Perminder Sachdev - selected publications

1 Reppermund, S., Zhuang, L., Wen, W., Slavin, M. J., Trollor, J. N., Brodaty, H., & Sachdev, P. S. (2014). White matter integrity and late-life depression in community-dwelling individuals: diffusion tensor imaging study using tract-based spatial statistics. *British Journal of Psychiatry, 205,* 315-320.
Notes: Background Late-life depression has been associated with white matter changes in studies using the regions of interest approach. Aims To investigate the cross-sectional and longitudinal relationship between white matter integrity and depression in community-dwelling individuals using diffusion tensor imaging with tract-based spatial statistics. Method The sample comprised 381 participants aged between 72 and 92 years who were assessed twice within 2 years. Depressive symptoms were measured with the Geriatric Depression Scale. Tract-based spatial statistics were applied to investigate white matter integrity in currently depressed v. non-depressed elderly people and in those with a history of depression v. no history of depression. The relationship between white matter integrity and development of depressive symptoms after 2 years were analysed with logistic regression. Results Individuals with current depression had widespread white matter integrity reduction compared with non-depressed elderly people. Significant fractional anisotropy reductions were found in 45 brain areas with the most notable findings in the frontal lobe, association and projection fibres. A history of depression was not associated with reduced fractional anisotropy. White matter changes in the superior frontal gyrus, posterior thalamic radiation, superior longitudinal fasciculus and in the body of corpus callosum predicted depression at follow-up. Conclusions Reduced white matter integrity is associated with late-life depression and predicts future depressive symptoms whereas a history of depression is not related to white matter changes. Disruption to white matter integrity may be a biomarker to predict late-life depression

2 Sachdev, P. S., Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N. et al. (2013). Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. *PLoS.ONE., 8,* e59649.
Notes: INTRODUCTION: Mild cognitive impairment (MCI) is associated with an increased risk of developing dementia. However, many individuals diagnosed with MCI are found to have reverted to normal cognition on follow-up. This study investigated factors predicting or associated with reversion from MCI to normal cognition. METHODS: Our analyses considered 223 participants (48.9% male) aged 71-89 years, drawn from the prospective, population-based Sydney Memory and Ageing Study. All were diagnosed with MCI at baseline and subsequently classified with either normal cognition or repeat diagnosis of MCI after two years (a further 11 participants who progressed from MCI to dementia were excluded). Associations with reversion were investigated for (1) baseline factors that included diagnostic features, personality, neuroimaging, sociodemographics, lifestyle, and physical and mental health; (2) longitudinal change in potentially modifiable factors. RESULTS: There were 66 reverters to normal cognition and 157 non-reverters (stable MCI). Regression analyses identified diagnostic features as most predictive of prognosis, with reversion less likely in participants with multiple-domain MCI ($p = 0.011$), a moderately or severely impaired cognitive domain ($p = 0.002$ and $p = 0.006$), or an informant-based memory complaint ($p = 0.031$). Reversion was also less likely for participants with arthritis ($p = 0.037$), but more likely for participants with higher complex mental activity ($p = 0.003$), greater openness to experience ($p = 0.041$), better vision ($p = 0.014$), better smelling ability ($p = 0.040$), or larger combined volume of the left hippocampus and left amygdala ($p<0.040$). Reversion was also associated with a larger drop in diastolic blood pressure between baseline and follow-up ($p = 0.026$). DISCUSSION: Numerous factors are associated with reversion from MCI to normal cognition. Assessing these factors could facilitate more accurate prognosis of individuals with MCI. Participation in cognitively enriching activities and efforts to lower blood pressure might promote reversion

3 Sachdev, P. S., Lee, T., Wen, W., Ames, D., Batouli, A. H., Bowden, J. et al. (2013). The contribution of twins to the study of cognitive ageing and dementia: the Older Australian Twins Study. *International Review of Psychiatry, 25,* 738-747.
Notes: The Older Australian Twins Study (OATS) is a major longitudinal study of twins, aged >/= 65 years, to investigate genetic and environmental factors and their interactions in healthy brain ageing and neurocognitive disorders. The study collects psychiatric, neuropsychological, cardiovascular, metabolic, biochemical, neuroimaging, genomic and proteomic data, with two-yearly assessments, and is currently in its third wave. The initial cohort comprises 623 individuals (161 monozygotic and 124 dizygotic twin pairs; 1 MZ triplets; 27 single twins and 23 non-twin siblings), of whom 426 have had wave 2 assessment. A number of salient findings have emerged thus far which assist in the understanding of genetic contributions to cognitive functions such as processing speed, executive ability and episodic memory, and which support the brain reserve hypothesis. The heritability of brain structures, both cortical and subcortical, brain spectroscopic metabolites and markers of small vessel disease, such as lacunar infarction and white matter hyperintensities, have been examined and can inform future genetic investigations. Work on amyloid imaging and functional magnetic resonance imaging is proceeding and epigenetic studies are progressing. This internationally important study has the potential to inform research into cognitive ageing in the future, and offers an excellent resource for collaborative work

4 Sachdev, P. S., Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N. et al. (2012). Risk profiles for mild cognitive impairment vary by age and sex: the Sydney Memory and Ageing study. *American Journal of Geriatric Psychiatry, 20,* 854-865.
Notes: OBJECTIVES: : To examine age- and sex-related differences in risk and protective factors for mild cognitive impairment (MCI) in community-based elderly individuals. DESIGN: : Cross-sectional study. SETTING: : The population-based Sydney Memory and Ageing Study. PARTICIPANTS: : A total of 757 nondemented, community-dwelling elderly individuals from an English-speaking background categorized as younger (70-79 years) or older (80-90 years). MEASUREMENTS: : Risk of MCI was determined for sociodemographic, lifestyle, and cardiac, physical, mental, and general health factors using age- (and sex-) adjusted multiple regressions comprising initially significant univariate factors. RESULTS: : The point prevalence of MCI within our sample was 39.1% overall: it was lowest in younger women (32.3%) and similar across men and older women (41.9%-43.6%). The risk of MCI across all participants was increased by the APOE 4 allele, high homocysteine, and heart disease; and decreased by better odor identification, visual acuity, and mental activity. Risk factors in all younger participants were slow 6-m walk, poor odor identification, and high homocysteine. Risk of MCI was associated in younger women with history of depression, less mental activity, slower 6-m walk, poorer visual acuity, and higher homocysteine; and in younger men with poorer odor identification and higher homocysteine. Older participants showed no significant risk factors for MCI, except for poorer visual acuity in men. Supporting these findings were statistically significant interactions that reflected the differences in risk factor profiles between age and/or sex groups. CONCLUSIONS: : Risk factors for MCI differ in men and women and vary with age. This has implications for preventing MCI and possibly dementia

5 Sachdev, P. S., Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N. et al. (2012). Risk profiles of subtypes of mild cognitive impairment: the S ydney memory and ageing study. *Journal of the American Geriatrics Society, 60,* 24-33.
Notes: OBJECTIVES: To compare the risk profiles of mild cognitive impairment (MCI) subtypes in a population-based elderly sample. DESIGN: Cross-sectional study. SETTING: The population-based Sydney Memory and Ageing Study. PARTICIPANTS: Seven hundred fifty-seven English-speaking, community-dwelling individuals without dementia aged 70 to 90. MEASUREMENTS: Comprehensive neuropsychological assessments were used to diagnose MCI and its subtypes, categorized as amnestic (aMCI) or nonamnestic (naMCI) and as single- (sdMCI) or multiple- (mdMCI) domain. Risk profiles were derived from

sociodemographic; lifestyle; and cardiac, physical, mental, and general health data. Whole-sample and sex-specific comparisons between aMCI and naMCI and between mdMCI and sdMCI were made using age- (and sex-) adjusted multiple regressions comprising initially significant univariate factors. RESULTS: Risk factors for MCI were presence of the apolipoprotein E (APOE) epsilon4 allele, heart disease, high homocysteine, poor odor identification ability, low visual acuity, and lower mental activity. The odds of having naMCI rather than aMCI were lower with greater levels of social activity and greater if taking antihypertensives, the latter particularly in men. The odds of naMCI were greater in men taking antidepressants or with a longer 6-meter walk time and in women with hypertension. The odds of having mdMCI rather than sdMCI were greater in participants with a history of depression or having the APOE epsilon4 allele. Greater odds of mdMCI were also associated with lower mental activity, particularly for women. For men, the odds of mdMCI were greater with the APOE epsilon4 allele and lower if diagnosed with high cholesterol. CONCLUSION: MCI subtypes exhibit distinctive, sex-dependent risk profiles. This is consistent with MCI subtypes having different etiologies and outcomes and supports the idea that subtyping MCI may offer predictive validity and clinical application

6 Valenzuela, M., Brayne, C., Sachdev, P., Wilcock, G., & Matthews, F. (2011). Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. *American Journal of Epidemiology, 173,* 1004-1012.
Notes: An active cognitive lifestyle has been linked to dementia incidence and survival, but the separate and combined effects of its subcomponents are not clear. Data were derived from the Medical Research Council Cognitive Function and Ageing Study, a population-based study of 13,004 individuals in England and Wales first interviewed in 1991-1992 and followed over a 10-year period for dementia incidence and 12 years for mortality. A Cognitive Lifestyle Score (CLS), defined as a composite of cognitive activity including education, occupational complexity, and social engagement, was available for 12,600 individuals in 3 stages of life. A higher CLS was protective of dementia (odds ratio = 0.6, 95% confidence interval: 0.4, 0.9). Sensitivity analyses found this main effect to be reliable and replicable even when considering just 2 components of the score, either education and occupation or education and late-life social engagement. No single CLS factor was associated with dementia incidence on its own. Survival differences did not reach statistical significance. Our data suggest that more years of education, as well as further stimulatory experiences in either midlife or late life. are necessary for a protective link with dementia incidence. There was little evidence of an effect of cognitive lifestyle on survival after dementia diagnosis

7 Valenzuela, M. & Sachdev, P. (2009). Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *American Journal of Geriatric Psychiatry, 17,* 179-187.
Notes: OBJECTIVES: Epidemiological and preclinical studies suggest that mental activity levels may alter dementia risk. Clinical trials are now beginning to address the key issues of persistence of effect over extended follow-up and transfer of effect to nontrained domains. The aim of this report was to therefore systematically review results from clinical trials, which have examined the effect of cognitive exercise on longitudinal cognitive performance in healthy elderly individuals. METHODS: MEDLINE, PubMed, and key references were used to generate an initial list of relevant studies (N = 54). These were reviewed to identify randomized controlled trials, which tested the effect of a discrete cognitive exercise training regime on longitudinal (>3 months) posttraining neuropsychological performance in healthy older adults. Seven RCTs met entry criteria. Prechange and postchange scores were integrated using a random effects weighted mean difference (WMD) meta-analytic approach (Review Manager Version 4.2). RESULTS: A strong effect size was observed for cognitive exercise interventions compared with wait-and-see control conditions (WMD = 1.07, CI: 0.32-1.83, z = 2.78, N = 7, p = 0.006, N = 3,194). RCTs with follow-up greater than 2 years did not appear to produce lower effect size estimates than those with less extended follow-up. Quality of reporting of trials was in general low. CONCLUSION: Cognitive exercise training in healthy older individuals produces strong and persistent protective effects on

longitudinal neuropsychological performance. Transfer of these effects to dementia-relevant domains such as general cognition and daily functioning has also been reported in some studies. Importantly, cognitive exercise has yet to be shown to prevent incident dementia in an appropriately designed trial and this is now an international priority

8 Sachdev, P. S., Chen, X., Brodaty, H., Thompson, C., Altendorf, A., & Wen, W. (2009). The determinants and longitudinal course of post-stroke mild cognitive impairment. *Journal of the International Neuropsychological Society, 15,* 915-923.
Notes: While post-stroke dementia has been extensively investigated, the large number of patients with mild cognitive impairment (MCI) following stroke has received less attention, and reports on the longitudinal course of such impairment are inconsistent in their findings. We examined patients with MCI (n = 45) or no cognitive impairment (NCI) (n = 59), based on consensus criteria following detailed neuropsychological assessments and magnetic resonance imaging (MRI) scans, and compared them with healthy control subjects (n = 84), all of whom were assessed at two time points, 3 years apart. The MCI at baseline in this group was judged to be vascular in etiology (vaMCI). Incident dementia was diagnosed in 24.4% of vaMCI and 8.5% of NCI subjects and no control subjects over 3 years, giving a rate of conversion of approximately 8% per year in post-stroke vaMCI. The vaMCI group showed greater decline in logical memory than the NCI group. Within the vaMCI group, those who developed dementia had great decline in language and executive function. Compared with NCI patients, those with vaMCI had more vascular risk factors and more white matter hyperintensities on MRI at baseline, but did not differ in their brain or hippocampal volumes. Neither MRI volumetric measures nor interval cerebrovascular events predicted decline in function. The major determinant of decline and categorical transition was impaired performance at baseline, suggesting that those with mild impairment post-stroke are more vulnerable to subsequent decline
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9 Sachdev, P. S. & Valenzuela, M. (2009). Brain and cognitive reserve. *American Journal of Geriatric Psychiatry, 17,* 175-178.

10 Sachdev, P., Wen, W., Chen, X., & Brodaty, H. (2007). Progression of white matter hyperintensities in elderly individuals over 3 years. *Neurology, 68,* 214-222.
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OBJECTIVE: The aims of this study were to examine white matter hyperintensities (WMHs) in the brains of elderly individuals, the rate of progression, the anatomic regions most vulnerable, and the predictors of change. METHODS: We examined 51 healthy volunteers (mean age 71 years) with T2-weighted brain MRI on the same scanner 3 years apart. WMH volumes were determined by an automated method, and the anatomic location of change was determined for both deep WMHs (DWMHs) and periventricular WMHs (PVWMHs). RESULTS: The total brain WMH volume increased by 39.6%, i.e., 13.2% per year, with the change in DWMH being 43.8% and 29.7% in PVWMH. The increase was significant in all regions except the occipital lobe and cerebellum. Age, sex, and cerebrovascular risk factors were not significant predictors of WMH progression. The main predictor of progression was baseline level of WMH. The number of WMH lesions increased by a mean of 1.78, and the progression was mainly accounted for by an increase in very large (>16 mm) lesions. Eight subjects showed a slight decrease in WMH. CONCLUSIONS: White matter hyperintensities are progressive in most elderly individuals with an increasing rate of progression as the burden of lesions increases. The rate of progression is greater in deep white matter and in the anterior brain regions. Risk factors for progression are not well understood, and genetic and other environmental factors must be examined. Quantitation of white matter hyperintensities may serve as a surrogate marker of the progression of small vessel disease

11 Valenzuela, M. J. & Sachdev, P. (2006). Brain reserve and cognitive decline: a non-parametric systematic review. *Psychological Medicine, 36,* 1065-1073.
Notes: BACKGROUND: A previous companion paper to this report (Valenzuela and Sachdev, Psychological Medicine 2006, 36, 441-454) suggests a link between behavioural brain reserve and incident dementia; however, the issues of covariate control and ascertainment bias were not directly addressed. Our aim was to quantitatively review an independent set of longitudinal studies of cognitive change in order to clarify these factors. METHOD: Cohort studies of the effects of education, occupation, and mental activities on cognitive decline were of interest. Abstracts were identified in MEDLINE (1966-September 2004), CURRENT CONTENTS (to September 2004), PsychINFO (1984-September 2004), Cochrane Library Databases and reference lists from relevant articles. Eighteen studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Cognitive decline studies were integrated using a non-parametric method after converting outcome data onto a common effect size metric. RESULTS: Higher behavioural brain reserve was related to decreased longitudinal cognitive decline after control for covariates in source studies (phi=1.70, p<0.001). This effect was robust to correction for both multiple predictors and multiple outcome measures and was the result of integrating data derived from more than 47000 individuals. CONCLUSIONS: This study affirms that the link between behavioural brain reserve and incident dementia is most likely due to fundamentally different cognitive trajectories rather than confound factors

12 Valenzuela, M. J. & Sachdev, P. (2006). Brain reserve and dementia: a systematic review. *Psychological Medicine, 36,* 441-454.
Notes: BACKGROUND: Behavioural brain reserve is a property of the central nervous system related to sustained and complex mental activity which can lead to differential expression of brain injury. Behavioural brain reserve has been assessed using autobiographical data such as education levels, occupational complexity and mentally stimulating lifestyle pursuits. So far there have been several epidemiological reports but no systematic review to put conflicting results into context. Our aim was to quantitatively review evidence for the effect of brain reserve on incident dementia. METHOD: Cohort studies of the effects of education, occupation, premorbid IQ and mental activities on dementia risk were of interest. Abstracts were identified in MEDLINE (1966-September 2004), CURRENT CONTENTS (to September, 2004), PsychINFO (1984-September 2004), Cochrane Library Databases and reference lists from relevant articles. Twenty-two studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Studies were combined through a quantitative random-effects meta-analysis. RESULTS: Higher brain reserve was associated with a lowered risk for incident dementia (summary odds ratio, 0.54; 95% confidence interval, 0.49-0.59). This effect was found over a median of 7.1 years follow-up and resulted from integrating data across more than 29000 individuals. Notably, increased complex mental activity in late life was associated with lower dementia rates independent of other predictors; a dose-response relationship was also evident between extent of complex mental activities in late life and dementia risk. CONCLUSIONS: This study demonstrates robust evidence that complex patterns of mental activity in the early, mid- and late-life stages is associated with a significant reduction in dementia incidence. Randomized control trials based on brain-reserve principles are now required

13 Sachdev, P. & Kiloh, L. G. (1994). The nondepressive pseudodementias. In V.O.B.Emery & T. E. Oxman (Eds.), *Dementia: Presentations, differential diagnosis, and nosology* (pp. 277-297). Baltimore,MD: Johns Hopkins University Press.