Rationale and Aims of the PATH Through Life Project

Aims

The PATH Project is a prospective longitudinal investigation of depression and anxiety, substance use, and cognitive ability throughout the adult life span. Its aims fall into three main broad themes:

1. to delineate the course of depression, anxiety, substance use and cognitive ability with increasing age across the adult life span;
2. to identify environmental and genetic risk factors influencing individual differences in the course of these characteristics;
3. to investigate interrelationships over time between the three domains of (i) depression and anxiety, (ii) substance use, and (iii) cognitive ability and dementia.

Background

Rates of anxiety and depression, degree of substance use and levels of cognitive ability are not constant over the adult life span but show systematic patterns with age. Recent studies suggest that anxiety and depression decline in prevalence with increasing age from early/mid-adulthood through to old age [1]. Substance abuse and dependence show a similar decline [2]. Trajectories of cognitive ageing vary over different cognitive domains, but there is a general pattern that abilities reach a plateau and decline thereafter [3]. The age at which the plateau is reached can range from early adulthood to late in life, depending on the skills involved. Much of the research on age trends in these different psychological domains has been cross-sectional, which has necessarily confounded age differences with cohort differences. A more accurate picture is emerging from longitudinal investigations, where the acknowledged confounding of period effects with age effects introduces less difficult [4], but this picture is incomplete as yet.

Longitudinal study is also essential for investigating individual differences in change over time, for each of these psychological domains. For anxiety, depression and substance use there is evidence of considerable instability over time, whether measured as discrete states or as scores on continuous dimensions. Even in the cognitive domain, which is characterised by relative stability, the rank ordering of individuals can change significantly over time and this can be considerable over extended periods (i.e., decades of ageing). There has been a paucity of longitudinal research on factors influencing such changes over the adult age span, and past research has tended to focus either on developmental changes in children and adolescents or on cognitive decline in the elderly.

Because of the lack of research over the full adult lifespan, the CMHR established the PATH Project in 1999. Three cohorts of different ages were established with the plan to follow these for twenty years. The first cohort of individuals aged 20-24 years was interviewed in 1999 and the second cohort aged 40-44 years was examined in 2000, while participants aged 60-64 were in 2001. The second Wave of collection commenced in 2003, and will be completed by 2006. By 2007 2 Waves of data will be available.

Significance

The PATH Project has four special strengths that will influence its scientific contribution across the domains outlined above. *First*, it will make an important contribution to our understanding of the role of cohort effects and age effects in determining age differences

across the adult life span in anxiety and depression, substance use, and cognitive abilities. Currently, much of our knowledge of age differences is based on cross-sectional information. The *second* significant strength of the PATH Project is the capacity to bring together a comprehensive and unique set of risk factors for a large general population sample. *Third,* longitudinal analyses will help explain what factors influence change over time in these outcomes, and the interrelationships between them, at the individual level. The PATH Project will cover the adult life span, initially from age 20 to age 64; a period of life that has been studied less extensively in longitudinal research than either childhood or later adulthood, in relation to psychological development. *Fourth,* the project commences with three age cohorts that have their distinct characteristics associated with mental health and well-being. The youngest cohort is at an age of high levels of substance use and is approaching the peak for prevalence of depression and anxiety. Individuals are beginning to move through a period of establishing their independent living, occupational careers, partnerships and family formation. The middle cohort is in a period where some experience changes in employment, partnership changes, their own children moving towards independence, increasing risk of physical ill-health, early white matter changes and declines in some areas of cognitive functioning. About half of the women will experience menopausal changes by age 50. The oldest cohort is at a stage of retirement from paid work, more frequent physical morbidity (and mortality), and more significant variability in cognitive function.

Research Plan

Study design

The PATH Project uses a cohort-sequential design. The youngest group was aged 20-24 when first surveyed in 1999 then again in 2003 when they were aged 24-28, and will be re-interviewed at four-year intervals until 2019. At that time they will be aged 40-44, matching the initial age range of the second cohort, which was first surveyed at that age in 2000. The third and final cohort were surveyed for the first time in 2001, aged 60-64, and will be followed until they are 80-84 years old. Thus in a 24 year program, the PATH Project will cover the entire adult life span from 20 to 84 years of age.

Measures being collected include genetic risk factors from DNA collected by cheek swabs (in collaboration with the John Curtin School of Medical Research), early life adversity, other personal history (including past mental health problems and substance use, adolescent transitions, marital history and family formation), personality measures, life stress and social support, diet (in collaboration with CSIRO Human Nutrition), occupational stress (in collaboration with the National Centre for Epidemiology and Population Health), recent anxiety and depression, recent substance use, and cognitive abilities.

Anxiety and depression

Anxiety and depression can be conceptualised in terms of diagnostic categories or in terms of continuous dimensions [5]. Whichever way they are conceptualised, there is considerable overlap between anxiety and depression, with high co-morbidity of the disorders and high correlations between dimensions [6]. This high co-morbidity suggests that there is some commonality in aetiology. In the PATH Project, both diagnostic and dimensional approaches are incorporated. We have also collected data to allow investigation of the following issues:

Age. A number of studies have reported a lower prevalence of anxiety and depression in old age [1]. Some researchers have interpreted this as indicating that old age is protective [7], whereas others argue for a cohort effect, with younger cohorts having a greater risk of depression [8]. Because virtually all the evidence is from cross-sectional studies, it is difficult to distinguish ageing effects from cohort effects. Another potential source of apparent age differences is bias in assessment methods. Bias would arise if depression manifested differently in different age groups. We are one of the few groups to have taken the issue of assessment bias seriously [9,10]. We will continue to apply advanced psychometric techniques to PATH data. Differences in anxiety and depression across age groups may also reflect differential exposure to risk factors at various life stages or differences in emotional responsiveness or coping strategies.

Gender. There is a higher female prevalence of anxiety and depression which has not been adequately explained [11]. There is some evidence that the gender difference may reduce in old age, suggesting the value of a lifespan perspective. The data will allow investigation of a variety of hypotheses involving hormones, genetics, coping style, social adversity, and role differences.

Personality and early life vulnerability factors. Personality measures of neuroticism are known to be major predictors, but newer measures may prove to be superior at separating vulnerability from chronic symptomatology [12]. Childhood adversity also increases vulnerability, but the mechanism is not understood. The availability of MRI data (see below) will allow an investigation of novel explanations involving an effect of early trauma on hippocampal and amygdala volumes [13].

Occupation. Various occupational transitions are known to be associated with depression, but the causative status is still debated [14], underlining the value of longitudinal data. Job demands are also thought to be important, including low control, low social support and high demands [15], but have not been investigated in the Australian context.

Brain changes. MRI scans on the 60+ and 40+ age cohorts will allow the investigation of white matter changes as a risk factor for depression and anxiety [16, 17]. It will also be possible to examine the effects of depression on hippocampal volume and the mediating effects of cortisol levels [18].

Genetic factors. Candidate polymorphisms may have differential effects at particular stages of life. We will be examining functional polymorphisms affecting neurotransmitter or other aspects of brain functioning. We are particularly interested in haplotype analysis (involving multiple functional polymorphisms within the one gene) and in gene-environment interaction. We believe there are advantages in using general population data for examining genetic risk factors [19].

Physical health. Depression (but not anxiety) predicts mortality [1], but the mechanisms are not understood. Depression may simply be co-morbid with physical diseases or it may be a risk factor for other diseases. There is some evidence that it is a risk factor for dementia [20] and for cardiovascular disease [21]. The PATH Project will have relevant data on these variables.

Substance use

The emphasis at CMHR on high prevalence mental disorders applies also to substance use, where alcohol, marijuana (especially in younger age groups) and tobacco use are sufficiently prevalent to justify investigation using general population samples. As with other outcomes, we have used both dimensional and categorical measures of substance use (e.g., hazardous and harmful levels of alcohol consumption defined by NHMRC

guidelines). For alcohol and marijuana use we have also collected information on problems associated with use (including signs of dependence) in addition to consumption level.

Our prime interest in substance use is the possible relationships with other outcome measures, including comorbidity with anxiety/depression and associations with cognitive deficits. However there are other hypotheses to be explored in relation to substance use in its own right. For alcohol use especially, there is evidence that consumption declines longitudinally in early adulthood [22], but age differences observed in later adulthood may be due to cohort effects rather than ageing. The PATH Project will help disentangle these alternative explanations. We will also use longitudinal analyses to investigate factors that predict relative increases or decreases in consumption over time. Potential chronic and acute influences include partnership histories, having children, paid employment, other economic factors, physical health, social support and stressful life events [23]. The team already has experience in alcohol consumption research through collaboration with the 1958 British Birth Cohort, and will extend analyses to include tobacco and marijuana use. We will also investigate the association between early-life risk factors and substance use in adulthood at different stages of the life span. Previous work has shown that parental divorce as a risk factor shows a persistent or even increasing effect size in relation to substance use in adulthood [24,25] and we can expand these analyses to incorporate a wide range of measures of early-life environmental adversity as well as candidate polymorphisms.

The wide range of past and contemporary risk factors for adult psychopathology will enable detailed analyses of the extent to which associations (i.e., comorbidity) between the domains of depression/anxiety, substance use and cognitive abilities can be accounted for by common risk factors and how such interrelationships develop over the life-span [26]. Although there has been an explosion of research interest in co-morbidity in recent years, very little work has been carried out on its developmental origins.

In relation to alcohol use, CMHR has a specific interest in the mental health of abstainers as well as heavy or problem drinkers. This comes from several studies showing a U- or J-shaped pattern for measures of depression, anxiety or general psychological distress in relation to level of alcohol consumption, such that moderate drinkers have the least symptomatology [27-29]. Longitudinal analyses are needed to determine whether those with mental health problems give up alcohol, whether risk factors in established abstainers progressively manifest as depression and anxiety or whether moderate consumption may have protective effects. Such analyses can be carried out when the first follow ups of the three PATH cohorts are carried from 2003-2005.

Cognitive ability and dementia

Memory and intelligence have long been recognised as reflecting a number of cognitive domains or components rather than single abilities [30]. This is particularly relevant to the study of cognitive change across the lifespan, as it is known that some abilities increase through early adulthood, stabilise in midlife and decline only very late. Other abilities, such as fluid intelligence decline from early adulthood and show a steeper course over the life span. Much research into these developmental changes has been based on cross-sectional studies, and restricted to specific age ranges – the very young or the very old. There is also evidence from studies of the norming of intelligence test scores that show that these scores have improved dramatically over the last half of the

century [31]. The gains have occurred most strongly in tests of fluid ability, which are the same tests that show strong ageing effects.

The PATH Project will investigate cognitive change (and dementia) across the lifespan, identify predictors of growth and deterioration in cognitive domains, and examine associations among changes in sensori-motor, physiological, physical, brain morphological and cognitive indices. Although there has been considerable research on risk factors for Alzheimer's disease, comparatively little is known about factors associated with milder age-related cognitive decline [32]. The factors behind the major historical improvement in cognitive test scores are also not understood. Although risk factors for Alzheimer's disease have received much more attention, most cohort studies have begun when subjects are already aged 70 or over, making the causative status of any associations difficult to determine. Such associations could arise due to the subclinical effects of disease on exposure or the effects of subtle memory problems on reports of exposure. We consider that cognitive change, mild cognitive impairment and dementia require investigation in parallel. Consequently, both categorical (eg, clinical diagnoses) and continuous (test scores across cognitive domains) measures are taken.

Specific areas of investigation include:

1. Evaluation of intra-individual and inter-individual differences in the rates and patterns of cognitive decline, and their predictors;
2. Examination of possible risk and protection factors for Alzheimer's disease or vascular dementia, including lifestyle factors (mental and physical activity, social support, adverse life events, smoking, alcohol consumption), medications (oestrogen, anti-inflammatories, anti-hypertensives, psychotropics), medical factors (hypertension, hypotension, homocysteine, cholesterol, cardiovascular disease, depression, white matter changes), dietary factors (antioxidants, folate, caloric intake), neurocognitive reserve (pre-morbid intelligence, education, total brain and hippocampal volume) and genetic factors (e.g., APOE, A2M);
3. Evaluation of the relationship between white matter, hippocampal and total brain volume indices and clinical syndromes of mild cognitive impairment (eg, mild cognitive impairment [33], age associated memory impairment, ageing-related cognitive decline), and examination of the validity of such syndromes and their relationship to pre-clinical dementia diseases;
4. Predictors of cognitive growth and deterioration, and mortality, including psychological (eg, emotional states, subjective view of impairment), personality, social, physical, chemical, genetic, brain morphology and health-related variables;
5. The investigation of whether more basic or 'primitive' cognitive processes (such as cognitive speed) account for 'higher level' changes in memory or reasoning;
6. Examination of associations among domains of cognitive performance and evaluation of lagged relationships of age-related change over time, and cohort effects within as well as across cognitive domains.

This research will contribute to an understanding of risk and protective factors across the full adult lifespan, the nature of cognitive ageing processes, the enhancement of cognitive ability and prevention of cognitive decline, the physiological and genetic basis of individual rates of change and the status of normal ageing as qualitatively distinct or otherwise from Alzheimer's disease. The advantages of the study are the potential to examine life-span data covering 60 years from three cohorts, the opportunity to relate

behavioural changes and risk factor data to brain changes as measured by MRI, the establishment of the clinical diagnosis of dementia diseases and the use of a community based rather than a volunteer sample. In particular, the investigation of the association between brain changes such as white matter lesions, hippocampal and cingulate volumes and cognitive change in a community setting from early middle age will make the PATH Project one of the most significant data sets worldwide in which to study brain /behaviour relationships.

Statistical analysis of the PATH Project

The study design will eventually permit the direct comparison of similarly aged groups of individuals from widely separated birth cohorts, thus directly addressing the aim of distinguishing ageing effects from cohort effects. These analyses will involve multiple regression models for repeated measures data. More powerful comparisons with the same aim will also be possible, making full use of the entire project dataset, based on latent growth analysis [34]. This second approach will involve building and validating appropriate structural equation models (SEM) with causative paths designed to allow both cohort effects and individual effects to moderate the shared patterns of change over the 20 years.

Finally, these structurally complex models must be investigated using probability models appropriate to the various data types being collected, such as binomial for diagnostic categories, or normal for at least some dimensional measures of disability. For many psychological scales we have found that discrete probability distributions such as the negative binominal family are more appropriate than the more commonly used normal distribution.

Some important analyses arising from the PATH Project are likely to require new statistical methods. Investigating genetic associations in a combined sample of 7000 individuals would be prohibitively expensive if approached naively, and sequential sampling methods will be applied in order to screen candidate loci for promising associations prior to comprehensive ascertainment of genotype. Beyond epidemiology, this uniquely extensive dataset will permit us to investigate new statistical approaches to nosology, revalidating or revising the psychometric scales in the light of 20 years of observation on three age groups.

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