frontal and temporal regions 1 month after chemotherapy relative to baseline (Figure 1 and Table 1) (McDonald *et al*, in press). These changes do not occur in breast cancer patients who are not treated with chemotherapy or healthy controls. One year later, these gray matter alterations show partial but not complete recovery, consistent with previous work in retrospective samples. fMRI and PET have also shown differences in brain function during tasks tapping episodic memory and executive functions, including working memory (de Ruiter *et al*, 2010). Mirroring the cognitive literature, altered patterns of brain activation have been found both prior to adjuvant treatment and following chemotherapy or hormonal treatment. Both structural and functional neuroimaging approaches have shown alteration in frontal brain regions, consistent with the most commonly affected cognitive processes in prior neuropsychological studies. Ongoing research examining variables that contribute to cancer- and treatment-related cognitive and brain changes (eg, genetic variability and other bioarkers, age, cognitive reserve, and other medical comorbidities) will be critical to identifying potential risk factors that may increase individual vulnerability (Ahles *et al*, in press). Preclinical research in animal models can be expected to further enhance the understanding of underlying mechanisms. Finally, identification of optimal treatment approaches will be an important future direction.

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DISCLOSURE

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Ahles TA, Saykin AJ (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer* **7**: 192–201.

Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS *et al*. (2010). Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of age and cognitive reserve. *J Clin Oncol* (in press).

de Ruiter MB, Reneman L, Boogerd W, Veltman DJ, van Dam FSAM, Nederveen AJ *et al* (2010). Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Hum Brain Mapping* (in press); e-pub ahead of print 28 July 2010, at http://onlinelibrary.wiley.com/doi/10.1002/hbm.21102/pdf.

Jansen CE, Miaskowski C, Dodd M, Dowling G, Kramer J (2005). A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. *Cancer* **104**: 2222–2233.

McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ (2010). Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. *Breast Cancer Res Treat* (in press); e-pub ahead of print 6 August 2010, at http://www.springerlink.com/content/5686768t1q25287p/fulltext.pdf.

Meyers CA, Perry JR (eds) (2008). *Cognition and Cancer*. Cambridge University Press: Cambridge, MA.

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NICO-TEEN: Neural Substrates that Mediate Adolescent Tobacco Abuse

Adolescents are especially likely to initiate tobacco use and are more vulnerable to long-term tobacco dependence. Although the importance of factors such as environmental conditions, genetics, sex differences, and constituents of tobacco other than nicotine has been recognized, relatively little is known about the neural mechanisms that mediate enhanced sensitivity to tobacco abuse during adolescence.

Recent preclinical studies have led to our working hypothesis that enhanced tobacco abuse during adolescence is promoted by: (1) enhanced positive effects of nicotine; and (2) reduced negative effects of nicotine and withdrawal from this drug during adolescence compared with adulthood (O'Dell, 2009). Thus, the inadequate balance favoring strong positive effects of nicotine over reduced negative effects produces enhanced vulnerability to tobacco abuse during adolescence.

Much work comparing age differences to nicotine has focused on the mesolimbic dopamine pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) where dopamine is increased by nicotine but decreased during withdrawal (Mansvelder and McGehee, 2002). These neurochemical effects are age dependent, as nicotine increases NAcc dopamine to a greater extent in adolescent *vs* adult rats (Shearman *et al*, 2008). Also, we reported that nicotine withdrawal decreases NAcc dopamine to a lesser extent in adolescent *vs* adult rats (Natividad *et al*, 2010). These studies suggest that mesolimbic dopaminergic mechanisms are important in modulating adolescent vulnerability to tobacco abuse.

Our working hypothesis is that the age differences in dopamine have their origin in the VTA where excitatory mechanisms regulate dopamine release in the NAcc. This is based on our observation that nicotine withdrawal decreases glutamate levels in the VTA of adult, but not adolescent, rats. Because excitation in the VTA is not reduced, adolescents show smaller reductions in NAcc dopamine during withdrawal. This hypothesis is consistent with evidence that excitatory systems that facilitate dopamine are overdeveloped during adolescence (McDonald and Johnston, 1990). Taken together, we hypothesize that adolescents show enhanced nicotine reward and reduced withdrawal through enhanced excitation of VTA cell bodies that release dopamine in the NAcc.

Our hypothesis has important clinical implications. First, reduced sensitivity to withdrawal during adolescence implies that the diagnostic criteria developed for tobacco dependence in adults, based primarily on withdrawal, are inappropriate for adolescents. A corollary is that treatments focusing on alleviating withdrawal will

probably fail in adolescents, a hypothesis supported by a study comparing adolescent and adult smokers (Smith *et al*, 2008). Our neurochemical data also suggest that adolescents may be less sensitive to current treatments that facilitate dopamine (such as Zyban), as they may not show deficits in dopamine during withdrawal. Given the strong rewarding effects of nicotine during adolescence, the best strategy for reducing tobacco abuse may be to strictly reduce access to nicotine-containing products during this developmental period. Furthermore, pharmacological treatments for adolescent smokers may target the strong rewarding effects of nicotine that appear to be mediated through mesolimbic dopamine and upstream glutamatergic mechanisms that modulate this reward pathway. Future work is needed to validate the role of these mechanisms in adolescent tobacco abuse, and to examine whether they also mediate long-term vulnerability to tobacco abuse in adults that initiated smoking during adolescence.

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DISCLOSURE

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Mansvelder HD, McGehee DS (2002). Cellular and synaptic mechanisms of nicotine addiction. *J Neurobiol* **53**: 606–617.

McDonald JW, Johnston MV (1990). Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res Rev* **15**: 41–70.

Natividad LA, Tejeda HA, Torres OV, O'Dell LE (2010). Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. *Synapse* **64**: 136–145.

O'Dell LE (2009). A psychobiological framework of the substrates that mediate nicotine use during adolescence. *Neuropharmacology* **56**: 263–278.

Shearman E, Fallon S, Sershen H, Lajtha A (2008). Nicotine-induced monoamine neurotransmitter changes in the brain of young rats. *Brain Res Bull* **76**: 626–639.

Smith AE, Cavallo DA, Dahl T, Wu R, George TP, Krishnan-Sarin S (2008). Effects of acute tobacco abstinence in adolescent smokers as compared with nonsmokers. *J Adol Health* **43**: 46–54.

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Epigenetic Modifications in Neurons are Essential for Formation and Storage of Behavioral Memory

Understanding the molecular mechanisms that produce and maintain long-lasting changes in brain function is critical for numerous areas of neuroscience research, and is especially relevant in the context of learning and memory. Increasing evidence now indicates that epigenetic modifications in neurons may be essential mechanisms for both the formation and storage of behavioral memory. For example, the formation and recall of contextual fear memories increases histone tagging (acetylation) in the hippocampus (Levenson *et al*., 2004). Blocking histone acetylation impairs both long lasting synaptic plasticity as well as behavioral performance (Korzus *et al*., 2004). Similarly, inhibition of histone deacetylase (HDAC) activity rescues these deficits and improves memory formation (Korzus *et al*., 2004; Levenson *et al*., 2004). Finally, normal aging-related memory impairment is associated with the lack of a specific histone acetylation mark, which can be rescued by treatment with an HDAC inhibitor to restore memory function (Peleg *et al*., 2010).

DNA methylation, a second form of epigenetic marking, also has a critical role in memory formation and consolidation. Contextual fear conditioning induces rapid methylation of a memory suppression gene (*protein phosphatase 1*, *PP1*) and demethylation of plasticity genes (*reelin* and *brain-derived neurotrophic factor*, *BDNF*) in the hippocampus (Lubin and Sweatt, 2007; Miller and Sweatt, 2007). Moreover, inhibition of DNA methyltranferases, which are required for DNA methylation, prevents memory formation (Lubin and Sweatt, 2007; Miller and Sweatt, 2007). Interestingly, both histone and DNA methylation changes that occur in the hippocampus after learning are relatively transient compared with the lifetime of a memory, indicating that other mechanisms are involved in long-term memory storage. However, a recent study found that learning can induce long-lasting DNA methylation changes in the anterior cingulate cortex, and that these changes are essential for the recall of remote memories for up to a month after conditioning (Miller *et al*., 2010). This finding is particularly exciting because it (1) reveals a molecular change that lasts long enough to subserve the maintenance of long-term memory, and (2) indicates region-specific regulation of DNA methylation that is largely in line with the functional roles of the hippocampus and cortex in memory consolidation and storage, respectively.

Taken together, these findings indicate that epigenetic mechanisms are key regulators of long-term memory and reveal several potential therapeutic targets for the amelioration of memory-related diseases. Nevertheless, a number of important questions remain to be answered. For example, it is unclear whether diverse histone marks and DNA methylation profiles operate in relative isolation or are integrated as part of an 'epigenetic code' to generate meaningful changes in gene expression and behavior. In addition, it is unclear how cell-wide changes associated with epigenetic modifications interact with synapse-specific changes long believed to underlie learning and memory processes. Finally, it is uncertain how specific epigenetic modifications are targeted within a cell and how the kinetics underlying such modifications may differ between brain regions to confer circuit-specific epigenetic patterns. Future studies will be required to