developed impulsive choice behavior when the serotonergic system in the brain was destroyed (Wogar et al., 1993; Poulos et al., 1996; Mobini et al., 2000). On the basis of these findings, it has been proposed that serotonin is involved in delay discounting. However, because serotonergic neurons have a wide range of projection and a large number of serotonin receptor subtypes exist, many questions remain about the functional role of serotonin in impulsive choice. Consequently, various computational models of serotonin (Daw, Kakade and Dayan, 2002), including temporal discounting (Doya 2002), have been proposed and are being investigated (Tanaka et al., 2007, 2009).

Recently, we applied this computational approach to patients with obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD). We found that patients exhibited different choice behavior and different neural activities from those of healthy controls in delay discounting tasks. The application of computational techniques in clinical research has been attracting attention in recent years. Current disease classifications based on symptomatology are greatly affected by biological heterogeneity, and their pathogenesis is difficult to elucidate by, for example, gene analysis, which makes the development of therapy based on etiology difficult. The use of computational techniques is expected to overcome this problem and we believe our approach described here will contribute to achieving this goal.

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Speaker 4: Go Okada, Japan
Title: Cortisol modulation of emotion regulation neurocircuits in PTSD
Go Okada1, Sean T. Ma2, S. Shaun Ho2, Stephen Taylor2, James L. Abelson3, Israel Liberzon1
1 Department of Psychiatry and Neurosciences, Hiroshima University 2 Department of Psychiatry, University of Michigan

Abstract
Objectives: There is growing evidence that many emotion-regulation processes operate at implicit levels, and the ability to regulate emotions without the need for conscious effort is important for mental health. The glucocorticoid hormones (cortisol in humans) are crucial for stress responses and adaptation, and posttraumatic stress disorder (PTSD) has been associated with both cortisol dysregulation and abnormalities in brain regions involved in emotion regulation. However, how cortisol affects implicit emotion regulation in PTSD, until now has not been studied. In the present study, we examined the effects of exogenous synthetic cortisol (hydrocortisone, HCT) administration on emotion regulation neurocircuits in individuals with and without PTSD.

Methods: Here, we used administration of HCT, functional magnetic resonance imaging (fMRI) and the shifting emotion appraisal task (SEAT) which probes neurocircuits of two types of implicit emotion regulation i.e., attention shifting and cognitive appraisal to examine the effect of cortisol on emotion regulation neurocircuits. Using counter-balanced, placebo-controlled, double-blind, within-subject design, 11 individuals diagnosed with PTSD and 11 healthy controls were scanned with blood-oxygen-level-dependent sensitive whole-brain fMRI on 3.0 Tesla GE Sigma System, while performing the SEAT on two separate occasions, once following 100mg HCT administration and once following Placebo administration. Preprocessing of fMRI data and analyses were conducted in Statistical Parametric Mapping 8 (SPM8; the Wellcome Trust Centre for Neuroimaging).

Results: Experimental manipulation robustly activated neurocircuits involved in emotional regulation by attention shifting and cognitive appraisal respectively. Shifting attention to background context resulted in significant activation in the place processing areas such as parahippocampal place area and attention control areas such as dorsolateral PFC. Cognitive appraisal elicited significant activity in the broad area of medial and lateral PFC. Differential cortisol modulations of task related activation were observed in the hippocampus and subgenual anterior cingulate cortex (sgACC) between in controls and in patients with PTSD. The left hippocampus activation during shifting attention to background context was decreased by HCT administration in patients with PTSD while increased in Controls. Differential activation during cognitive appraisal was significant in the sgACC, and this effect is mainly driven by enhanced activation of this area by HCT administration in patients with PTSD.

Conclusions: We used a probe of the implicit emotion regulation processes to assess how cortisol affects the emotion regulation neurocircuits, and demonstrated that elevation of cortisol is associated with reduced activity in the hippocampus during shifting attention to background context and increased activity in the sgACC during cognitive appraisal only in patients with PTSD. These results suggest that the way hormonal activity affects the brain regions involved in emotion regulation is altered in patients with PTSD, possibly reflecting altered sensitivity of the glucocorticoid receptor in these regions in patients with PTSD.

S27: CINP –ICGP Panel Molecular Mechanisms of Late Life Mood and Cognitive Disorders: Targets for Prevention and Intervention
Chair: Gwenn Smith, USA
Co-Chair: Jeong Lan Kim, Republic of Korea

Speaker 1: John O’Brien, UK
Title: Neuroinflammatory changes in late life depression: the NIMROD study
John T O’Brien1, Li Su1, Yetunde O Faluyi2, Young T Hong2, Tim D Fryer2,3, Guy B Williams2,3, Robert Arnold1, Luca Passamonti2, Patricia Vázquez Rodriguez2, Ajenthan Surendranathan1, W Richard Bevan-Jones1, Franklin Aigbhirio1, James B Rowe3,4
1 Department of Psychiatry, University of Cambridge, UK, 2 Wolfson Brain Imaging Centre, University of Cambridge, UK, 3 Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK, 4 Medical Research Council, Cognition and Brain Sciences Unit, Cambridge, UK, 5 Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK.
Abstract

Introduction: Late life depression is known to be associated with specific clinical features, such as cognitive impairments, to have a poor outcome and to be a risk factor for future dementia. Vascular factors have been implicated in aetiology, but neuroinflammation has not been well studied despite being a highly plausible mechanism and potentially tractable target. In our previous work we have shown an increase in inflammatory cytokines in the blood in older depressed subjects, in the current study we aimed to show whether we could demonstrate an increase in central (brain) inflammation in vivo using PET imaging.

Methods: Within the Cambridge Neuroimaging of Inflammation in MemoRy and Other Disorders (NIMROD) study we have recruited 5 older depressed subjects who had met DSM-IV criteria for major depression and 13 controls. Subjects had full clinical and cognitive assessment and venipuncture for CRP measurement. Brain imaging was performed with PET for 75 minutes following bolus iv injection of [(11C)PK11195 (500MBq) and multi-modal 3T MR imaging was also undertaken. Using regional reference tissue modelling of the dynamic PET data corrected for CSF contamination, non-displaceable binding potential ($BP_{ND}$) was estimated using region of interest analysis.

Results: Depressed subjects (Dep) and controls (Con) did not differ in age, sex ratio, education or global cognition (MMSE score) but had significantly higher blood CRP levels than controls (mean (SD): Dep 6.4 (5.1); Con 1.0 (1.2); p<0.05). Though largely recovered from their depression at time of imaging, depressed subjects had significantly raised [(11C)PK11195 $BP_{ND}$] compared to controls in several regions (for example, anterior cingulate mean (SD): Dep: 0.118 (0.061); Con: 0.025 (0.067); p = 0.025).

Conclusions: We found evidence of both central and peripheral inflammation in older subjects with depression, with changes in areas including the anterior cingulate, known to play a key role in the regulation of mood. Neuroinflammation may be an important mechanism in late life depression and merits further investigation as a potential target for novel therapeutics in a condition which responds poorly to conventional antidepressant therapy.

Speaker 2: Gwenn Smith, USA

Title: Molecular Imaging of Serotonin Degeneration and Alzheimer Neuropathology in Late Life Depression and Mild Cognitive Impairment

Gwenn S. Smith, PhD, Frederick S. Barrett, PhD, Alena Savonenko, MD, PhD, Yun Zhou PhD, Dean F. Wong MD, PhD, Clifford I. Workman, PhD

Abstract

The neurobiological substrates underlying the transition from normal aging and mild cognitive impairment (MCI) to Alzheimer’s disease (AD) are poorly understood, as are the mechanisms underlying the role of late-life depression (LLD) that is associated with increased risk of cognitive decline. AD pathology is associated with cognitive impairment and functional decline in both MCI and LLD. Substantial advances in neuroimaging instrumentation and radiotracer chemistry have enhanced the ability to study in vivo an increasing number of neurotransmitters, neuromodulators, and, importantly, neuropathological processes. This is an unprecedented opportunity to understand the neurobiology of early stage AD by testing mechanistic hypotheses derived from human post-mortem data and transgenic amyloid mouse models in the living human brain in the preclinical stages of AD. An understanding of the neurobiology of the early course of AD and of clinical progression is critically needed to identify individuals at risk, as well as to identify therapeutic targets for prevention and treatment. Several lines of evidence strongly support the investigation of serotonin degeneration associated with beta-amyloid deposition (Aβ). Transgenic amyloid mouse models show selective vulnerability of cortical monoamine projections, serotonin to a greater extent, in contrast to modest cortical and hippocampal neuronal loss. The pattern of MA degeneration in the mice is remarkably similar to MA pathology in Alzheimer’s disease (AD) and parallels the course of cognitive deficits in the mice. Serotonergic deficits are a consistent finding in AD and in recent neuroimaging studies in LLD and MCI. Multi-modality molecular imaging methods were employed to test these observations from the mouse models in patients with LLD, MCI and normal controls.

MCI, LLD and demographically matched normal controls underwent clinical and cognitive evaluations, magnetic resonance imaging and high resolution positron emission tomography (HRRT) with well-established radiotracers for the serotonin transporter (SERT; [(11C)-DASB], Aβ ([(11C)-PiB]) and regional cerebral blood flow (rCBF; [(15O)-water], respectively). SERT binding was correlated with cognitive measures (verbal and visuospatial memory).

Reduced 5-HTT was observed in MCI and LLD compared to controls in cortical and limbic areas affected by AD pathology, as well as sensory and motor areas, striatum and thalamus that are typically spared. The reduction in 5-HTT was greater and more extensive than grey matter atrophy or reduced rCBF in both groups compared to controls. Lower cortical SERT was associated with worse performance in tests of verbal and visuospatial memory, to a greater extent in MCI than controls.

The decrease of SERT in MCI and LLD observed in the present study, suggests that the serotonin system may represent a target for prevention and treatment, particularly the post-synaptic receptors (5-HT4 agonists, 5-HT6 antagonists) that may not be as severely affected as SERT. Studies are in progress to determine whether serotonin degeneration may be involved in the MCI to dementia transition and whether serotonin degeneration is related to other aspects of AD neuropathology.

Speaker 3: Hidesha Yamashita, Japan

Title: Vascular neuropathology in geriatric psychiatry - depression, cognitive disturbance, and dementia

Hidesha Yamashita1, Seiji Hama2, Taro Murakami2, Shigeto Yamawaki2

1Department of Psychiatry and Neuroscience, Graduate School of Biomedical and Health Science, Hiroshima University, Hiroshima, Japan 2Department of Neurosurgery, Graduate School of Biomedical and Health Science, Hiroshima University, Hiroshima, Japan

Abstract

A growing body of evidence supports an association between cerebrovascular disease and geriatric depression. The term “vascular depression” has been used to describe a subtype occurring later in life and characterized by brain changes that may be related to depression onset.

Over previous decades, several generations of hypotheses have linked depression to the etiology or pathophysiology of dementia.

The likely biological mechanisms linking depression to dementia include vascular disease, alterations in glucocorticoid steroid levels and hippocampal atrophy, increased deposition of amyloid-β plaques, inflammatory changes, and deficits of nerve growth factors.