medication development. Recently, we provided evidence that integrins containing the β_3-subunit (*ITGB3*) influence the serotonin system through, in part, a direct interaction with the serotonin transporter (SERT, *SLC6A4*) (Carneiro *et al*, 2008, AM Carneiro and RD Blakely, unpublished results). These findings provide a physical basis for multiple studies that have reported associations of both *ITGB3* and *SLC6A4* (and gene × gene interactions) with autism risk. The SERT/β_3 complex may provide an important framework for SERT regulation that likely relies on the clustering of integrins and integrin-associated proteins. Thus, targetting this complex may prove fruitful in rectifying altered serotonergic signaling in multiple neuropsychiatric disorders.

In addition, integrin-$\alpha_V\beta_3$ modulates glutamatergic signaling in the CNS. Activation of $\alpha_V\beta_3$ by ligand binding leads to selective activation of MAPK-linked signaling pathways (Watson *et al*, 2007), as well as plasma membrane trafficking of AMPA-type glutamate receptors (Cingolani *et al*, 2008). These changes alter synaptic scaling, leading to alterations in the long-term potentiation of neuronal signaling. Further studies will no doubt seek to extend these findings to determine their relationship to behaviors such as learning and memory.

Nonselective peptide ligands and novel subunit-specific ligands are used to pursue the role of integrins in neuronal function. Integrin-β_3 ligands are based on the Arg-Gly-Asp sequence present in the binding domain of extracellular matrix proteins. Cyclic Arg-Gly-Asp peptides show nanomolar $\alpha_V\beta_3$ affinities, whereas isoxazoline compounds (currently under clinical trials) show femtomolar affinities (Miller *et al*, 2000). Although these compounds were initially developed for *in vivo* mapping of malignant tumors and cancer treatment, they also provide exciting leads for reagents that can target $\alpha_V\beta_3$-specific pathways in neurons. Furthermore, they provide a platform for developing blood–brain barrier penetrant ligands that can probe *in vivo* contributions of integrin signaling to behavior and possibly novel treatments for devastating brain disorders.

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DISCLOSURE

The author declares that except for income received from primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Neuropsychopharmacology Reviews (2010) **35**, 338–339; doi:10.1038/npp.2009.134

Imaging advances in developing new medications for addiction

Brain imaging has provided important insights into the clinical neurobiology of addiction for more than 20 years, beginning with the pioneering Positron Emission Tomography (PET) studies of Volkow *et al* (1988), and continuing to recent studies showing that cocaine addiction is associated with changes in dopamine function that are predictive of choice to self-administer cocaine (Martinez *et al*, 2007). However, because of their cost and radiation hazards, PET studies of addicted subjects who are undergoing clinical trials have been limited.

Although BOLD fMRI has some disadvantages, such as lack of an absolute measure of blood flow or neuronal activity, it has the advantages of repeatability, cost, and safety over PET. One area in which fMRI has shown promise in medication development for addiction is as a predictor of treatment response in clinical trials. Recently, Brewer *et al* (2008) showed that fMRI brain activation during performance of a Stroop task in cocaine-dependent subjects before treatment was predictive of subsequent treatment response. Other studies are underway in several centers using fMRI as a baseline predictor of treatment response in clinical trials for cocaine dependence, which should provide important information about the neurobiology of medication response in addiction.

A second area that shows promise for fMRI in medication development for addictions is in the study of acute effects of medications on brain function in addicted individuals. The use of fMRI in this manner, also termed pharmacoMRI or phMRI, has potential as a tool to drive medication development by providing additional information about the effects of medications before their use in costly, time-consuming phase II clinical trials (Wise and Tracey, 2006). The rationale for using phMRI in medication development for addictions is based on the following: (1) behavioral research has shown that addicted individuals show differences in behavioral performance in tasks such as cue reactivity and behavioral inhibition compared with non-addicted subjects; (2) fMRI of addicted subjects while performing these tasks has shown patterns of brain activation

that differ from non-addicted subjects; (3) acute effects of novel compounds on brain activation patterns in addicted subjects while performing these tasks could provide additional information about the pharmacodynamics, and hence the potential utility of these compounds for treatment of addictions. The potential usefulness of this approach has been shown by a recent study showing that an acute dose of methadone reduced fMRI brain activation associated with heroin-related stimuli in opiate addicts (Langleben *et al*, 2008); however to date, phMRI has not been routinely used as a tool for medication development for addictions.

Basic science advances in understanding addiction raise hope for a future with more effective therapeutic strategies for this chronic, relapsing brain disorder. Yet, the progress of candidate medications on the pathway to patients is slow and of the numerous compounds studied for treatment of addictions, few have reached the FDA approval (Vocci and Elkashef, 2005). Novel brain imaging methods, such as phMRI, offer the potential to provide important information about medications for addictions, which could aid in the development of pharmacotherapies for addictions.

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DISCLOSURE

The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2010) **35**, 339–340; doi:10.1038/npp.2009.98

Sex-related functional asymmetry in the limbic brain

At a macroscopic level, the brains of both men and women are very similar. However, closer inspection shows striking differences between the sexes in the structure–function relationships in the brain. Interpersonal, emotional, and occupational success depends critically on effective navigation of the social world. At the same time, individuals of each sex have different goals—only women bear children, and this basic function likely sets the agenda for the individual and societal goals of many women. Men do not bear children and may be driven by an agenda emphasizing acquiring and maintaining resources and power. Thus, sex differences in social-emotional regions of the brain might be adaptive. The limbic regions of the brain and closely connected regions, especially the ventromedial prefrontal cortex (VMPC) and amygdala, are important for social-emotional processing. Furthermore, as nearly all brain regions have homologous versions in each hemisphere, this may be a substrate on which divergent selection resulted in sex-related functional asymmetry.

Studies of neurological patients have shown that the right VMPC and amygdala appear to be critical for social-emotional functioning and decision making in men, whereas the left VMPC and amygdala appear to be more important for these functions in women (Tranel *et al*, 2005; Tranel and Bechara, 2009). For example, a man with a unilateral right VMPC lesion, who was well educated and had worked successfully as a minister, was entirely unable to return to any form of gainful employment after his brain damage. He requires supervision for daily tasks and demonstrates severe disturbances in behavior and emotional regulation, including impulsivity and poor judgment. By contrast, a man with a unilateral left VMPC lesion was able to return to his job at a grain elevator and remains successfully employed there. He is remarkably free of disturbances to his social life and emotional functioning (Tranel *et al*, 2005). Moreover, preliminary evidence from the Trust Game, a multiplayer neuroeconomics task, suggests that women with left VMPC lesions and men with right VMPC lesions trust others less (ie, they invest less in others) and display more frequent acts of negative interpersonal reciprocity (ie, they return less than the amount invested). Similarly, women with lesions to the left amygdala and men with lesions to the right amygdala appear less risk averse than do men and women with lesions to the opposite amygdala. This evidence converges with other research, including (1) fMRI studies showing similar patterns of lateralized activations in these regions in response to social and emotional paradigms (eg, Killgore and Yurgelun-Todd, 2001; Cahill *et al*, 2004); (2) studies showing sex differences in orbitofrontal-dependent behavioral paradigms, such as the Iowa Gambling Task (eg, Overman, 2004); and (3) studies showing increased functional connectivity with the right amygdala of men and with the left amygdala of women (eg, Kilpatrick *et al*, 2006). Altogether, such evidence suggests that the right VMPC and amygdala in men as well as the left VMPC and amygdala in women are important for social-emotional functions. Potentially, the left limbic dominance observed in women reflects a need for expertise in interpersonal relationships (eg, the need to bear and rear children, maintain in-group