clearer over the next 10 years.
Answer 2:
Understanding of human brain networks represented by neuroimaging is particularly likely to advance considerably in this time period. To make progress as fast as possible the key issues will be sharing of good quality large scale datatsets, and sharing and some degree of standardisation of data analytic tools and methods.

Name: Sarah Caddick
Affiliation:
PhD, Neuroscience Advisor, Lord Sainsbury of Turville, Gatsby Charitable Foundation
Answer 1:
The biological basis of cognitive behavioural therapy (CBT).
Currently, CBT is one of the most successful treatments we have for many types of behaviours associated with, or central to, many mental disorders, however little if anything is really understood about the biological mechanisms that are responsible for its efficacy. A solid understanding of the neuronal mechanisms in play could lead to more specific treatments, improved efficacy, and the ability to standardise treatments to be deployed more widely than they are at present.
Answer 2:
Clinical practitioners are largely separate from the neuroscientists that could explore the therapies they have created and deliver with relative success. I would advocate for a targeted consortium based project that brings together these two groups, to explore each side of the problem, and the evidence. I suspect that with a core foundation of support over 10 years, the two groups would deliver what is needed:
a clear understanding of neuronal mechanisms that will allow refinement and tailoring of current therapies in a standardised and rigorous way for each type of behavioural disorder, and the introduction of new CBT therapies based on computational psychiatry research.

Name: Philip Campbell
Affiliation:
PhD, Editor-in-Chief, Nature, London, UK
Answer 1:
To me, an expansion in research into the effectiveness of psychological treatments (PTs) coupled with neural circuitry involved is an obvious priority. Psychological treatments do make a difference, and at a time when traditional translation routes in drug discovery are weak, this avenue is all the more important.
But the availability of randomised controlled trials in PTs is too often lacking, not least in areas that receive lots of publicity and promotion, such as mindfulness therapies, as well as those that receive much less publicity, such as schizophrenia and self-harm. And coupling such trials with imaging, EEG, MEG, and other techniques, as well as genome sequences and other biological data, and optogenetics in animal models, must surely be a hopeful area of research for both fundamental insights and human health. Given that trials and follow-ups can be achieved within 10 years, one can hope for real progress, even though studying children and adolescents is also a priority, which requires follow-ups over decades.
Answer 2:
Of course money will be needed for this. So too will leadership and cultural change if the multidisciplinary opportunities are to be fulfilled. However, I'd be optimistic about this: where money is available and everyone can focus on common goals, the different disciplines can usually find ways of working together. A key problem is the lack of an industry associated with these agendas, equivalent to the pharma industry, other than the gaming and brain-training sectors, and I don't know what one can do about that.

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Table 2 (*Continued*).

Name: Sandra Ceccatelli
Affiliation:
MD, PhD, Professor and Chair, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden
Answer 1:
In spite of the increased knowledge and the huge amount of detailed data on the healthy and diseased nervous system that were generated in the past decades, there have been very low progress in the treatment of neurological and psychiatric disorders. This is certainly due to the complexity of the brain, which has been and still will be one of the greatest challenges for present and future scientists. Modern neuroscience has adopted Reductionism as a strategy to approach the complex problem "nervous system" and focus on isolated aspects. In a way this approach has been successful and generated large amount of information on specific aspects. However, we still do not have an integrated understanding of the brain based on various organizational levels, from molecules to behaviour and this is most likely a major problem that has arrested the development of drugs for brain pathologies. What is needed are new ways of thinking, methods/approaches to integrate the available knowledge and identify new targets for diagnosis and treatments. The focus should also be on the identification of risk factors and early endpoints, which should lead to adequate preventive strategies. By linking genes and molecules with behaviour in experimental and clinical studies we may understand the neurobiological basis for individual variability, making the foundation for personalised medicine, which has already giving benefits in other disciplines, including oncology, cardiology and haematology.
Answer 2:
It may sound obvious, but I believe that to achieve a novel way of integrated thinking we need to promote the interactions among scientists with different expertise, from basic to clinical level. From my experience I can say that to establish a fruitful dialogue among neuroscientists working on different areas is extremely difficult, above all when experimentalists meet clinicians. A link is missing and I am starting to think that drug companies may fill that role, at least partially. We need to have access to their knowledge from CNS research (not only), to get to know about the problems they have faced, the failures, the negative results, the limitations of the experimental approaches and animal models, the struggle to identify predictive, diagnostic, efficacy biomarkers. We have an incredible amount of knowledge that needs to be (re)evaluated, (re)interpreted and integrated and this could be the ground for new industrial/academic interactions.

Name: Vinton G Cerf
Affiliation:
PhD, Vice President and Chief Internet Evangelist, Google
Answer 1:
I think we will have figured out how memory works; not just the basic physiology of changes when memories are formed but that way in which memories are encoded and recovered via interconnected patterns of neurons, dendritic links, etc. There is already evidence that we can turn off a memory (learned behavior) in mice. The mapping of neural interconnections in the brain is underway. You may find it useful to get Ray Kurzweil's latest book: How to Create a Mind. We are moving beyond earlier efforts to encode semantics into computer systems. There is a knowledge graph at Google that has almost 600 million nodes and billions of interconnections—but that is just the beginning. So I think we will be approaching memory and semantics from both the biological and the computational directions.
Answer 2:
Probably the most important thing is to bring together experts in different fields who may not normally have any contact and to expose them to what we know, what we speculate, what we don't know, to see what emerges from the discussion. This feels to me like a big opportunity for bio-informatics, computational biology, artificial intelligence, linguists and others to interact. I happen to believe that experiencing the real world informs the development of language. I think Ray Kurzweil takes the view that language may have arisen in the context of cognitive capacity to plan, invent, execute, teach, learn.

Name: Sherry Coutu
Affiliations:
Chairman of the board: Artfinder, Duofertility & Silicon Valley comes 2 the UK
Board member: Raspberry Pi, Cambridge Assessment, Cambridge University Press Advisory Board Member: Linkedin, Care.com, Tyze.com
Answer 1:
I think that a number of cancers and other interdisciplinary medicine disorders (e.g. neurological and psychiatric) will be solved in the future and that what will be needed is the ability for private companies or charities or educational institutions to be able to access the data in machine readable format so that trends and relations (and reverse cohort analyses) can be performed. In 'the tech world' where I come from, data scientists pore over enormous amounts of data in order to improve their bottom line and their competitive advantage. These very same people could turn this expertise to the NHS data, were the data to be accessible and licensable on an affordable basis. If it has been 'government funded' in the first place, then it should be available (for free) if used for medical purposes.

I think the answer is data-science and that the UK is well placed to be able to solve problems that no other country can. I hope that we do it – the stakes are high and the window of opportunity is now and for the first time, spotting the trends and 'finding the signal' in the noise is affordable. We only need to apply the skills to the problem.
Answer 2:
Mandating that any data is free and in machine readable format. Historically institutions thought they should charge for it or develop these themselves which stifles innovation.

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Table 2 (*Continued*).

Name: Stephen Emmott & Andrew Blake
Affiliation:
Stephen Emmott
Head of Computational Science
Professor of Computational Science at the University of Oxford. Visiting Professor of Intelligent Systems at University College London. Distinguished Fellow of The National Endowment for Science, Technology & the Arts.
Andrew Blake
Distinguished Scientist and Laboratory Director Microsoft Research Cambridge
Visiting Professor of Informatics University of Edinburgh. Visiting Professor of Machine Intelligence, University of Cambridge. Fellow of the Royal Academy of Engineering. Fellow of IEEE. Fellow of the Royal Society.
Council member of the EPSRC.
Answer 1:
Arguably, neuroscience is driven largely by techniques (e.g., fMRI, GFP imaging, two-photon microscopy, psychophysics), rather than by questions. As a result, we do not even know what the right questions are that we need to ask. Interestingly, to this end, 'big-scale' projects such as the Human Brain Map is aimed at mapping what the brain 'is', not what the brain 'does'. One could argue that the most important problem we could try to even determine, and hopefully start to answer, is '*what is it that the brain actually does*'.
Answer 2:
• A strong research focus on 'process-based' models of the brain. That is, on the development of models (or even 'a' model) of the brain based upon theoretical / conceptual constructs of *what* the brain does, rather than simply mapping what it actually is (i.e., the Human Brain Map project: anatomy for the 21st Century).
• Encourage comparisons between prevailing views of physiologically-based 'neural networks' and machine learning based accounts of neural networks that aim to account for the ability to 'learn' (e.g., image recognition) through, e.g., Convolutional Neural Networks [CNN's]. Such machine learning models are rich both in feedback and feedforward connections, just like the brain, but make explicit *why* one really needs feedback and feedforward connections. It would be fruitful for neuroscientists to look for such structures – and processes – in the brain, and at the signals that occur at various points in these structures.
• To identify what conceptual and computational methods and techniques (such as those above) are required to be able to ask (and ultimately start to answer) the right questions.
• Train a new generation of new kinds of neuroscientists – scientists with a different way of thinking that embraces computational metaphors, models and methods. They would be scientists who are scientifically first-rate both in the broader biological sciences domain, and also in computational theory and techniques.

Name: Elizabeth Fisher
Affiliation:
Professor, FMedSci, FSB
Department of Neurodegenerative Disease
UCL Institute of Neurology
London
Answer 1:
Invest in informatics: There are two large scale mouse genetics projects underway globally at the moment. The first is to knock out every gene in the mouse, creating > 20,000 new mouse lines. The second is to phenotype these animals providing a wealth of information and data applicable to basic biology and to human disease. The latter project (the International Mouse Phenotyping project) has so far had over $250 million dollars invested in it by e.g. Wellcome Trust and, e.g. £40M by the MRC. The UK is a huge player and the current president of the project is Professor Steve Brown, who is also director of MRC Harwell.
These projects have generated a tremendous requirement for **informatics** to support the primary data capture, analysis and dissemination to the wider scientific community, including the neuroscience, biotech and pharma communities. The diversity of data being collected is immense, ranging from qualitative descriptions of phenotypic observations, through quantitative measurements, to 2D and 3D imaging data and eventually more specialised secondary phenotyping. The coordination of this diverse dataset is a significant informatics challenge with every single mutant mouse gene knockout currently generating on average 20,000 data points (and of course this will increase as tests become more sophisticated). The downstream computational analysis of this wealth of data requires significant informatics efforts which are currently in their infancy to develop novel methods to integrate this data with **human datasets** to predict candidate human disease genes and understand basic biological mechanisms. NIH (USA) recognises this, and recognises the UKs leading role in informatics by awarding roughly £2M EACH to the Sanger Institute and to MRC Harwell to develop informatics resources, capitalise on the data generated, and in doing so train new cohorts of informatics scientists. We should maintain our lead in this field which can only get more and more important for all aspects of science including neuroscience and which is pulling in foreign (NIH) funding to the UK currently.
Answer 2:
Restoring the railway line between Oxford and Cambridge is critical for enhancing the communication between the three main Neuroscience centres in the UK: Oxford, Cambridge, London. So creating an astonishing intellectual mass well-connected to major airports and with the advent of Crossrail this also brings everyone into direct connection with the Eurostar system. It also gives a range of possible housing that is relatively affordable for young families and badly paid postdocs/PhD students. And includes plenty of brownfield sites for burgeoning biotech/pharma.

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Table 2 (*Continued*).

Name: Russell G Foster
Affiliation:
President of the British Neuroscience Association
BSc PhD FSB FRS
Head, Nuffield Laboratory of Ophthalmology, Fellow, Brasenose College, University of Oxford, Oxford, UK
Answer 1:
Understanding the links between sleep disruption and mental illness: Sleep is a complex state arising from an interaction between multiple brain regions, neurotransmitter pathways and hormones, none of which are exclusive to the generation of sleep. This complexity makes sleep very vulnerable to disruption. Small changes in brain function can have a big impact on sleep, and disrupted sleep leads to health problems ranging across increased stress hormones, heart disease, weight abnormalities, reduced immunity, increased risk of cancer, and emotional and cognitive problems.
Many mental illnesses are commonly associated with highly disturbed sleep, but the importance of this disruption is frequently overlooked. Significantly, many of the health problems that arise from disturbed sleep are also found in mental illness, but these problems are rarely linked back to sleep abnormalities. Emerging data from human studies and animal models suggests that parallel brain pathways are affected in mental illness and sleep disturbance. By bringing together molecular and systems neuroscientists, psychiatrists, psychologists, and bioengineers the following key objectives could be achieved:
• Understand the causal relationships between sleep disruption and psychoses, testing the hypothesis that pathways common to both account for the comorbidity, using preclinical and clinical approaches.
• Develop evidence-based interventions that correct sleep disruption and improve health and quality of life in patients with mental illness.
Answer 2:
Facilitation:
A new approach for neuroscience: In the past decade significant advances have been made in our understanding of the structure and function of the central nervous system. Detailed information has emerged about the molecular and cellular basis of core functions of the brain that provide the physical substrate for brain involvement in autonomic, endocrine, sensory, motor, emotional, cognitive and disease processes. These developments, and advances in bioinformatics and computational modelling place the neuroscience community in a position to address the bigger picture of how the brain functions through multiple coordinated levels to produce both normal and abnormal behaviour.
Traditionally questions in neuroscience have been addressed by single laboratories holding project level support. It is evident, however, that major advances in the neurosciences depend increasingly upon a critical mass of researchers using integrated approaches and shared facilities. Furthermore, the expansion of experimental medicine is providing new research opportunities at all levels. The human genotype to phenotype link, arising from close cooperative contacts between clinical and non-clinical researchers, is an increasingly important driver in elucidating fundamental mechanisms and evidence-based therapeutics.
Key aims for me would be to promote:
• Vastly improved communication at all levels between neuroscientists and clinician scientists in major research institutions. For example, provide *fit-for-purpose* neuroscience coordinators who understand neuroscience and would be capable of leading and driving activities that would de-silo neuroscience researchers across and between institutions. Coordinators would be sufficiently sophisticated to understand the potential links and help facilitate communication across all sectors. Such posts do exist within research institutions but are in general undertaken by individuals who lack specialist training in neuroscience and have poor leadership skills.
• Fund, promote and expand integrative research programs across the neurosciences and between different research groups and clinician scientists. For example, expand the model of the Wellcome Trust strategic award which provides the infrastructure – often in terms of research personnel—to allow researchers from varied backgrounds to work together towards a common and specific research goal.
• Reward neuroscientists and clinician scientists for working and publishing together. Currently authorship on multi-author papers is an impediment for career advancement rather than being seen as a badge of success. We must applaud and not marginalize those neuroscientists who demonstrate successful cooperation and a commitment to sharing resources, knowledge and expertise to deliver first-class research.

Name: Uta Frith
Affiliation:
DBE, FRS, FBA, FmedSci, Emeritus Professor of Cognitive Development UCL, London, UK and Visiting Professor at Aarhus University, Denmark
Answer 1:
Social Cognitive neuroscience is a flourishing discipline but the interesting work is only just beginning. I believe that by extending research into the evolutionary origin of social abilities and their development throughout the life span, significant progress could be made towards the most exciting scientific aim for the 21st century: understanding how the mind/brain works. While this grand aim is unlikely to be accomplished within the next ten years, it should be possible to obtain knowledge about the neuro-cognitive basis of social cognition.

Answer 2:
While there has been progress on agency detection and 'Theory of Mind', other components of social cognition have been neglected. Such components include ingroup/outgroup categorisation, social hierarchy mapping, as well as processes underlying the pressure to conform to majority behaviour and those underlying social identity and self awareness. We still do not know whether there are separate reward systems in the brain for social and non-social stimuli.
Research so far has benefited from looking at disorders that are marked by abnormalities in social communication, e.g., autism, schizophrenia and some genetic syndromes. These provide a window to the existence of otherwise hidden cognitive components. Future research will benefit in turn from the understanding and treatment of these disorders.
At present research is hampered by lack of technical facilities that allow neuroimaging in children. Technological advances need to be made and they will only be made if there is a demand. Thus, I would recommend closer collaborations between neuroscientists, engineers, and VR game designers. Together groups of such people would be able to design far more interesting experimental scenarios than are currently in use. One noticeable gap is the lack of psychometrically validated measures that could be used to assess individual differences and to monitor changes with therapeutic intervention.

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Table 2 (*Continued*).

Name: Guy Goodwin
Affiliation:
FMedSci, President Elect of the European College of Neuropsychopharmacology (ECNP)
W.A. Handley Professor of Psychiatry,
University Department of Psychiatry,
University of Oxford,
Warneford Hospital
Answer 1:
We do not know whether it is possible to prevent severe mental illness arising in young people. A sustained multi-centre study could answer this question, if it was sufficiently large.
Answer 2:
Cooperation between research active centres in psychiatry, and a serious reform of the regulatory barriers to pragmatic clinical trials. We currently have the ludicrous situation that the **same** intervention in a clinical trial is hedged around by nit-picking obfuscatory ethical and regulatory demands while in ordinary practice can be prescribed without any restriction whatsoever. Pragmatic clinical trials should be made easy to incorporate into practice.
Name: John Hardy
Affiliation:
Professor and Head of the Department of Molecular Neuroscience and Chair of Molecular Biology of Neurological Disease at the UCL Institute of Neurology. University College London, London, UK
Answer 1:
I think the biggest problems in Alzheimer's disease are organisational. I think we have a reasonably good idea of the mechanism of the disease (though I do think we need to know the normal function of APP and amyloid). The biggest problem is getting access to large numbers of patients early in the disease and even before disease manifestation and enrolling them in clinical trials. While there are clearly ethical issues in this, there are also bureaucratic hurdles. Ethics applications are really burdensome and the process is slow: especially, for example, in Down syndrome, in which research was basically stopped by ethics regulations. As you know, all Down patients get Alzheimer's. We should be trying mechanistic therapies in this population.
In other disease areas, Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, we still need more basic work to define the pathway to disease: but we should be building up patient cohorts now so we can do trials in these groups as we do understand more.
Answer 2:
One thing which would clearly help is less regulation. We all spend far too much of our time, filling in paperwork.. the human tissue act, the animal rights legislation (the toughest and most burdensome in the world).
I also think that every person at age 60 should have a health MOT which included a brain MRI. We need anonymous patient data too to be easily available. What factors at age 60 predispose to AD 15 years later? We should have population wide screening at that age both to see risk factors and to have a basis for comparison 15 years later. The data should be computerised (!!!!!! obviously. . . but often isn't). My guess frankly would be that this form of universal health exam would, in itself, identify a huge number of preventable risk factors (high blood pressure, high blood sugar, high cholesterol) and would certainly allow a doctor who ordered an MRI in the same person at age 70 to quickly see if there had been atrophy and make diagnoses earlier and easier. At the Mayo, they used to do an annual health evaluation for execs (at a price of course). This would be a very good thing to do here
Name: Hermann Hauser
Affiliation:
PhD, FRS, FReng, CBE.
Partner, Amadeus Capital Partners Ltd, Cambridge, UK
Answer 1:
In a word: SpiNNaker (Spiking Neural Network architecture), Professor Steven Furbers project to use 1 million ARMs (Advanced RISC Machines) to simulate 1bn neurons at the spiking level in real time.

This is part of the €1bn European Flagship program on the Brain that has just been announced. It will allow us to study quite complex neural networks which are many levels deep and therefore could exhibit some of the more sophisticated functions of the brain.
Answer 2:
Many people using SpiNNaker to try out their theories on how the brain works.

Name: Steven Hyman
Affiliation:
Harvard University Distinguished Service Professor
Director, Stanley Center for Psychiatric Research
Broad Institute of MIT and Harvard, Cambridge, MA, USA
Answer 1:
I think there are two problems of large scale that are tractable- and even if not finished in 10 years, they would produce actionable results:
Genetics of brain disorders with high heritability (autism, schizophrenia, bipolar, ADHD, perhaps OCD, Tourette). The technologies are in place. What is needed is for the UK to support global consortia over the many years it will take. The Cardiff group are already involved, but this needs real patience on the part of funders, and then an understanding of what genetics is for: it is to gain biological clues to pathogenesis and treatment.
Obama announced United States Government support for mapping the human brain. What is needed is both a wiring diagram and map of functional connectivity in humans. Without this, imaging remains somewhat untethered. More importantly, many neuropsychiatric disorders are disorders of synapses and circuits. How can we understand these disorders without this basic map?
I distinguish this from the Continental Blue Brain Project (BBP) because they are modeling without knowing what to model. What we need is hard-won technology based empirical interrogation of genes and brain.
Answer 2:
New models of research support are needed, for example- long support of global consortia with good flexible governance. What neuroscience can now attain, but not in the small lab model, is fundamental information about the organ we work on and the genes that are so critical in building it.

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Table 2 (*Continued*).

Name: Thomas Insel
Affiliation:
Director, NIMH/NIH/DHHS, Bethesda, USA
Answer 1:
The Holy Grail of neuroscience is understanding how the brain encodes, processes, and stores information. We describe the human brain as an information processing machine, like a computer. In truth, we actually have a very limited understanding of how the brain functions, although we know that this astonishing computational machine works unlike any computer ever designed by man. To crack the code of brain processing over the next decade, we need to record brain activity at a scale that is far more comprehensive than single cell recording and far more detailed than current neuroimaging techniques. Our most comprehensive recording efforts today detect spikes from 100 neurons simultaneously. Increasing our ability to record from thousands to hundreds of thousands to millions of neurons is a grand challenge for the next decade in neuroscience. This becomes possible by marrying techniques from nanotechnology and neuroscience as well as developing analytical techniques to manage the extraordinary amount of data from massive parallel recording. Already we are seeing the promise of comprehensive recording in simple model organisms, where soon we will be able to track the activity of every neuron in a behaving nematode. Scaling up these efforts to mammals and ultimately to human circuits will not only teach us how the brain works but should yield an entirely new approach to information technology.
Answer 2:
We need better tools. Neurophysiology in 2013 looks a lot like neurophysiology in 1993. We need a grand challenge effort bringing together neurophysiologists, nanotechnologists, bioinformaticians, and many others to develop the next generation of recording tools. This could be done via an organized plan to scale up from simple model organisms to more complex systems. This project, like the genome project, may be as consequential for the tools generated as for the ultimate goal of mapping the mind.

Name: Thomas Jessell
Affiliation:
Professor, Columbia University, Centre for Neurobiology and Behaviour, Biochemistry and Molecular Biophysics
Answer 1:
One disease that should yield to scientific advance is Amyotrophic Lateral Sclerosis, an almost invariably fatal motor neuron degenerative disease. Several target pathways have now been identified, and small molecule drug inhibitors are available that in principle should slow or block disease progression.
Answer 2:
What is needed to drive these advances is effective collaboration between academia, biotech and big pharma. The compounds exist, evidence of efficacy in mouse models of the disease should lead to phase 1 clinical trials within the next 5 years, and indications of human efficacy within 10.
The UK government could have a big role in driving such a collaboration.
Name: John Krystal
Affiliation:
MD
Robert L. McNeil, Jr., Professor of Translational Research
Chair, Department of Psychiatry, Yale University School of Medicine
Chief of Psychiatry, Yale-New Haven Hospital, New Haven, USA
Director, Clinical Neuroscience Division, VA National Center for PTSD, VA Connecticut Healthcare System, West Haven, USA
Answer 1:
The Psychiatry Genomic Project: with current technologies and sufficient investment in sample collection, it would be possible in 10 years to identify all gene variants that individually have a substantial impact on the risk for several disorders, particularly autism and schizophrenia.
Answer 2:
A critical question for this type of project would be whether it would be possible to leverage this effort against other large scale genetics initiatives for this disorder. Perhaps there are sufficiently large and well-characterized datasets available, but what would be needed would be commitment to conduct the whole genome sequencing (not just the exomes).
John Krystal additional comments:
The Human Developing Connectome Project: To conduct a large scale, high resolution, study of the developing human brain in a large cohort (MRI, DTI, fMRI functional connectivity, etc.). The study should be large and long enough to explore the emergence of psychopathology as neurodevelopment.
21st Century Psychiatry Project: A program to establish programs to train a generation of psychiatrists in molecular, translational, cognitive neuroscience and to prepare them to incorporate the advances in science as they develop clinical and research careers.
The UK Prevention Study: To evaluate the impact of 1) educating the public (through schools, public advertisement, etc.) about signs of risk symptoms (magical thinking, cognitive impairment, affective symptoms, social withdrawal) that may portend the emergence of schizophrenia and bipolar disorder, 2) establish a network of teams capable of evaluating these "high risk" adolescents and providing cutting edge intervention (family therapy, cognitive remediation, medication, etc.) in order to determine whether this type of early detection and intervention forestalls the development of disabling psychiatric disorders (schizophrenia, bipolar disorder). This should be a randomized trial in order to determine if and for whom this type of intervention is helpful (building on the progress in developing a national early detection system in Norway).
UK Partnership for Psychiatry Drug Development: To fund a large scale psychiatry drug development initiative modeled after the NCATS "repurposing" program. The objective would be to fund, on a large scale, the testing of novel pharmacotherapy mechanisms for psychiatry using translational neuroscience approaches in proof-of-mechanism/proof-of-principle experimental design. The intention is to stimulate reinvestment in psychiatry drug development by the pharmaceutical industry, particularly UK companies (like GSK) that have withdrawn from psychiatry drug development.
Name: Alan I. Leshner
Affiliation:
Chief Executive Officer, Executive Publisher, Science American Association for the Advancement of Science, USA
Answer 1:
I believe that over the next 10 years we will learn a tremendous amount about the common brain mechanisms underlying the array of addictions.
The original conception was that each addiction was unique in mechanism but, of course, the brain did not evolve for addiction to non-natural substances, and as the neuroscience of addiction has advanced over the past 10 years, we have seen shared mechanisms characterizing not only all drugs of abuse but also things like compulsive gambling and compulsive overeating.
Answer 2:
A major limiting factor has been the inadequacy of animal models of addiction as opposed to heavy drug taking...we need to have better models of the compulsive quality of addiction. Shaham and others (2002, 2003) have given us good models of relapse (cue induced or stress-induced relapse for example), but we still seem to lack a really good model of the compulsion aspect. I believe some of this limitation has come from an over-dependence on the reinforcement model of drug taking, which may (or may not) be correct or sufficient. So we will only develop new and likely improved animal models when the field is willing to go beyond the more traditional reinforcement paradigms to study the phenomenon.

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Table 2 (*Continued*).

Affiliation: Professor at the Department of Psychology, Peking University, Beijing, China.

Answer 1:

The emergence of consciousness is only necessary if the brain intends to precisely represent objects and events occurring in complex surroundings. **What are the basic principles underlying consciousness?** With the increase of our knowledge of various aspects of neuroscience, I feel confident that in the next 10 years we will reach a deeper understanding of the nature of consciousness.

Answer 2:

If researchers from different areas in neuroscience, psychology, computer science, biology, and philosophy set up the same target and build up all types of investigation collaborations, the approach to the problem proposed above could be facilitated.

Name: Simon Lovestone

Affiliation:

Professor of Old Age Psychiatry, Director of Research, King's Health Partners, NIHR Biomedical Research Centre for Mental Health, King's College London Institute of Psychiatry, London

Answer 1:

In relation to Alzheimer's disease the need is simple but elusive. On the one hand we need therapeutic targets and on the other we need a means to test these in man. The problem is that we have some but not enough targets and the only way to test such targets today is with trials that would have to be too big and too long to be economically viable either for the pharma that would have to conduct them or the health services that would have to fund the therapies that resulted if such trials were ever conducted.

To break these two problems down a little more, there is no doubt whatsoever that some targets have been identified – BACE1, plaque clearance through immune-modulation, gamma-secretase, etc. But these targets all aggregate around amyloid and there are insufficient targets for other elements of the Alzheimer's disease pathogenesis. So:

Problem number 1: Identify other, non-amyloid, targets in AD pathogenesis by understanding the amyloid cascade, by determining the role of inflammation and other processes and by clarifying how these processes interact.

Problem number 2: To identify biomarkers (howsoever defined) indicative of pathology. Such markers could be used for stratification, for early disease identification, for PoC and target engagement studies and in experimental medicine/phase II studies

Answer 2:

What is needed to resolve problem number 1—A greater focus on non-amyloid processes, a focus on improving animal models that translate to humans, an exploitation of recent advances in understanding pathogenesis through genomics and biomarker studies.

However, discovery of novel therapeutic targets is of little value if they cannot be tested in man. The current approach of performing studies in people with established and sometimes very extensive pathology including neuronal loss makes a positive outcome from a clinical trial highly unlikely and it is of little surprise that all trials are reporting negative findings. The risk is that excellent therapeutics will be lost because of trials that are biased heavily towards a fail-outcome. One approach to better clinical trials are very long term, very large trials approaching a true preventative strategy. Such trials are hugely expensive and few will be conducted. Another is trials in highly susceptible individuals (familial gene carriers, people with Down's syndrome, etc.) and such trials are promising and underway but logistically challenging given the numbers of potential subjects. A third, and more conventional approach, is of true experimental medicine and rigorous phase II trials enabling effective and rapid decision-making. Learning how to end a therapeutic sooner is the critical task. In order to do this one needs biomarkers. So:

What is needed to resolve problem number 2—Critical to biomarker identification is collaboration and sharing of data across cohorts, continents, study groups and technology platforms. Obviously suitable cohorts need to be identified, appropriate studies conducted and data analysed effectively. However, beyond this, it is the re-use of existing datasets, the expansion of data through cohort aggregation, the validation of data by collaboration and the pre-competitive co-operation of pharma and academia that will resolve the problem of biomarkers for Alzheimer's.

Name: Chris Lowe

Affiliation:

Professor and Director of the Institute of Technology, Department of Chemical Engineering and Biotechnology, University of Cambridge

Answer 1:

Biomarker discovery for neuroscience, neurodegenerative and neuropsychiatric disorders via blood analysis of low abundance proteins/peptides. Once validated biomarkers are identified, these can be used to verify animal models as true analogues of human degenerative/psychiatric disorders and used in de novo drug discovery. Such biomarkers can be used to stratify patients in terms of symptoms, drug response and ultimately lead to personalised medicine for these disorders. By analogy to e-Medicine this will eventually lead to e- and m-Psychiatry (m = mobile).

Answer 2:

More molecular training for psychiatrists, possibly via a Master's course.

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Table 2 (*Continued*).

Name: Husseini Manji
Affiliation:
MD, FRCPC
Global Head for Neuroscience at Janssen Research and Development, LLC, a division of Johnson and Johnson
Answer 1:
Use 'Big Data Systems Biology' and combination of EMR, biomarker, remote mobile data to a) discover/validate biosignatures to reduce patient homogeneity (which would translate to markers of response), b) understand disease course, and develop diagnostic and prognostic markers and enable 'predict and preempt', using data from longitudinal studies, including use of read-outs from point of care and remote monitoring platforms c) implement Systems Biology approaches to connect molecular profiles to patient readouts, genome to phenome, computational drug repositioning (using co-morbidity and side-effects data e.g. at the interface of CNS and immunology), understand poly-pharmacology (suggest multi-target opportunities) and identify new targets and pathways for synaptic plasticity/cellular resilience phenotypes from combination of preclinical and clinical data (hence 'reverse translation').
This approach will leverage clinical and hospital based data assets from the EU area, such as, IMI (EMIF), EPIC (www.epiconline.ie), Heinz Nixdorf, UK Biobank (see attached) to name just a few. Also, we can leverage data from our various integrated care studies based out of Europe (Lower Saxony, Geriactive (out of Poland), TRIL, South Essex, etc.). In addition, this project could leverage connectomics type data that will be collected and standardized in the EU via the 1.3 Billion dollar funding to the Human Brain Project.
Answer 2:
The other obvious asset required is access to data. So mechanisms to share and pool data pre-competitvely. And also IP frameworks to share findings. Inability to get such terms worked out often leads to splintered efforts
Husseini Manji additional comments:
- Multi-target approaches to Alzheimer's disease: This is linked somewhat to the project above in that it starts off with identifying networks of proteins that may be implicated in disease (AD). But this goes a step further and implements specific drug-design strategies to develop multi-targets ligands that would target these networks, and phenotypic assays that would be used to measure 'quantitative endophenotypes' optimize these compounds in a medium throughput manner. This approach could also use stem cell lines (which in and of itself is a very worthwhile project to fund). A systematic, unified approach to multi-target drug optimization and development which combines systems/network biology, phenotypic screening, chemogenomics based multi-target ligand design could potentially offer power and unique interventions in AD (and this also walks the talk of our holistic solutions commentary which argues that we need to hit multiple targets for complex diseases).
- The broad area of Biomarker development for mood disorders and antidepressant treatment response.
- Genetic stratification of response to distinct antidepressant drug classes.
- Elucidation of the role that pro-inflammatory cytokines play in the pathophysiology and treatment of depression.
- Characterization of the neurobiological (e.g., genetic) correlates of resilience versus vulnerability to the development of mood disorders following physiological stressors that include immune challenge (e.g., using interferon or LPS) or catecholamine depletion (e.g., using alpha-methyl-para-tyrosine). Emerging evidence suggests that these challenges are robust in their ability to induce depressive symptoms in susceptible individuals – based on family history of mood disorders – irrespective of their personal history of depression.

Name: Stine Hove Marsling and Peter Høngaard Andersen
Affiliation:
Stine Hove Marsling
Senior Global Public Affairs Manager
Public Affairs Denmark
Lundbeck
Peter Høngaard Andersen

cand.scient., dr.med.
Senior Vice President
Global Public affairs and corporate patents
Lundbeck
Answer 1:
Societal benefits would include the provision of both prevention and effective treatments for a large and growing patient population, whom today do not receive adequate treatment. Because of the impact of these diseases on not only health, but also people's ability to function socially and at work. Addressing this area offers huge potential savings for society, reducing healthcare costs and social benefit expenditure while increasing employment and productivity.
The symptom-based treatment approach for managing these diseases needs to be enhanced with the application of treatment approaches that take advantage of the latest evidence and tools available. Furthermore, the number of untreated patients is high. Hence, there is a major unmet medical need which, if properly addressed, will improve the health and quality of life of patients and their families.
Answer 2:
To facilitate this happening, a number of activities need to be prioritized: (i) implement preventive activities in society, i.e. modeled over the plan from the Canadian mental health commission. (ii) Incentivize research in a better understanding of disease biology of mental disorders. (iii) Update disease definition in mental disease to reflect a molecular basis rather than the 150-year-old symptom based system used today. (iv) Incentivize clinical research to develop novel methodologies to quantify clinical benefit of treatments and ensure these novel methods reflect true medical needs. (v) Ensure the regulatory framework and payer incentives reflects reality of what society needs and facilitate innovation within the brain disease area. Success for these activities are best secured in a public private partnership setup as this would allow the pharmaceutical industry to enter a high risk healthcare area and to start collectively a dialogue with a range of stakeholders beyond health and research needed to address this huge healthcare challenge.
Name: David Menon
Affiliation:
MD PhD FRCP FRCA FFICM FMedSci
Professor and Head, Division of Anaesthesia, University of Cambridge
Consultant, Neurosciences Critical Care Unit
BOC Professor, Royal College of Anaesthetists
Professorial Fellow, Queens' College, Cambridge
Senior Investigator, National Institute for Health Research, Cambridge, UK

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Table 2 (*Continued*).

Answer 1:

Acute brain injury (traumatic brain injury, intracranial haemorrhage, ischaemic stroke) represents a major cause of acute mortality and morbidity, and residual disability and societal burden in the UK and Europe, and some acute insults can increase the risk of late dementia. While increased resources could clearly improve care, substantial benefits could be achieved through organisational changes and investment in novel (cost-effective, and even potentially cost saving) new technologies. Improvements in the organisation of care delivery, care transitions and data communication are of wider importance, but are especially relevant for neurological diseases, since technology needed for optimized acute care is expensive and demands centralization, even acute cognitive outcomes take time to declare themselves, and acute conditions may be associated with late cognitive decline.

Answer 2:

- Organisational changes: Centres with larger patient volumes, specialist services, and/or evidence based protocols provide more effective access to definitive care and deliver better outcomes for traumatic brain injury, subarachnoid haemorrhage and ischaemic stroke. Streamlined patient pathways could deliver cost neutral (or even cost saving) improvement in clinical outcomes, and provide organisational substrates for comparative effectiveness research (see below), with political fallout from the required reorganization mitigated by care partnership models.
- Improved management of transitions of care. There have been substantial improvements in the interface between pre-hospital and emergency care, and emergency and inpatient services. However, there are still substantial deficiencies in the handover of patients between acute care and rehabilitation, and rehabilitation and community services and primary care. Addressing this issue could save lives, reduce disability, improve rehabilitation and increase cost-effectiveness.
- Improved information flows within and between primary, secondary and tertiary care. Communication between hospitals is still limited to electronic versions of paper documents and digital imaging. Communication between primary and hospital care and between patients and their doctors is at least 20 years out of date. Modernizing communication will require legislative and regulatory effort, but will ensure that doctors have the best information when they treat individual patients, empower patients as active partners in health care, increase organisational efficiency, and provide framework for high quality comparative effectiveness research and quality improvement (which may offer more effective pathways to evidence based medicine than RCTs).
- Investing in new treatments and technologies. Specific areas of or potentially rewarding research and development include zero power autonomous systems. Such technology could deliver wearable ICU monitoring, allowing us to take technology to individual patients in pre-hospital and post-ICU settings, rather than having to corral them into an environment where the technology can be delivered. Such technology could also have a role in promoting wellness, detecting individuals at high risk of disease, monitoring these individuals for the early detection of transition to disease, and supporting declining cognition in a variety of ways. Pharmacological cognitive modulation could be used to enhance residual cognitive function, and recent data on selective memory modulation in addiction suggests ways to make a substantial impact on drug abuse, smoking and possibly obesity. Additionally, effective web based communication could provide a cost-effective way to deliver cognitive therapies and monitor their impact.

Name: Richard G M Morris

Affiliation:

FRS, Professor, Centre for Cognitive and Neural Systems, The University of Edinburgh, Edinburgh, UK

Answer 1:

Contemporary neuroscience is characterised by a number of grand challenges ranging from the development of the brain, the representation of diverse forms of information in its neural and biochemical activity, through to questions about aging and neurodegeneration. All are important and time-honoured problems—research on these should and will continue. However, if I were to pick out a single tractable problem that could be addressed and hopefully solved in the next ten years is that of why and how cognitive and behavioural treatments for mental illness actually works. There is growing evidence that they do work, such treatments are now being rolled out into primary care in the United Kingdom, and it would be extremely valuable on behalf of the patients and families affected to have access to information of ongoing improvements and the efficacy of such treatments. While many of these have been developed on the basis of behavioural principles guided by modern cognitive psychology, it would be valuable to have an understanding of the neural mechanisms underlying efficacy.

Answer 2:

This could be done in the next ten years, but would require an opening of minds on the part of clinical psychologists and neuroscientists to their different ways of thinking and working, a new understanding of the distinct priorities of these two disciplines, and a recognition that collaborative mutual effort would be worthwhile in the long run even if the initial hurdles to effective joint working may be difficult.

Name: V Hugh Perry

Affiliation:

Chair of the MRC Neuroscience and Mental Health Board and Professor, Centre for Biological Sciences, University of Southampton, Southampton General Hospital, Southampton, UK

Answer 1:

In the next ten years it will be possible to understand how risk
factors such as vascular disease, obesity, diabetes, that are
associated with cognitive decline in the elderly and the onset or
progression of dementia, contribute to loss of function of the ageing brain

Answer 2:

The Neuroscience community needs to work with biomedical scientists from other disciplines to understand how age related changes in our physiology will impact on the ageing brain. This requires a change in culture towards a 'whole organism systems approach' rather than the current division of disciplines.
The government also has a role to play in encouraging people to take more exercise and eat a healthy diet

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Table 2 (*Continued*).

Name: Anthony G Phillips
Affiliation:
PhD, FRSC, FCAHS
President of the International College of Neuropsychopharmacology (CINP), Scientific Director/Directeur Scientifique, CIHR Institute of Neurosciences, Mental Health and Addiction, Professor, Department of Psychiatry, University of British Columbia, Senior Scientist
UBC VCHRI Brain Research Centre, British Columbia, Canada
Answer 1:
The prospect of Machine-Brain is ripe for significant translation, as shown by team led by John Donoghue, a neuroscientist at Brown University (see also "Brain Chip Helps Quadriplegics Move Robotic Arms with Their Thoughts"). Amongst the many applications one can envisage, the following are particularly exciting:
• The development of superb prostheses that include the sensation of touch along with proprioceptive feedback that ensures smooth and integrated movement of artificial hands, arms, legs and feet.
• Extending this list, there are very real prospects for exquisitely sensitive and accurate 'artificial' eyes and cochlea that would initially restore vision or hearing to individuals that have recently suffered the loss of vision or hearing.
• The knowledge gained through the restitution of motor and primary sensory function would also have a profound impact on the development of sophisticated robotics that could mimic human-like interaction with the world around them.
• As the Brain Sciences develop the capacity to translate functionally relevant electrical signals from both cortical and sub-cortical regions, and then to integrate this information with computers, this will provide the means to ascertain the conscious state of individuals in various levels of consciousness.
• A new field of stimulation-induced neuro-rehabilitation would follow with initial application in the treatment of stroke and traumatic brain injury.
• Parallel work would find applications in areas of clinical neuroscience focused of cognitive and emotional deficits.
• Accelerated research on biophotonics could reveal alternative and possibly superior means for efficient brain–machine interfaces than electrical transmission
• Towards the end of this decade of translational brain sciences, the accumulated knowledge would likely find many applications in computer technology of use in daily living, by which mental instructions could be used to activate specific programs thereby providing information or a service, on command.
Answer 2:
In order to realize the tremendous potential of machine–brain interface research, it will be essential to encourage leaders in computer sciences and electrical engineering to join forces with cognitive neuroscientists in new multidisciplinary research programs that also serve as high quality training programs that will create new specialists who can move seamlessly between these different disciplines. A minimum of 3–5 programs of this nature should be created immediately and funded at an appropriate level by public private partnerships.

Name: John D Pickard
Affiliation:
Professor of Neurosurgery in the University of Cambridge, Chairman/Clinical Director of the Wolfson Brain Imaging Centre and Divisional Director for NHS Neurosciences at Addenbrooke's Hospital, Chairman of the Joint Neurosciences Council and Honorary Civilian Consultant for Neurosurgery to the Army, Cambridge, UK
Answer 1:
Acute brain injury is not just a single abrupt event but the start of a chronic disease with dynamic processes that remain active for years that result in physical and neuropsychological problems, which represent a substantial burden on the individual and society. For example, in the UK, there are some 0.5 million (~1% of the population) attendances at Emergency Departments every year of which 25,000 (5%) are moderate or severe leading to a range of disabilities including complete dependency and the vegetative state. Head injury in childhood is associated with an increased risk of psychopathology, emotional lability, apathy and criminality in adulthood.
Answer 2:
Advan in prevention and acute care starting at the roadside, timely surgical intervention through intensive care has reduced poor outcomes by some 40%. In contrast, the field of neurological rehabilitation is not yet built on solid scientific or theoretical foundations. There is now compelling evidence from the use of all the tools available to modern human neurosciences that learning and brain injuries induce plasticity and reorganization in the adult and developing brain. While many mechanisms have been described at multiple levels of analysis (Cognitive, Systems and Cellular) as proof of principle in experimental animals or human subjects, their relevance to human diseases needs much further clinical validation and integration. An integrated approach is now required, based on a coherent critical mass of basic and clinical neuroscientists and clinicians, that will test novel principles and translate them in to evidence-based, cost-effective clinical care.

Name: Jack Price
Affiliation:
Institute of Psychiatry, King's College London, London, UK
Answer 1:
Now is the right time to launch a serious attempt to tackle neurodevelopmental disorders. For many years, progress in the study of autism, ADHD, and schizophrenia was excruciatingly slow. Our understanding was poor and our therapies primitive. More than one in ten of our children suffer from a neurodevelopmental disorder, yet there is not a single medicine licensed for use in autism, while most of our neuroleptic drugs are antediluvian. Until recently, a shortage of good scientific leads in this arena led neuroscientists to concentrate on more promising opportunities. But important strands of research are now coming together. Genetics is finally delivering candidate genes in these most heritable of disorders. Neuroscientists are realizing that the gene discoveries make sense. These are genes that build synapses and connect nerves, processes at the heart of these disorders. Neuroimaging has identified brain structures and functions disrupted by these aberrant processes, and cell biologists and physiologists are uncovering the molecular basis of these disturbances of neural function.
Answer 2:
The key now is to build multi-disciplinary teams — clinicians, neuroscientists, geneticists — converging on the opportunities this research has revealed. In the UK, we are good at this 'team science' at the interface of research and medicine. Create multi-disciplinary teams around neurodevelopmental disorders, and the next decade will bring true progress.

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Table 2 (*Continued*).

Name: Andy Richards
Affiliation:
PhD, Chair of Ixico, Abcodia, Novacta, Altacor and Cambridge Temperature Concepts.
Director or Psychology Online, Cancer Research Technology, Babraham Bioscience Technology, and Arecor.
Member of BBSRC Council
Answer 1:
Combining multiple modes of detection within the neurosciences will lead to important advances in the way we diagnose, monitor, understand and manage mental health conditions. Within the next ten years it will have been possible to have amassed a vast, broad and deep base of longitudinal neuroscience relevant data on a large and varied population (encompassing diverse groups of healthy, symptomatic, pre-diagnosed and diagnosed patients). Much of this phenotypic data will be captured not in controlled clinical trials but in everyday life through the interaction of individuals with devices capable of passive monitoring e.g. smart phones, tablets, games and PCs augmented by sensors embedded in these and attached/communicating to these (measuring, e.g. movement, temperature, sleep, etc.). For this dataset to be useful and usable, it will have to link to more established clinical information such as those arising from validated cognitive and neuropsychological tests, imaging data, biochemical markers, and increasingly genetics and genomics; which will inevitably require linkage to electronic medical records and personal health data. It will need individual engagement and motivation to be a major component of our thinking.
The analysis of these datasets when integrated with more formal clinical data will increasingly become the basis for diagnosis (especially early diagnosis in critical areas such as dementia) and the basis for measuring outcomes of therapy. It will allow the more effective use of and personalisation of existing therapies including pharmacological and psychological therapies and improved self-help. It will identify and select appropriate patients for the trials of new therapies (especially in the early stages of diseases) thereby increasing the chances of success of new disease modifying therapies emerging.
Answer 2:
In order for this to happen within ten years we will have to start working proactively on how diverse sets of individual and clinical data can be linked in a useable yet secure way. The new breed of 'data scientists' who analyse large datasets and who are highly sought after in the digital world need to be attracted into the neurosciences. More importantly, a new ecosystem must be encouraged. It will require interaction between those from different disciplines and within communities that rarely interact at present. In particular the traditional neuroscience community will need to reach out to those in the new digital health world including those in: mobile, IT, social networking, telemedicine, Edtech and even gaming, as these are many of the players capable of both collecting data and more importantly motivating individuals to collect data and change behaviour. The ecosystem will have to be diverse, encompassing those in academia, medicine, patient groups, entrepreneurial businesses and established industry. This is not a parochial endeavour and cannot be achieved by an introspective academic, NHS alone or UK myopia.

Name: Trevor W. Robbins
Affiliation:
CBE FRS FMedSci
Professor of Cognitive Neuroscience and Experimental Psychology Director, Behavioural and Clinical Neuroscience Institute Head of Dept. Psychology, University of Cambridge, Cambridge, U.K.
Past President of the British Neuroscience Association http://www.bna.org.uk/

Answer 1:
What is required are better specifications of the behavioural and neural endophenotypes of mental disorders based on well-defined psychological constructs and neural circuitry and how they relate to (i) programmes of brain development and functional organisation (ii) genetic and epigenetic factors (iii) valid psychological theories, e.g. of learning or executive function. These endophenotypes are required to:
• improve psychiatric diagnosis, away from DSM criteria and provide more objective and accurate phenotypic descriptions suitable for genetics and embracing co-morbidities, as well as designing new therapies (cognitive or other).
• aid bidirectional translation by stimulating more powerful and accurate animal models and providing purer clinical samples for experimental medicine studies and clinical trials of drugs or other treatments
• define vulnerability and risk and allow for clinical interventions (behavioural or pharmacological) to prevent the transition to chronic states such as addiction, treatment resistant depression and dementia.
There are promising indications that these issues are starting to be addressed but there now needs to be a concerted effort over the next decade to provide definitive results.
Answer 2:
Multidisciplinary collaborating groups of clinicians, basic neuroscientists, imaging scientists, geneticists and cognitive neuroscientists. A research culture in which there is less emphasis on clinicians having to be 'independent' scientists and necessarily leading such collaborations—greatly improved multi-centre NHS networks, reduced bureaucracy in the regulation of research, reduced stigma for patients with mental illness. Improved access to necessary animal facilities. Enhanced academic-industrial collaboration. Rapid import of latest techniques e.g. via DREADS and optogenetics, improved PET ligands and more sophisticated imaging analytical methods.

Name: Peter Stern
Affiliation:
M.D., Ph.D.
Senior Editor, SCIENCE, Cambridge, UK
Answer 1:
• A fully functional and reliable brain-machine interface. This will be needed for all sorts of prostheses to work properly. I assume that the ones from brain to e.g. artificial limb will be there first. A bit more tricky will be other way round from e.g. artificial sensory input (retinal implant, cochlear implant, etc.) to brain. What is needed are miniaturized long lasting reliable systems that can stay in the body for a lifetime and ideally get their energy (battery recharging, etc.) directly from the body.
• Along the same lines: real time fMRI feedback systems. The patient sees the change in the required parameter while the brain scanner is producing the image. A different type of brain-machine interface so to say.
• A complete understanding of the connectivity in the brain. From cellular to circuit to systems level. This will need a lot of computing power. I expect, though, that it will less be a question of hardware and a lot more of software instead. We need smart algorithms to make sense of the huge amount of data produced. It will also need large scale communication and cooperation between very different disciplines. From electron microscopist to anatomist all the way to the engineer who builds the next generation brain scanning device.
• An understanding of the interplay (and the mechanisms behind the interaction) between the different systems that make us perceive the world as a coherent whole. A modern solution of the binding problem if you like.
• An understanding of the processes and systems involved in memory storage (and retrieval). There has been a lot of progress recently and there are plenty of hypotheses floating around. However, if we are honest there is still a large amount that we don't understand, or simply don't know. How come that memories can so easily be retrieved? How does the system know which parts belong together and thus need to be simultaneously activated when they are stored in such a distributed way? The latter is going to be a tough one and will definitely take the full10 years.

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Table 2 (*Continued*).

Answer 2:

What is needed is research efforts in materials science, e.g. miniaturized, longer lasting, more flexible electrodes, systems to harness the energy of the body, optimization of the electrode placement, etc.
What is needed is investment in software. Development of sophisticated algorithms—perhaps best done by researchers who are familiar with the underlying scientific questions.
What is needed is plenty of communication and collaboration between disciplines that at first glance seem miles apart, e.g. electron microscopist and software engineer.
Maybe we could encourage joint degrees from faculties that are not used to talking to each other.
What is needed is plenty of efforts in visualization of complex interactions (perhaps even using multisensory procedures). Many of these insights will come to scientists when they try to show and explain higher-order interactions in a non-linear way.

Name: Mark Tricklebank

Affiliation:

Senior Research Fellow in the Psychiatric disorders drug hunting team and Director of the Lilly Centre for cognitive Neuroscience, Surrey, UK

Answer 1:

I am convinced that Alzheimer's and other long term neurodegenerative conditions will be solved in the next ten years

Answer 2:

We need a more adventurous regulatory climate and better appreciation of what the drug industry can offer. More precompetitive collaboration and better interactions between the industry and academics and greater involvement of clinicians in basic and industrial research. Mental health and neurodevelopmental disorders are also areas of potential success but again regulatory hurdles are huge as well as the ethical concerns around early diagnosis. But the more that basic biology is applied to research in these areas the better will be the chances of success.

Name: Daniel Umbricht

Affiliation:

Translational Medicine Leader Neuroscience, F. Hoffman—La Roche, Ltd.
Professor, University of Zurich, Zurich, Switzerland

Answer 1:

- Development of pharmacological treatments for core aspects of neurodevelopmental disorders in particular autism and Down's syndrome
- Understanding of and development of pharmacological treatments for core disabling aspects of schizophrenia, namely negative symptoms

Answer 2:

- Development of ecologically valid animal models that are based on mechanistic understanding of key function such as social reward, social cognition, use of stem cell research to understand synaptic pathology and development of behavioral biomarkers, assays and valid clinical readouts for clinical studies as a result of collaborations between industry and academia.
- Development of behavioral assay probing the reward/motivational system, development of ecologically valid animal models

Name: Nora Volkow

Affiliation:

Director of the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH) in Bethesda, Maryland, USA

Answer 1:

Our ability to diagnose and manage a broad range of psychiatric disorders has reached an inflection point thanks to the recent acceleration in genetic and neurobiological advances. Genetics and neuroscience now have the tools to reconceptualize disorders of the mind as disorders of the brain by linking their roots and trajectories not to traditional, subjective phenotype-based entities but to objective, well-defined sets of biomarkers. It is time to rethink mental disorders, and recognize that they are disorders of brain circuits likely caused by developmental processes shaped by a complex interplay of genetics and experience.

Answer 2:

One of the main lessons we have learned from systems neuroscience is about the existence of deep relationships between allelic variation and the development of neural circuits underlying complex cognition and behavior. A by-product of this understanding, which should become the focus of research in the next decade, is the recognition that the **genetics of mental illness may actually overlap to a large extent with the genetics of brain development**, whereby a range of normal and abnormal outcomes may be modulated by different biological and environmental contexts.
A strategic agenda designed to harness the full potential of our genetic and imaging technological prowess should pair future investments in genomics with commensurate efforts in high-throughput **epigenomic technologies** capable of teasing apart the positive and negative effects of experience, as a powerful approach for understanding the critical effects of early-life events and environments on adult patterns of behavior. For epigenetic marks that alter transcription are bound to be critical contributors to mental illness including substance use disorders, even in the absence of common or rare structural genetic variants.
In addition, we must finally come to terms with the fact that the current diagnostic categories for psychiatric disorders present very little correspondence with the cumulative findings in genetics and neuroscience. Thus, it would be advisable that the next decade of psychiatric research be guided by a unifying approach to develop new **ways of classifying and describing psychopathology based on the characterization along neurocircuitry, genetics, cognitive domains and symptom presentation domain and their trajectories from early development into adulthood.**
Finally, major barriers that could prevent this vision from crystallizing lie in a) a culture that hampers the **free flow of scientific information** in and out of growing genetic, brain imaging, epigenetic, clinical, and behavioral databases, and b) the **inadequate level of training and infrastructure development** (e.g., analytical and modeling tools) that will be needed to tackle the enormously complex data sets that are being generated by our combined attempts to understand how the brain works in health and disease.

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Table 2 (*Continued*).

Name: Torsten Wiesel
Affiliation:
M.D, President Emeritus, Vincent and Brooke Astor Professor Emeritus, Rockefeller University, USA
Answer 1:
There are many excellent scientists working in the area of neurodegenerative diseases, an area of great scientific interest but also with important health and social consequences. The current ideas of the mechanisms causing the death of neurons in these diseases are still debated in the scientific community. It is therefore critical to give room for new ideas and innovative research that could open the door to a real understanding of the problems. This will require a mobilization of outstanding scientists from all areas of natural sciences to search for the mechanisms that govern the growth, maintenance and degeneration of neurons and glia cells. After all, it is only after we know the normal operation of a system that we can hope to solve malfunctions. This is true for all neurodegenerative diseases such as Alzheimer's, Parkinson's, ALS and Huntington's. In the immediate future it may be possible to at least identify the means to slow down the progression of the disease and perhaps even design preventive measures during the next decade. In the long term the hope is obviously to prevent and cure these degenerative conditions but as with cancer we must be patiently optimistic.
Answer 2:
The most important step is to create an environment for faculty and students at universities and research institutes where they have the freedom to carry out their research independently with adequate resources and no strict time limitations. This is particularly important for students in training and above all for young scientists as they build their own laboratories and establish themselves as original and imaginative investigators. In science we are often hampered by dogmas and the younger members of our community are often fresh enough to break new grounds and open the doors to true discoveries.
Name: John Williams
Affiliation:
PhD FRCPE, Head of Clinical Activities, Head of Neuroscience & Mental Health, Wellcome Trust, London, UK
Answer 1:
In 10 years time we need to be in a position to see the discoveries that we are currently making in neuroscience start to impact directly in the clinic.
Whether it is offering a diagnosis based on imaging, genetics, cognitive function or a combination of all three we can and will be able to offer patients greater insight into their disorders and begin to offer interventions that target specific deficits in function.
Answer 2:
To make this happen we need to recognise that this is an enterprise that requires a critical density of researchers, technologies and above all patients. We need a willingness of researchers and funders to work and fund across disciplinary boundaries. 'Fully loaded' neuroscience clusters bridging institutions, disciplines and technologies are the way forward.

Name: Malcolm Young
Affiliation:
Professor, Chief Executive Officer, e-Therapeutics
Answer 1:
Neuroscience was named and founded on the basis of a multidisciplinary programme aimed at understanding brain structure and function. This broad approach was exemplarised by the early Neuroscience Study Programmes, most of them edited by E.O. Schmidt. Every discipline, from physiology to electronic engineering, from biochemistry to computing science was involved in defining the research agenda. But this approach, which had a strong chance of producing breakthroughs in fundamental understanding, was not sustained. Neuroscience was rapidly colonised by molecular reductionist approaches, and now neuroscience is not a multidisciplinary approach to understanding brain function, but the branch of molecular biology that deals with nervous tissue.
Like all molecular reductionist approaches, the application of these tools to brain tissue produces a great deal of data, but very little insight into system function, because systems level integrative functions are held constant or ignored. This approach has not produced any major breakthrough in understanding brain function, and it will not, for fundamental reasons. The data mountain produced at enormous expense by molecular neuroscience has also not been leveraged by pharmaceutical companies, many of which have withdrawn from CNS research in recent years because of very low new drug productivity in this area.

Significant Tractable Deliverable in 10 years

The original goal of neuroscience was to understand how brains work. How can this major scientific unknown be broken down into tractable chunks? One way is to consider the elements of any explanation of how anything works. There are three elements. First, one must understand how the system is organised. Second, one must understand the processes that go on inside the system. Third, one must understand how these processes interact within the system's structure to produce the behaviour of the system. With these three elements the explanation is complete. It is not necessary to know the finest detail of molecular organisation except insofar as these details inform these three elements.
The first and second elements are more tractable than the third element, but all are potentially tractable in a systematic 10-year programme. Delivering any of them would mark a major breakthrough, while delivering all of them would be transformational.
Answer 2:
Money alone will not help to deliver a major breakthrough. The founders of Neuroscience were right that a multidisciplinary approach is required, not an approach based almost to exclusion on taking the system apart and determining what its components are made of.
What is required is a space in which multidisciplinary systems level analysis, motivated by a specific response to the three elements required for an explanation of brain function, can take place. This could be in the form of an Institute, supported in part by a host university with an interest in this area. This could perhaps be along the lines of the Newton Institute in Cambridge, which tends to focus on specific questions to be addressed rather than on the propensity of universities and their researchers to seek to maximise their research income, rather than to deliver knowledge that is useful. A specifically multidisciplinary dramatis personae would be needed, and the initiative could not be led by a molecular reductionist.
Deliverables, and inputs, would be particularly strong in robotics, adaptive microprocessor design, and therapeutic psychiatry and neurology.

Source: Bruce Altevogt, Edward T Bullmore, Sarah Caddick, Philip Campbell, Sandra Ceccatelli, Vinton G Cerf, Sherry Coutu, Stephen Emmott, Andrew Blake, Elizabeth Fisher, Russell G Foster, Uta Frith, Guy Goodwin, John Hardy, Hermann Hauser, Steven Hyman, Thomas Insel, Thomas Jessell, John Krystal, Alan I Leshner, Liang Li, Simon Lovestone, Chris Lowe, Husseini Manji, Stine Hove Marsling, Peter Høngaard Andersen, David Menon, Richard G M Morris, V Hugh Perry, Anthony G Phillips, John D Pickard, Jack Price, Andy Richards, Trevor W Robbins, Peter Stern, Mark Tricklebank, Daniel Umbricht, Nora Volkow, Torsten Wiesel, John Williams, and Malcolm Young.

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understand the healthy, creative brain and how new discoveries and innovations are formed in the mind (see, e.g. Lawrence et al., 2008). Keeping a healthy mind is an active process and it will require working at it everyday. It is far better to detect mental health problems early than to let them slowly develop over time without treatment. For example, the duration of untreated psychosis in schizophrenia is related to worsening of cognition and symptoms (Amminger et al., 2002; Chang et al., 2013; Joyce et al., 2002). For those who do develop a mental health problem, early effective treatments are needed. These may be pharmacological, psychological, cognitive and combined. Patients will need to take an active role in their treatments to ensure they retain good cognition and functionality and not respond passively to treatments, as though they have no role in recovery. For example, learning and relearning in depression is important following both pharmacological and cognitive behavioural treatments (Roiser et al., 2011). Treatment resistance is relatively frequent in depression, whereby there is inadequate response following antidepressant drug treatment (Fava, 2003; Fava and Davidson, 1996). By patients taking an active role in learning and relearning, it may be that response to treatment improves. Antidepressant treatment in combination with cognitive behavioural treatment (CBT) may facilitate this learning process. Furthermore, novel fast acting antidepressant drugs are in development (e.g. drugs altering NMDA receptor function directly such as ketamine or indirectly; Zarate et al., 2006). In addition, antidepressant drugs which improve depressive symptoms, cognition and functionality are also in development (e.g. multi-model activity profile). Given how common depression is in society, early detection and early effective treatment are key to preserving functionality, as chronicity and relapse are associated with poorer cognition. The new concept of monitoring our brain health should reduce stigma in regard to mental health problems. In the future, symptoms which are on a continuum in common disorders such as depression and ADHD, for example sadness and impulsivity respectively, may be considered as problems of daily living.

Understanding the neurobiological basis of brain function in health and disorder is essential. With our current and novel neuroscience innovations, tools and techniques (Table 1) and well thought out concepts for how this can be achieved, great progress is possible within a 10 year framework (Table 2). These concepts for rapid progress include understanding the neural basis of pharmacological and psychological treatment, defining the underlying neurobiology of disease processes, identifying new molecular targets for treatment and promoting knowledge of the neural basis of resilience. This research will require a mixed funding model of large scale studies with extensive data sharing and smaller, creative and future-vision proof-of-concept studies. Novel training programmes are needed which train young neuroscientists who can cross-talk and interact with other relevant disciplines to truly realize the potential of neuroscience to unlock brain health and create healthcare opportunities. Realization will rely on effective integration and collaboration between basic and clinical neuroscientists in academia and industry and entrepreneurs in bioinformatics, machine learning, brain–machine interface, games–industry, mobile and tablet industries and nanotechnology (see Fig. 2).

Policy makers can promote this happening effectively by:

- Stimulating effective interaction between different sectors and stakeholders.
- Encouraging the entrepreneurial potential for laboratory to real world translation.
- Reducing the regulatory burden.

Other initiatives can ensure a successful exchange of ideas, know-how and new collaborations towards better brain health. For example, The Wellcome Trust Workshop initiative in neuroscience, innovation and technology spearheaded by Dr. John Williams aims to stimulate engagement between those with expertise in neuroscience, bioinformatics and entrepreneurs and industries, including the pharmaceutical, games, computing and technology ones.

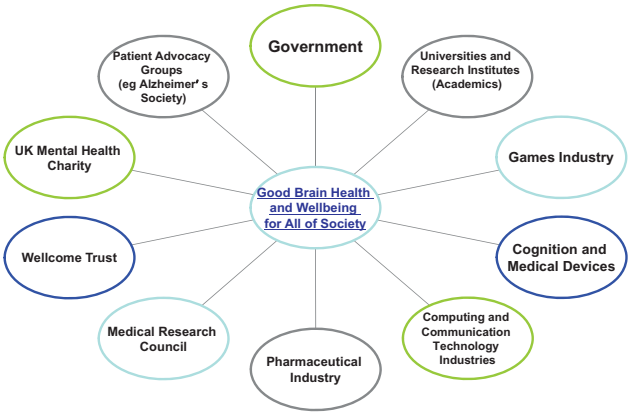

Fig. 2. The impact of neuroscience, innovation and technology: brain health in a flourishing society.

In the UK, we have great expertise in a range of relevant disciplines that could be integrated to promote both good brain health and to stimulate the economy. Currently, we are not realizing the potential, but through policy makers engaging with relevant disciplines and key stakeholders, this could easily be achieved. There are stakeholders keen to facilitate these developments within the entrepreneurial pockets of Silicon Fen in Cambridge, London-based companies and also Oxford and Manchester, as well as elsewhere. Mental health, like good physical health, has to be worked at. It is not something that can just be expected to happen without active participation by society and government. However, with the impact of neuroscience, innovation and technology, brain health in a flourishing society can be achieved within the next 10 years.

Disclosure statement

Barbara Sahakian consults for Cambridge Cognition, Servier and Lundbeck. She holds a grant from Janssen/J&J. She has share options in Cambridge Cognition.

Acknowledgements

I thank Sir John Beddington, previous Government Chief Scientific Adviser, for inviting me to write this article and Sir Mark Walport, Government Chief Scientific Adviser, for permitting its publication. I thank all those Experts who contributed to Table 2, Jacqueline P Robbins and Martin Ducker for design and execution of Table 1 and Jay N Giedd for providing Fig. 1. I also thank Jacqueline P Robbins, Martin Ducker, Clare Killikelly, Muzaffer Kaser, Joalice Stark, Andrew Blackwell and Jennifer Barnett for discussion.

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Please cite this article in press as: Sahakian, B.J., What do experts think we should do to achieve brain health? Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.04.002