response rate of 38%), and patients with depressive symptoms could have been more inclined to consent than those without such symptoms. Furthermore, initial inclusion criteria were weighted towards patients with depressive symptoms. This sample bias implies that the reported prevalence of depression in the study cannot be extrapolated to community or out-patient samples, but this should not affect the overall validation results. Second, compared with scores reported in other studies of patients with PD, the rating-scale scores reported by Williams *et al.*[8] were generally lower, which resulted in recommended cut-off scores for a diagnosis of depression that were equal to, or even below, those recommended in the general population. The authors note that a higher cut-off score was expected, but cannot provide a plausible explanation for their outcome.

The finding that most depression rating scales perform equally well for screening in patients with PD is reassuring given that these scales are all frequently used in research and clinical practice. Depression scale properties were robust across demographic and clinical characteristics, suggesting that these scales are applicable to many PD populations. However, the discriminative validity of these scales for other mood syndromes, such as anxiety disorders and apathy, was not assessed by Williams and colleagues. Furthermore, as in most validation studies, patients with cognitive decline were excluded. Individuals with PD and cognitive decline are at risk of depression, yet no reliable screening instruments exist for this subgroup of patients.

None of the scales studied is capable of capturing depressive symptoms or changes in mood that are related to on–off fluctuations in patients with motor and non-motor fluctuations. Thus, although the findings of this study are robust in PD overall, diagnosis of depression in different stages of PD presents additional challenges that are not met by existing scales. One should also note that many of these scales were not developed for screening of depression, and the UPDRS depression item was designed for clinician-based assessment rather than patient self-reporting, which may have contributed to the poor performance of this scale.

In summary, Williams *et al.*[8] show the utility of a number of rating scales for screening for depression in PD. However, these instruments do not replace the need for a clinical diagnosis. As most scales have similar clinimetric properties, aspects of convenience and cost will be considered when choosing a particular instrument. In many scenarios, short patient-completed scales could perform equally well as long and/or clinician-rated scales that require training—a finding that could influence the design of large-scale trials or epidemiological studies in PD.

Notably, the performance of the nine scales for rating depression severity in PD was not examined. The ability of scales to measure change in depressive status may differ considerably from their performance as a screening tool. In the Movement Disorder Society's published critique of depression rating tools,[4] the scales that gave the most accurate measurement of depression severity were different from those that were optimal for detecting depressive disorders. Whereas screening scales may be useful in clinical trials as tools to implement inclusion or exclusion criteria, scales that measure severity will be more useful for assessing treatment responses. Construct validity, divergent validity for diagnosis of other syndromes, and clinimetric performance in different PD subgroups have not been studied for most scales. These characteristics require further investigation, and validation of scales with new assessment methods, such as the Item Response Theory, are still awaited.

*Department of Clinical Neurosciences, Institute of Neurology, University College London, Rowland Hill Street, London NW3 2PF, UK (**A. Schrag**). Department of Psychiatry, Maastricht University Medical Centre, P. O. Box 5800, 6202 AZ Maastricht, The Netherlands (**A. F. Leentjens**). Correspondence to: A. Schrag a.schrag@ucl.ac.uk*

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The authors declare no competing interests.

1. Reijnders, J. S., Ehrt, U., Weber, W. E., Aarsland, D. & Leentjens, A. F. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov. Disord.* **23**, 183–189 (2008).
2. Schrag, A., Jahanshahi, M. & Quinn, N. What contributes to quality of life in patients with Parkinson's disease? *J. Neurol. Neurosurg. Psychiatry* **69**, 308–312 (2000).
3. Weintraub, D., Moberg, P. J., Duda, J. E., Katz, I. R. & Stern, M. B. Recognition and treatment of depression in Parkinson's disease. *J. Geriatr. Psychiatry Neurol.* **16**, 178–183 (2003).
4. Schrag, A. *et al.* Depression rating scales in Parkinson's disease: critique and recommendations. *Mov. Disord.* **22**, 1077–1092 (2007).
5. Leentjens, A. F., Verhey, F. R., Lousberg, R., Spitsbergen, H. & Wilmink, F. W. The validity of the Hamilton and Montgomery–Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. *Int. J. Geriatr. Psychiatry* **15**, 644–649 (2000).
6. Weintraub, D., Oehlberg, K. A., Katz, I. R. & Stern, M. B. Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. *Am. J. Geriatr. Psychiatry* **14**, 169–175 (2006).
7. Mondolo, F. *et al.* The validity of the hospital anxiety and depression scale and the geriatric depression scale in Parkinson's disease. *Behav. Neurol.* **17**, 109–115 (2006).
8. Williams, J. R. *et al.* A comparison of nine scales to detect depression in Parkinson disease: which scale to use? *Neurology* **78**, 998–1006 (2012).

ALZHEIMER DISEASE

Insulin resistance and AD —extending the translational path

Suzanne Craft

Two recent studies have carefully characterized amyloid-related brain insulin resistance in animal models of, and patients with, Alzheimer disease (AD). The researchers show that exendin-4, a glucagon-like peptide 1 receptor agonist, ameliorates pathology and symptoms in a mouse model of AD, suggesting a novel therapeutic approach to this disease.

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The idea that defective insulin signalling contributes to Alzheimer disease (AD) pathogenesis was first proposed by Hoyer more than 20 years ago.[1] Numerous clinical and epidemiological studies have since established that type 2 diabetes increases AD risk, and that targeting insulin levels or modulating sensitivity to insulin affects

cognitive, imaging, and biochemical parameters in adults with AD or its presumed prodrome, amnestic mild cognitive impairment (MCI). Evidence regarding the mechanistic underpinnings of these relationships has been sparse, however, as far fewer studies have systematically characterized insulin signalling in animal models of AD or in human brain tissue.

> "...defective insulin signalling is a characteristic feature of the AD brain"

Two recent studies, published in the *Journal of Clinical Investigation*, have made important contributions in this regard.[2,3] In one study, Talbot *et al.* showed convincingly that defective insulin signalling is a characteristic feature of the AD brain.[2] The study confirms previous reports that a key signature of insulin resistance—phosphorylation of insulin receptor substrate 1 at serine residues 312, 616, or 636 (IRS-1pSer312, 616 or 636)—exists in the AD brain in basal states,[4] and extends these findings using *ex vivo* insulin-receptor stimulation to provide evidence of functional insulin resistance. Although these results are intriguing, caution is warranted when interpreting results from *ex vivo* stimulation of postmortem brain tissue. The researchers should be commended for their careful control of the time interval from death to postmortem, and for providing data from rodent studies to validate and support the findings in humans.[2] Such controls, however, cannot entirely correct for variable causes of death, or for differing disease states immediately before death, which can greatly affect tissue responsivity to various interventions. Nevertheless, the authors demonstrate convincingly that postmortem brain tissue from patients with AD is less responsive to near-physiological doses of insulin than is tissue from non-AD cases.

One mechanism that has been proposed to underlie brain insulin resistance in AD is neurotoxicity mediated by oligomeric amyloid-β. In the study by Talbot *et al.*, amyloid load in control, MCI and AD cases was negatively correlated with the level of tyrosine phosphorylation of the insulin receptor, and showed positive correlation with levels of IRS-1 serine kinases.[2]

Importantly, high levels of insulin resistance markers were associated with poor performance on tests of working and episodic memory, independently of levels of amyloid and neurofibrillary tangles, suggesting that insulin signalling has a direct effect on cognitive status. This observation may help to explain the finding that adults with either amnestic MCI or nonamnestic MCI (the latter group being presumed not to have prodromal AD) showed increased basal levels of IRS-1 serine kinases. However, the researchers did not conduct *ex vivo* stimulation studies to determine whether both groups have comparable functional insulin resistance.

The question remains, therefore, as to whether insulin resistance has a specific pathogenic role in AD, or whether it represents a brain stress response to oligomeric amyloid-β. Increased brain insulin resistance in nonamnestic MCI could be due to another stress-inducing stimulus such as brain ischaemia. Conversely, induction of peripheral insulin resistance is known to modulate levels of amyloid-β in animal and human models,[5–7] suggesting that insulin resistance might precede elevations in oligomeric amyloid-β in a subset of adults with AD. Further work is required to elucidate the relationship between insulin resistance in the brain and in the periphery. Although most of the patients studied did not have diabetes, it is worth noting that peripheral insulin resistance is a pathological condition that commonly occurs in the absence of diabetes, as compensatory hyperinsulinaemia enables glucose to be maintained at levels below the threshold for diagnosis of diabetes.

The companion paper by Bomfim *et al.*[3] takes the story of brain insulin resistance and AD further down the path to clinical translation. Whether results of their studies of human basal IRS-1pSer overlap with the data presented by Talbot *et al.*[2] is unclear, as both studies included cases from the same University of Pennsylvania brain bank. Several additional experiments conducted in this second study, however, provide important new information. In one such experiment, Bomfim *et al.* used a primate model of AD in which adult cynomolgus monkeys received intracerebroventricular infusions of amyloid-β oligomers.[3] They observed increased IRS-1pSer636 levels in the hippocampus and temporal cortex of treated monkeys compared with a sham-operated monkeys. Elevated levels of phosphorylated c-Jun N-terminal kinase —which has been linked to IRS-1 serine phosphorylation in diabetes and peripheral insulin resistance—were also detected in these brain regions. The investigators reported comparable findings in APP/PS1 mice (an animal model of AD), corroborating previous findings in 3xTg-AD mice.[3] These results support the potential for oligomeric amyloid-β to induce brain insulin resistance.

The next experiments by Bomfim *et al.* addressed possible therapeutic approaches to block the AD-promoting effects of insulin resistance. In neuronal cells in culture, both insulin and exendin-4, an insulinotropic agonist of the glucagon-like peptide 1 (GLP-1) receptor, prevented the increased serine phosphorylation and decreased tyrosine phosphorylation of IRS-1 caused by application of amyloid-β. *In vivo*, intraperitoneal injection of exendin-4 in APP/PS1 mice reduced hippocampal IRS-1 serine phosphorylation and amyloid burden, while improving spatial memory.[3]

The effects of exendin-4 are encouraging, although they might not be directly attributable to GLP-1 receptor-mediated effects in the brain. Indeed, GLP-1 receptor agonists have well-documented effects on peripheral variables, including insulin levels, dyslipidaemia, blood pressure, and other vascular factors,[8] which have all been shown to affect brain insulin signalling pathways, amyloid burden, and memory in rodent models of AD. Future studies aimed at relating metabolic parameters to observed brain changes will help to address this issue.

> "...high levels of insulin resistance markers were associated with poor performance on [memory] tests...."

Although the two recent papers[2,3] propose that GLP-1 receptor agonists have superior efficacy to interventions that raise insulin levels in the brain, no head-to-head comparisons were made, and both insulin and exendin-4 had beneficial effects. Additionally, as would be predicted on the basis of these results, intranasal insulin has shown therapeutic benefit in adults with early-stage AD in a phase II clinical trial.[9] Thus, both approaches could have merit, and the broader the range of therapeutic options to address defective brain insulin signalling in AD, the better.

In summary, the careful characterization of defects in brain insulin signalling and the reversal of AD pathology and symptoms by correction of these defects in *in vivo* models represent considerable advances in our

understanding of the relationship between insulin action and AD. The findings also provide much-needed novel targets for development of new drugs to bolster the AD therapeutic armamentarium.

Geriatric Research, Education, and Clinical Center, S-182, Veterans Affairs Puget Sound, 1660 South Columbian Way, Seattle, WA 98108, USA.
scraft@u.washington.edu

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1. Hoyer, S. & Nitsch, R. Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type. *J. Neural. Transm.* **75**, 227–232 (1989).
2. Talbot, K. *et al.* Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J. Clin. Invest.* **122**, 1316–1338 (2012).
3. Bomfim, T. R. *et al.* An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. *J. Clin. Invest.* **122**, 1339–1353 (2012).
4. Ma, Q.-L. *et al.* β-Amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *J. Neurosci.* **29**, 9078–9089 (2009).
5. Cao, D., Lu, H., Lewis, T. L. & Li, L. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *J. Biol. Chem.* **282**, 36275–36282 (2007).
6. Ho, L. *et al.* Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB J.* **18**, 902–904 (2004).
7. Zhao, L. *et al.* Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer's disease intervention. *J. Neurosci.* **24**, 11120–11126 (2004).
8. Sivertsen, J., Rosenmeier, J., Holst, J. J. & Vilsboll, T. The effect of glucagon-like peptide 1 on cardiovascular risk. *Nat. Rev. Cardiol.* **9**, 209–222 (2012).
9. Craft, S. *et al.* Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch. Neurol.* **69**, 29–38 (2012).

STROKE

Bringing care to the patient—quick treatment at any cost?

Exuperio Díez-Tejedor and Blanca Fuentes

A new concept in stroke emergency care is to bring specialized units and neuroimaging facilities to the patient in order to reduce time to treatment. But does this strategy have an effect on stroke outcome, and is the cost of these units worth the time saved?

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Owing to the development and implementation of stroke units in hospitals and to the Declaration of Helsinborg on stroke management by the WHO and The European Stroke Committee in 1995 (updated in 2006),[1] the nihilism surrounding care in patients with acute stroke has been left behind, and there is widespread awareness of the need to provide urgent, specialized care to these individuals.[2] The acceptance and generalization of the 'time is brain' concept,[3] and the proven efficacy of intravenous thrombolytic therapy when applied within 3.0–4.5 h after the onset of stroke,[4,5] have driven research to develop new models of care that reduce time from stroke onset to neurological assessment and initiation of therapy. A new study has analysed the efficacy of a new stroke care model—the so-called mobile stroke unit—in reducing the time to treatment in patients with acute stroke.[6]

Implementation of the 'stroke code', which allows emergency services to give priority for attention and rapid transfer of patients with acute stroke to hospitals with a stroke unit, has reduced prehospital and intrahospital times for care, and consequently increased the percentage of patients with ischaemic stroke who are treated with intravenous thrombolytic therapy.[7] Recently, new measures to improve intrahospital care, aimed at reducing door-to-CT and door-to-treatment times, have been suggested.[8] Development of telemedicine in stroke care (telestroke) has reduced time to intravenous thrombolytic administration in patients admitted to hospitals without a stroke unit, as the audiovisual connection with another hospital with a stroke unit enables quick and specialized assessment of stroke, as well as the reading and interpretation of cranial CT images, all of which facilitate the decision to initiate therapy.[9]

Despite these advances, one of the main factors that affects whether a patient can receive intravenous thrombolytic therapy or not is the time from stroke onset to patient's arrival at the hospital (that is, <4.5 h for intravenous thrombolysis and <8 h for endovascular procedures). The latest innovation has been to bring stroke-specialized care and neuroimaging facilities to the patient in the form of a specialized ambulance, termed the mobile stroke unit. These units enable early assessment of the patient after stroke (including CT scanning to rule out the presence of cerebral haemorrhage) and facilitate the rapid selection of patients who are eligible for intravenous thrombolytic therapy, so that treatment can be initiated before arrival at the hospital. In the new single-centre, quasi-randomized (week-wise randomisation of patients to either mobile stroke unit or conventional hospital-based system), non-blind study, Walter *et al.*[6] showed that this new ambulance system reduced the time to treatment decision and to initiation of intravenous thrombolytic therapy in patients with ischaemic stroke who were eligible for this treatment. However, this reduction in time to treatment did not have a statistically significant effect on the number of patients treated with intravenous thrombolytic therapy or on the functional recovery of these patients.

Several methodological limitations of this study call into question the generalization of this care system for all patients with stroke. First, the study was focused only on the reduction of time to treatment, not on the effect of the ambulance system on increasing the percentage of patients with ischaemic stroke treated with intravenous thrombolytic therapy, or on the most important factor: functional outcomes. Moreover, the study was terminated early as only 100 of the required 200 patients were enrolled. This early termination limited interpretation of the efficacy of the system, as improvements in the outcome variables (NIH Stroke Scale score, Barthel Index rating and modified Rankin Scale score) were considered only as secondary objectives and, therefore, the small sample size reduced power to demonstrate an effect on these variables.