202. BEREAVEMENT AND DEPRESSION: IMMUNE CONCOMITANT

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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 sequel 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

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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

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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 an amphetamine 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

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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
dopamine receptor subtypes to varying working memory load after establishing that a modified rodent spatial working memory task, the discrete-trial variable-delay alternation task, had important elements of human working memory paradigms. For example, performance remained submaximal and stable at second-long retention intervals, was dependent on retention interval and proactive inhibition, and on the integrity of the medial prefrontal cortex. Consistent with clinical findings, low dose amphetamine produced a delay-dependent improvement in performance while higher doses impaired performance at all retention intervals. D1 receptor blockade produced the predicted dose- and delay-dependent impairment. D2 receptor blockade had no effect. Activation of metabotropic glutamate 2/3 (mGlur 2/3) receptors, which in the prefrontal cortex inhibits the slow asynchronous phase of glutamate release, also produced a delay-dependent impairment. Low doses of an AMPA/kainate antagonist had similar effects as the mGlur2/3 agonist. In contrast, the detrimental effect of NMDA receptor blockade was independent of memory load, with the higher dose resulting in chance-level performance at all retention intervals. These findings suggest the following: (1) activation of NMDA receptors is necessary for the initiation of the mnemonic encoding, (2) during the retention phase, WM is maintained by slow components that include the asynchronous phase of glutamate release resulting in “sustained” (second-long) postsynaptic activation of glutamate receptors, and phasic release of dopamine resulting in activation of D1 receptors.

206. DORSAL AND VENTRAL PFC RESPONSES TO WORKING MEMORY DIFFER IN SCHIZOPHRENIA


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How dorsal prefrontal cortex (PFC) neuronal pathology in schizophrenia might be reflected in neuroimaging studies of schizophrenic patients (SCZ) remains an area of active debate. One potential confound is that dorsal and ventral PFC are often grouped together under general labels (‘hypofrontality’) applied to putative physiological abnormalities of PFC function identified by imaging studies. In healthy subjects, there is growing evidence for a functional distinction between dorsal ‘executive’ (e.g., manipulation or inhibition) and ventral (maintenance) PFC sub-regions in the context of cognitive operations like working memory (WM). We looked for such a distinction in the fMRI response to varying WM load in SCZ and matched controls using the n-back WM task. We concurrently collected an independent in-vivo measure of neuronal pathology using 1H-MR CSI (n-acetylaspartate or NAA measures). We found a distinction between dorsal and ventral PFC in their fMRI response to varying WM load and also in the relationship of these responses to WM performance and NAA measures. While both dorsal and ventral PFC fMRI responses were abnormal, only the dorsal PFC response differed from controls in all three analyses. In particular, the magnitude of the abnormal response in dorsal PFC was the only regional fMRI response predicted by the magnitude of PFC pathology in SCZ (i.e., PFC NAA measures). These data suggest that there is greater impairment of dorsal v. ventral PFC function in SCZ and that a failure to appropriately modulate activity within dorsal PFC may be the most germane physiological signature of PFC neuronal dysfunction in SCZ.

207. DEVELOPMENT OF NON-PEPTIDE ANTAGONIST LIGANDS ACTING FOR CRF1 RECEPTORS

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Evidence has been accumulated suggesting that CRF mediates the endocrine, autonomic, behavioral and immune responses to stressful stimuli. Immunohistochemical and anatomical data supported the notion that this peptide fulfills all of the characteristics of a bona fide neurotransmitter. CRF exerts its actions through interaction with multiple CRF receptor binding sites. The cloning of these multiple receptors for CRF as well as the recent discovery of non-peptide receptor antagonists for CRF receptors have begun a new era of study for this neurotransmitter. The receptors for CRF fall into two distinct classes encoded by different genes and have been termed the CRF1 and CRF2 receptors belonging to the superfamilly of the class B G-protein coupled receptors. Heterologous expression of the human receptors in mammalian cell lines has made possible the identification of non-peptide, high affinity, and selective receptor antagonists. These compounds which can functionally inhibit the actions of CRF on the in vitro stimulation of cAMP or ACTH release from cultured rat anterior pituitary cells. In addition, they attenuate CRF or stress-induced elevations in plasma ACTH levels in rats demonstrating that pituitary CRF1 receptors can be blocked. When administered systemically, these compounds cross the blood-brain barrier and interact directly with central CRF receptors in brain regions rich with this subtype as evidenced by ex vivo receptor autoradiography. While the discovery of specific or selective CRF1 receptor antagonists has not yet been forthcoming, a great deal of evidence is emerging that suggests that CRF1 receptor antagonists will prove useful in the discovery and development of potential orally active therapeutics for various neuropsychiatric disorders.

208. CORTICOTROPIN RELEASING FACTOR: NEW DATA AND NEW THERAPEUTIC VISTAS

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CRF is located outside of the hypothalamic pituitary adrenal axis and these limbic CRF systems have been hypothesized to mediate behavioral responses to stressors. CRF has multiple sites of action and injections of CRF antagonists have been particularly effective in reversing behavioral responses to stressors. CRF antagonists reverse the behavioral responses produced by many different physical and psychological stressors including withdrawal from drugs of abuse. In addition, CRF has recently been shown to be activated during acute withdrawal from ethanol, stimulants,