202. BEREAVEMENT AND DEPRESSION: IMMUNE CONCOMITANT

S.E. Keller, S.J. Schleifer, J.A. Bartlett, A. Goldklang
UMDNJ-New Jersey Medical School, Newark, New Jersey

Bereavement is a common stressor, with spousal/significant other bereavement one of the major life stressors experienced. Early research on immune modulation by psychosocial processes therefore utilized bereavement as a stressor when searching for immune alterations. In the early 1980s several reports documented immune findings following spousal or significant other bereavement. Since the most common psychological sequela of bereavement is depression, the depression/immunity relationship has been pursued since the early studies of bereavement and immunity. A number of manuscripts have reported various immune findings associated with adult depression and have been presented in meta-analytic reports. These findings include decreases in T4 cells and mitogen stimulation with increasing age, and a general decrease in NKCA. Since the immune system develops with age and since depression may represent differing entities within differing age groups, the relation between depression and immunity was explored across differing developmental cohorts. First the immune depression relationship was examined as separate case/control experiments examining children, early adolescents, late adolescents, early adulthood, middle age and elderly. Finally, all of these “separate” studies were combined to appreciate the developing relationship along the age dimension. The immune depression relation in children and adults have been previously reported. We examined a total of 284 adolescents, 32 with MDD and 252 without current MDD. The percent of T4 cells and T cells were increased, while the percent of NK and B cells were decreased. When age and gender were partialled none of these effects remained significant. Analysis of Partial Variance revealed lower mitogen response and NKCA in the depressed adolescents. Contextualizing these findings along with those of other age groups and the “seamless” age analyses will be presented. An age immune relational continuum is postulated.

203. WORKING MEMORY: CONSTRUCTS, NEURAL CIRCUITS, AND PHARMACOLOGICAL MODULATION

A. Belger, J.H. Krystal
Department of Psychiatry, University of North Carolina at Chapel Hill

Working memory is a complex psychological construct, necessary for the performance of higher cognitive functions such as language and reasoning. Numerous studies have demonstrated significant working memory deficits in schizophrenic patients, across modalities and domains, and have generated a need for understanding the psychological, neural and pharmacological bases of these deficits. Cognitive models of working memory have described multiple components, including a visuospatial sketchpad, a phonological loop, and a central executive supervisory system managing and prioritizing access to the former two systems. Consistent with a multi-component cognitive model, early functional magnetic resonance imaging (fMRI) studies from our laboratory and others revealed a distributed neural circuitry underlying spatial and non-spatial working memory processes. Accordingly, while posterior cortical regions differentiated based on stimulus characteristics, dorsolateral prefrontal regions were activated across processing domains, consistent with the mapping of the central executive component onto that region. Subsequent fMRI studies employing other tasks, such as the oddball paradigm associated with P300 ERP generation and Stroop tasks, provided further evidence of a distinct role of prefrontal regions in executive processes underlying the selection of task-appropriate responses. Our recent fMRI studies also revealed that modulation of NMDA receptor function in healthy subjects mimics executive function deficits observed in schizophrenia, and preferentially disrupts prefrontal executive functions despite targeting widespread cortical regions. Finally, behavioral cognitive studies of working memory functions in schizophrenic patients suggested that performance deficits were linked to the “executive load” of the task, rather than the memory load or the delay of information retention. Thus, working memory impairments in schizophrenia are associated with deficient executive control processes secondary to widespread prefrontal cortex dysfunction that is also associated NMDA receptor dysregulation.

204. CLINICAL IMPLICATIONS OF THE INVERTED U-SHAPED CURVE RELATING D1 STIMULATION AND BEHAVIOR

P.S. Goldman-Rakic, S. Castner, G. Williams
Yale University School of Medicine, VA Medical Center 116A/2, West Haven, CT 06516, USA

Two primate models of experimentally induced dopamine dysfunction will be described: a chronic neuroleptic (Haldol) model that down-regulates D1 receptors in the prefrontal cortex and anamphetamine sensitization model that presumably enhances D1 stimulation. Both conditions produce profound but selective impairment in working memory tasks. However, a D1 agonist reverses the impairment in the case of D1 down-regulation and D1 antagonist reverses the impairment in the AMPH model. These results reveal the powerful role of the state of the D1 receptor in regulating the cognitive functions of the prefrontal cortex. Moreover, the effects of limited D1 receptor stimulation/blockade appear to induce long-lasting changes in the circuitry subserving working memory, when D1 acting drugs are withdrawn.

205. DISTINCT CONTRIBUTION OF GLUTAMATE AND Dopamine RECEPTORS TO THE TEMPORAL RANGE OF RODENT WORKING MEMORY USING A TASK WITH ELEMENTS OF HUMAN WORKING MEMORY

B. Moghaddam and J. Aultman
Department of Psychiatry, Yale University School of Medicine, VA Medical Center 116A/2, West Haven, CT 06516, USA

Understanding the mechanistic basis of working memory, the capacity to hold a representation “on line,” is important for delineating the processes involved in higher cognitive functions and the pathophysiology of thought disorders. We examined the contribution of glutamate and