The redefinition of Alzheimer's disease and its social and ethical consequences

Brocher Foundation, 14-15 April 2016

PROGRAMME

Thursday 14th April

10.00	Welcome		
10.15	**Plenary**	Carol Brayne	A population perspective on dementia and its relationship with ageing and dying across time
11.15	*Coffee*		
11.30		Jason Karlawish	The New House of Alzheimer's Disease
		Annette Leibing	Recent changes in the conceptualization of dementia: Ethnographic notes from Brazil
12.45	*Lunch*		
14.00		Silke Schicktanz	To know or not to know – is this the question? The ethics of imaginations, scenarios and later life planning based on predictive dementia tests
		Pamela Sankar	Future Tense: Anticipated stigma associated with elevated amyloid imaging results
15.15	*Coffee*		
15.45	Marion Droz Mendelzweig		Disclosing a MCI diagnosis to older patients: a "lost in translation" task
	Alex Hillman and Joanna Latimer		'Making the epistemic concrete': Tensions in the fabrication of dementia.
17.00	Close Day 1		
19.00	Drinks, dinner		

Friday 15th April

9.00	Start		
9.10	**Plenary 2**	Joanna Latimer	Thinking with Care: Dementia & the Biopolitics of New Cultures of Ageing
10.10	*Coffee*		
10.30	Richard Milne		From people with dementia to people with data
	Vincent Pidoux		Circuits, tests, and risks : Alzheimer disease in the (promised) age of translational neuroscience
	Marianne Boenink and Anna Laura van der Laan		One step backwards, two steps forward? Challenges of 'translation' in the AD field
12.30	*Lunch*		
13.30	Edo Richard and David Winickoff		Responses
14.00	Discussion and Next steps		
15.00	**Close**		

ABSTRACTS

One step backwards, two steps forward? Challenges of 'translation' in the AD field

Marianne Boenink and Anna Laura van der Laan (University of Twente)

Discourse on translational medicine (or research) often starts from the idea that it is a pity that so many insights and innovations from biomedical research do not end up in clinical use. Identifying which blocks are obstructing the pipeline and trying to remove them is thought to be crucial to stimulate translation. This approach has several problems (van der Laan & Boenink 2012). First of all, it assumes that biomedical innovations are generally desirable, which need not be the case. Secondly, it starts from a rather unidirectional idea of innovation, whereas actual innovation is much more complex. Moreover, good innovation might have to start on the side of the future users and their needs. Thirdly, the blocks that are identified are usually relatively external to science (like lack of funding, lack of communication between different actors, limiting ethical regulations). The procedures of science itself are not questioned. And finally, it at least suggests that innovation is a process that can be steered and shaped at will, and that we just need to pull the right plugs to make things work better.

The call for this workshop suggests that it is not self-evident that we should translate AD biomarkers into clinical practice. However, when pointing out that the boundary between research and clinical practice is rather porous, it seems invite thinking based on partly inverted, but similar presuppositions: don't we need better blocks in the pipeline to avoid premature introduction of these novel tools?

In this contribution, we want to approach translation in a different way that seems to avoid at least the first three pitfalls, and explore what 'backwards translation' might have to offer for thinking about AD biomarkers. Backwards translation has been put forward as a way to counter the science and technology driven bias of much translational research (XX). It argues that to improve the connection between lab and clinic, we had better start on the bedside and ask what clinicians' and patients' needs are. Using material about Dutch AD-diagnostic practice collected by Anna Laura van der Laan, we will reconstruct the different 'goods' AD diagnosis can bring. We will not use this to propose new, more relevant AD research, but to reflect on how biomarkers relate to this rich and complex practice. We will show that molecular biomarkers may have a role for some diagnostic processes, but much less for others. Moreover, the characteristics a good biomarker should have, are different for each setting. Becoming aware of this might help to be more modest about the number of situations where biomarkers can have added value and to prepare for careful implementation. However, introducing biomarkers only where they might have added value is not exactly unproblematic. The value of diagnosis is closely linked to the way AD is conceptualised, and introducing biomarkers might affect this conceptualisation in such a way that it becomes more difficult to choose to pursue alternative conceptions. If we consider the translational challenges for AD biomarkers, then, paying attention to the way AD is talked about in the public and medical domain is crucial.

A population perspective on dementia and its relationship with ageing and dying across time

Carol Brayne (University of Cambridge)

'Making the epistemic concrete'[1]: Tensions in the fabrication of

dementia.

Alexandra Hillman & Joanna Latimer (University of Cardiff)

This paper is concerned with the practices and strategies through which dementia can be made a 'known' entity, one that can be tested, investigated, diagnosed or treated. Scientists and clinicians working in the field of dementia must work alongside complexities and contradictions that challenge the capacity of dementia to remain a stable object of clinical and scientific investigation. Their work therefore necessitates a smoothing out of seemingly insurmountable problems, such as the connection between, and transition from, brain and mind. The complexities of mind, and its associations with social, material and bodily relations, are often made absent in the construction of dementia, particularly in the scientific domain. In the clinic, moments arise in which the mind can be made a significant presence in re-articulating the complexities of dementia in its symptomatic expression and association with human experience. What this article shows is the significant work being done by clinicians in navigating the tensions that ensue in maintaining dementia as a bounded and stable object of clinical attention, that must traverse representations of dementia as biological changes in the brain, while also accommodating human complexity, uncertainty and sociality.

The New House of Alzheimer's Disease

Jason Karlawish (University of Pennsylvania)

The House of Alzheimer's has historically been built on the solid foundation of dementia, a clinical disorder defined by signs and symptoms. It had many windows from which patients and their caregivers could look out of -- such as repetitious questions and stories, and problems with planning and executing daily tasks such as managing money, driving and cooking – but it had only one door, a door called dementia. The discovery of the genes and mechanisms of disease, also called biomarkers, of Alzheimer's disease are remodeling this house. Researchers are creating new foundations grounded in the presence of genes or biomarkers and their response to a drug intervention. This definition is often denoted as a "preclinical stage," and it is essential to develop method to prevent Alzheimer's. Someday soon, you won't have to be demented to have Alzheimer's disease. You won't even have to be ill, but just at risk of becoming ill.

Progress to achieve this future presents challenges to individuals, professionals and society. The contours of these challenges are best described using a perspective that incorporates ethics and policy but also disciplines such as social psychology and anthropology that allow us to incorporate into context the individual, family, and social determinants as well. We should expect a future when, from country to country, the disease label may be the same, but the experience of the disease – the illness – may be quite different. What will this illness be? Answering this question will help us to live in the new house of Alzheimer's disease.

For the individual, the knowledge her brain is at risk and now on treatment presents information that creates a form of looping effect between the label and her mind. This may create a stereotyped threat that changes her affective and neuropsychological functions.

How society interprets this new model of Alzheimer's disease will shape how patients experience their diagnosis. Patients may, for example, find the information threatening to relationships and therefore information they choose to keep private from family and friends. If they tell people, such as family or employers, they may experience changes in how they perceive themselves and their abilities. Society may well change as well, causing, for example, discrimination in the workplace or insurance, and changes in social interactions.

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[1] Rheinberger, H. (2010) Making the epistemic concrete: Twentieth-century histories of life. USA: Duke University Press.

Psychologists will have to consider whether these cognitively normal persons are in fact still normal and therefore still belong in normative cohorts, or should they be excluded from the category of "normal aging."

The concept of the disease will be defined by the conjoining of a test (such as a measure of brain amyloid) and a drug that affects the natural history (such as an amyloid drug). This marriage of a test and drug to define a disease, called a "theranostic," means the private interests who own the tests and drugs are not simply shaping the treatment of the disease but its very definition. The c-suites rhetoric to market and promote their drugs will shape the cultural and social framing of what is Alzheimer's disease. We might expect, for example, that Alzheimer's disease fractures into treatable forms, renamed by drug-test theranostics (e.g. brain amyloidosis) and untreatable forms.

Policy makers will struggle with assessing the value of these therapies prescribed to prevent future impairment. They will also need to tackle how to count the disease and therefore the size of the problem because persons who are largely healthy will differ substantively from persons who are ill with dementia. One number may not properly explain the problem of Alzheimer's disease.

Thinking with Care: Dementia & the Biopolitics of New Cultures of Ageing

Joanna Latimer (University of Cardiff)

In this paper I think through the biopolitics of dementia in the broader context of 'new cultures of ageing' that refigure ageing as on the one hand dynamic, and open to enhancement, and on the other as plagued by mismanagement, disease and concomitant disabling effects. I contextualize how dementia is being performed as the personification of the risk we all face in growing old because it undoes possibilities for the enactment of the valued person in contemporary modernity, to become as Margaret Lock (2013) asserts representative and symbolic of all that is most feared, and stigmatising, about ageing, especially loss of identity as sovereign subjects. Unpacking how dementia is made to represent the worst that ageing has to offer I draw out how there are alternative possibilities for how we construct dementia. For example, dementia is performed in biomedicine as located in the individual brain, rather than as co-constructed and relational - the effects and affects of complex social, cultural, biological and material interactions over time through which the person with dementia increasingly finds the world, and themselves, an inhospitable place to dwell. Here I offer for discussion a possible way out of simply treating people with dementia as diseased and in deficit. Through deconstructing the perspective that individuates ageing as the property of a singular organism I explore ways to realign with ageing and the aged, and celebrate all those things that cultures of enhancement and reform cut out.

Recent changes in the conceptualization of dementia: Ethnographic notes from Brazil

Annette Leibing (University of Montreal)

This talk starts with the recent changes in the conceptualization of dementia, especially the turn towards 'earliness'- – the ideal of early detection, early intervention, and prevention (Leibing, 2015). It will then look at the current landscapes of aging in Brazil by mapping how the international discourse on 'earliness' is (g)locally being absorbed or contested in that specific context.

Based on observations, interviews and document analysis from an ongoing multi-site ethnography, this talk provides first results from specialized sites (researchers, health professionals, and decision-makers at the

Ministry of Health), as well as from everyday life as it is affected by recommendations and practices of early detection and prevention of dementia.

Disclosing a MCI diagnosis to older patients: a “lost in translation” task

Marion Droz Mendelzweig (Institut et Haute Ecole de la Santé La Source, Lausanne)

Disclosing a diagnosis often generates an illness identity for the diagnosed person and his relatives. Drawn on an observation of the diagnostic procedures leading to the announcement made in Memory Clinics, this paper reflects on the blatant failure of the communication between the clinicians and the patients. Considering the lack of appropriation of the MCI label by the diagnosed patients, I will approach the ontological question of what MCI is. I will face the biomedical research and conceptual work aiming to delineate “normal” from pathological aging, based on the hypothesis of a pre-symptomatic phase, under the challenge of its communication to older patients. This background will serve to develop a critical view of the public health agenda that supports early detection on the basis of potential preventive behavior. In the midst of the on-going scientific debate associated with the use of the MCI diagnosis, my aim is to reflect on the dissonance between experts’ approach of the prodromal phase as a medicalized object and the lay approach to aging. The enduring difficulties to build up an unified understanding of “normal” aging will convey a social science reflexion on how health representations are being constructed through tensions.

From people with dementia to people with data: clinical labour in Alzheimer’s disease research

Richard Milne (University of Cambridge)

In response to two decades of failed clinical trials, characterised by researchers as doing ‘too little, too late and with the wrong people’, a ‘paradigm shift’[2] has occurred in Alzheimer’s disease research, whereby it has moved to recognise a long-term disease continuum and to identify and intervene at earlier and earlier stages. Rather than focussing on ‘people with dementia’, identified symptomatically in the clinic, the interest is increasingly on people with the earliest signs of disease, or those without any overt symptoms at all. Research in both academia and industry is increasingly focussed on the elaboration of the endophenotypes or biomarkers that characterise the disease continuum, and the translation of these into regulator-recognised clinical trial endpoints. At the heart of this work are collaborative data research structures. Their scale is taken to reflect the complexity of the disease, but also chimes with broader moves across the biological sciences to ‘bigger, faster, better’ (Davies et al., 2013) science. Examining this move to big data, I argue that the value of data and samples increasingly resides in their ability to re-attach to the bodies whence they came to enable the production of further data. I suggest that this return to the data subject represents a critical stage in the realisation of biovalue, and that considering the labour involved in the production and reproduction of data opens the door for alternative avenues of ethical focus and action

Circuits, tests, and risks : Alzheimer disease in the (promised) age of translational neuroscience

Vincent Pidoux (University of Lausanne)

Since its anatomo-clinical description at the beginning of the 20th century, Alzheimer disease (AD) has been portrayed as a progressive neurodegenerative disease associated with cognitive impairment, thus

[2] The term is taken here from the European Medicines Agency “The field of AD research and development witnessed a recent paradigm shift in the diagnostic framework of AD which is now considered a continuum with a long-lasting presymptomatic phase, with evidence of AD neuropathology, which precedes 10-20 years the onset of dementia.” (EMA, 2016)

belonging to the realm of neurology, of brain science, situated outside of the so-called *sine materia* mental disorders. Although its aetiology seems deeply rooted in neuroanatomy, AD has faced several important revisions of its classification, characterised by a collective production of « regulatory objectivity » and standards. This paper explores AD as it is challenged by a recent imperative of translational research, which aims at shortening the path from basic research to clinical practice. My aim is to situate the origins of this new translational imperative in neuroscience and mental health, and put AD in this context. I focus on old (neuropsychological tests) and new (diffusion MRI) technologies, and their socio-epistemic effects on *risk* hypotheses as new promised targets for drugs. I argue that these techniques, notions and hypotheses, which are supposed to offer new ways to bridge the *neuro* to the *cognitive* side of AD, the animal models to the understanding and care of patients, are to be understood less as ways to erase uncertainty than as new productive assemblages of entities (including new regimes of promises) which have potentially important effects on the ways AD is approached socially, scientifically, as well as at a policy level.

Future Tense: Anticipated stigma associated with elevated amyloid imaging results

Pamela L Sankar (University of Pennsylvania)

Amyloid imaging is potentially stigmatizing because of the stigmatized future it points to: Alzheimer's disease. In contrast to this future state, which is readily observable in a patient's countenance and behavior, the amyloid imaging result—a single number—or perhaps only a category that glosses the number as elevated or not elevated—exists only inside the recipient's mind or in a well-protected medical record. It can stigmatize its referent only if she deliberately communicates it. Thus to study the potential for stigmatization resulting from amyloid imaging, the SOKRATES study is asking people who have undergone imaging and received an elevated result to whom they disclosed the result and with consequences. The people we enroll are in a larger trial, characterized to subjects as an Alzheimer's prevention trial, that is testing a drug predicted to delay cognitive decline following the finding of elevated amyloid. We have enrolled 50 subjects who will be interviewed twice, once soon after they enroll in the parent study and receive their amyloid results, and again approximately a year later. We have completed all of the first round of interviews and about ten of the second round. I report here on a *preliminary* analysis of 21 randomly selected first round interviews.

Much of the literature on stigmatization associated with disease treats the disease as a unitary, determinative force; hence, inquiries as to whether genetic pre-disposition testing does or does not stigmatize its recipients. This is a sensible starting point for many conditions on which stigma literature focuses such HIV, cancer or epilepsy, conditions whose etiology, symptoms and course are such that they seem to eclipse a person's individuality. But stigmatization associated with testing for a future condition that is not yet and might never become manifest, is likely to be more subtle. This possibility suggests that a productive question in addition to whether or not amyloid imaging is stigmatizing is for whom and in what situations is it stigmatizing? Pursuing this line of inquiry a preliminary analysis indicates possible differences associated with age and gender.

"To know or not to know – is this the question? The ethics of imaginations, scenarios and later life planning based on predictive dementia tests"

Silke Schicktanz (University of Göttingen)

When diagnosis of a symptomatic disease shifts to a prediction of a disease in an asymptomatic stage a common problems occurs in ethical and legal debates: Is there a right not to know, a duty not to tell or a

right to know? An important approach to these debates is to critically question the epistemic status of the "knowledge" or 'information'

However, the current shaping of research and health care policies for the elderly and particularly, for those with dementia is also strongly influenced by social imageries. Here, I will take a normative point of view and examine how scenarios or anticipated implications are used for normative justifications in recommendations or ethical positions. For example, important social imageries are recently influenced by so call "worst case scenarios" which are picturing dementia as a loss of identity, the end of humanity, and a sheer financial burden for families and societies. In my contribution, I will examine in-depth how such future scenarios are used – in a particular cultural setting – as arguments for justifying a particular health and research policy. Hereby, I will draw partly on empirical studies of activities and positions of patient organization of Alzheimer dementia as important actors in the field of health care policy. By comparing their positions with the activities and positions within the academia I will further examine how the positions are depending on the cultural and national context. The arguments used as "worst case scenario" might differ and must be contextualized according to the public vs. private health care provision but also by collective memories and social ideals. By doing so, I will also provide an ethical analysis of how such arguments are built into the justification of current research activities to diagnose, prevent and care for people with dementia. Reflecting on the empirical findings, I will finally try to develop an ethical-theoretical framework how to identify, analyze and use the function of such scenarios in bioethics and health care policy of dementia.