COMMENTARY

The "Anhedonia Paradox" in Schizophrenia: Insights from Affective Neuroscience

Diego A. Pizzagalli

Emotional disturbances, and particularly anhedonia (the loss of pleasure), occupy a prominent place in conceptualizations of schizophrenia. Fitting these conceptualizations, hundreds of studies using clinical measures or self-report trait questionnaires, have linked schizophrenia to reduced experiences of pleasure (1). In stark contrast with these findings, laboratory studies have shown that, when exposed to pleasant stimuli across modalities (e.g., visual, auditory, gustatory), individuals with schizophrenia typically report hedonic responses similar to those of control subjects (2,3). These sets of findings are puzzling: why do individuals with schizophrenia typically not endorse statements such as "Beautiful scenery has been a great delight to me" but do report normative emotional experiences when exposed to pictures of attractive scenery (4)? Are in-the-moment experiences of pleasure preserved in schizophrenia, and if so, how can we reconcile these findings with clinical observations of anhedonia? Finally, can neuroimaging provide any clues that could illuminate the "anhedonia paradox" in schizophrenia?

An article in the current issue of *Biological Psychiatry* sheds important light on some of these issues (5). Dowd and Barch (5) used functional magnetic resonance imaging (fMRI) to probe the neural circuitry recruited, while individuals with schizophrenia and healthy control subjects rated their responses to emotional pictures, faces, and words with respect to valence (pleasant-unpleasant) and arousal (activation-deactivation). Four main findings emerged. First, (medicated) individuals with schizophrenia reported elevated trait anhedonia, as assessed by the Chapman Physical and Social Anhedonia scales (1). Second, compared with control subjects, patients reported less strongly valenced responses to both positive and negative stimuli, although the general pattern of affective ratings was similar across groups. Moreover, in both groups, elevated trait anhedonia correlated with lower valence scores in response to positive stimuli, and mediation analyses indicated that group differences in affective ratings were fully accounted for by anhedonia. Third, relative to control subjects, patients showed reduced activation to positive stimuli in the right ventral striatum (Figure 1A) and left putamen. Critically, groups showed statistically indistinguishable activations outside the striatum, highlighting a surprisingly high degree of similarity. Finally, among the patients, right ventral striatum activation in response to positive stimuli correlated negatively with anhedonia. Collectively, these findings indicate that affective and neural responses during emotional experience are largely preserved in schizophrenia and that most of the blunted responses to positive stimuli were linked to elevated trait anhedonia, rather than a diagnosis of schizophrenia.

It is striking that group differences were localized to the striatum, particularly in light of recent findings that are fundamentally advancing our understanding of putative core dysfunctions underlying anhedonia in schizophrenia. For example, Waltz *et al.* (6) tested healthy control subjects and medicated individuals with schizophrenia in a Pavlovian conditioning paradigm in which a small amount of juice was either administered 6 seconds after the presentation of a light (75% of trials) or delayed an additional 4 to 7 seconds (25% of the trials) (Figure 1B). Relative to control subjects, individuals with chronic schizophrenia displayed weaker activation in the midbrain and left putamen in response to unexpected juice deliveries (positive prediction error) but responded similarly to unexpected juice omissions (negative prediction error) (see also [7]) (Figure 1C). Notably, groups rated the juice as similarly pleasant, and these ratings did not correlate with self-reported avolition or anhedonia. These findings are consistent with emerging evidence in schizophrenia of reduced correspondence between affective responses to stimuli and motivated behavior.

A compelling demonstration of weakened affect-motivation coupling was provided by Heerey and Gold (8), who engaged participants in a task that required key presses to either prolong or reduce exposure time of pleasant and unpleasant pictures. Critically, in one condition, motor responses were required while the stimulus was shown on a computer screen, a condition intended to capture evoked responding (a possible proxy of liking). In a different condition, motor responses modified future presentations and thus required internal representations of the hedonic values of stimuli, a condition labeled representational responding (a possible proxy of wanting). Several notable findings emerged. First, among control subjects, the number of key presses per second correlated with liking ratings in both the evoked and representational conditions. In schizophrenia, this pattern was seen only in the evoked condition. Relative to control subjects, individuals with schizophrenia showed lower correspondence between key presses and self-reported affective ratings in the representational condition; notably, groups did not differ in the evoked condition (or in their affective ratings to the stimuli), suggesting that patients were able to generate behavior in the presence of an evocative stimulus, consistent with normative in-the-moment (liking) affective responses.

Second, among patients, social anhedonia correlated negatively with representational—but not evoked—responding, bolstering the notion that increased anhedonic scores in trait questionnaires might be largely due to deficits in generating, accessing, and/or maintaining representations of affective values of past or future events. Fitting this interpretation, representational—but not evoked—responding correlated positively with working memory abilities. While consistent with literature on dorsolateral prefrontal cortex dysfunction in schizophrenia (9), these findings—together with others (5–7)—also suggest a possible disconnect between self-reported experiences of pleasure and responsiveness in striatal pathways implicated in reward-based learning and motivated behavior. This disconnect might explain the lack of interest and motivation in pursuing potentially pleasurable activities, consistent with evidence of blunted anticipatory pleasure (3). Thus, the blunted motivation characteristic of schizophrenia appears to be due not to diminished hedonic

From the Department of Psychology, Harvard University, Cambridge, Massachusetts.

Address correspondence to Diego A. Pizzagalli, Ph.D., Department of Psychology, Harvard University, 1220 William James Hall, 33 Kirkland Street, Cambridge, MA 02138; E-mail: dap@wjh.harvard.edu.

Received Feb 24, 2010; accepted Feb 25, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.02.022

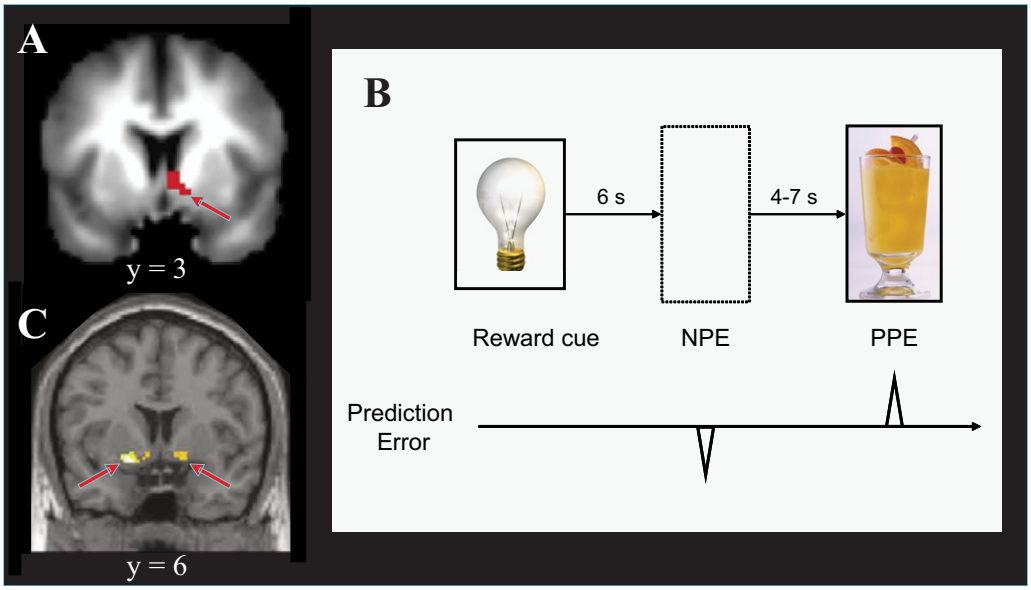

Figure 1. (A) Right ventral striatal region showing significantly reduced activation to positive stimuli in individuals with schizophrenia relative to control subjects in the study by Dowd and Barch (reprinted from *Biol Psychiatry* 67:902-911, copyright 2010, with permission from Elsevier [5]). **(B)** Schematic representations of the reward-related Pavlovian conditioning paradigm used by Waltz *et al.* (6) for probing neural substrates of reward prediction errors in schizophrenia. In 25% of the trials, delivery of reward (juice) was unexpectedly delayed after the presentation of a reward-predicting cue (a light); based on prior work, Waltz *et al.* (6) hypothesized that omission of an expected reward would elicit a negative prediction error (downward-pointing arrow), whereas unexpected juice delivery would elicit a positive prediction error (upward-pointing arrow). Relative to control subjects, individuals with schizophrenia showed weaker striatal activation in response to positive— but not negative—prediction error. **(C)** Bilateral ventral striatal regions associated with reward prediction error in a combined sample of control subjects and individuals with schizophrenia in the study by Murray *et al.* (adapted by permission from Macmillan Publishers Ltd: *Molecular Psychiatry* [7], copyright 2007). Relative to control subjects, patients showed significantly reduced activation to reward prediction error in a similar ventral striatal region. NPE, negative prediction error; PPE, positive prediction error.

responses but rather to impairments in representing the hedonic value of stimuli and response options and thus in translating such representations into goal-directed behavior (4).

Additional aspects of the study by Dowd and Barch (5) merit comments. First, among control subjects, anhedonic scores correlated negatively with bilateral caudate activation in response to positive stimuli. Notably, reduced bilateral caudate activation to rewards has been reported in major depression (10), and caudate volume was negatively correlated with anhedonic symptoms in both depressed (10) and unselected (11) subjects. These findings indicate that caudate dysfunction might be a transdiagnostic marker of anhedonia and warrant further research. Second, the authors used a relatively simple paradigm. In light of mounting evidence indicating that expressions of anhedonic behavior can be shaped by cognitive impairments (e.g., working or long-term memory deficits) (12,13), the use of a simple task devoid of substantial cognitive demands is a strength. For example, although schizophrenia is characterized by increased preference for small immediate rewards over larger future rewards, individuals with relatively preserved working memory abilities show the smallest discounting of future rewards (13). Moreover, in a study using a conditioning task, patients were able to develop an implicit preference for a more frequently rewarded stimulus, but this stimulus-reward association was lost after 24 hours (14). This suggests that reduced consolidation of long-term memory for rewards might contribute to anhedonic behavior. Collectively, these data indicate that schizophrenia may involve impairments in consolidating, retrieving, or maintaining affective responses or anticipating hedonic responses to future events. These impairments might be interpreted by both the individual and clinicians as a manifestation of loss of pleasure, in spite of preserved in-the-moment affective responses to stimuli.

Third, in the study by Dowd and Barch (5), neutral stimuli were rated as more arousing by individuals with schizophrenia than control subjects. This finding replicates prior reports of potentiated affective and physiological responses to neutral stimuli in schizophrenia (2,15). As emphasized by the authors (5), these findings represent an important methodological challenge for fMRI studies, in which responses to emotional and neutral conditions are typically contrasted. Group differences in the baseline (neutral) condition, such as those identified by Dowd and Barch (5), would clearly bias the outcome of the main contrasts of interest. To address these issues, studies could simultaneously acquire fMRI and peripheral physiological data and incorporate the latter in statistical modeling of the fMRI data (15).

Fourth, an important omission in most of the behavioral and fMRI studies probing hedonic deficits in schizophrenia—including the study by Dowd and Barch (5)—is that information about current smoking status and nicotine dependence is not reported. In healthy control subjects, nicotine potentiates ventral striatal activation (16) and the ability to modulate behavior as a function of rewards (17). Because smoking rates are up to fourfold higher in schizophrenia than in the general population, it is possible that differences emerging from studies of reward-related processing in schizophrenia are significantly affected by group differences in smoking status. Matching groups with respect to smoking status and/or implementing statistical control analyses will be needed for unambiguous interpretations.

In sum, schizophrenia is characterized by significant reward processing dysfunctions. However, in-the-moment affective responses to evocative stimuli (consummatory pleasure or liking) are surprisingly intact. In contrast, mounting evidence indicates that anhedonia in schizophrenia might stem from impairments in

generating, accessing, and/or maintaining representations of hedonic values, resulting in deficits in anticipatory pleasure (wanting) and goal-directed behavior (3,4). A better understanding of the precise psychological and neurobiological mechanisms underlying anhedonia will be a necessary step toward the development of better treatment interventions in schizophrenia. In this respect, findings emerging from studies rooted within an affective neuroscience approach—including the one featured in the current issue of *Biological Psychiatry* (5)—suggest that the future promises to yield rewarding outcomes.

The author was supported by National Institutes of Health R01 (MH68376) and R21 (MH078979) grants and a 2008 National Alliance for Research on Schizophrenia and Depression Independent Investigator Award during preparation of this article.

The author thanks Drs. Daniel G. Dillon and Ann M. Kring for helpful comments on an early draft of this article.

Dr. Pizzagalli has received consulting fees from Advanced Neuro Technology North America Inc. and AstraZeneca, and honoraria from AstraZeneca.

1. Horan WP, Blanchard JJ, Clark LA, Green MF (2008): Affective traits in schizophrenia and schizotypy. *Schizophr Bull* 34:856–874.
2. Cohen AS, Minor KS (2010): Emotional experience in patients with schizophrenia revisited: Meta-analysis of laboratory studies. *Schizophr Bull* 36:143–150.
3. Kring AM, Moran EK (2008): Emotional response deficits in schizophrenia: Insights from affective science. *Schizophr Bull* 34:819–834.
4. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA (2008): Reward processing in schizophrenia: A deficit in the representation of value. *Schizophr Bull* 34:835–847.
5. Dowd EC, Barch DM (2010): Anhedonia and emotional experience in schizophrenia: Neural and behavioral indicators. *Biol Psychiatry* 67:902–911.
6. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Salmeron BJ, *et al.* (2009): Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology* 34:1567–1577.
7. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, *et al.* (2008): Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry* 13:267–276.
8. Heerey EA, Gold JM (2007): Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. *J Abnorm Psychol* 116:268–278.
9. Bunney WE, Bunney BG (2000): Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. *Brain Res Brain Res Rev* 31:138–146.
10. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al.* (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166:702–710.
11. Harvey PO, Pruessner J, Czechowska Y, Lepage M (2007): Individual differences in trait anhedonia: A structural and functional magnetic resonance imaging study in non-clinical subjects. *Mol Psychiatry* 12: 767–775.
12. Burbridge JA, Barch DM (2007): Anhedonia and the experience of emotion in individuals with schizophrenia. *J Abnorm Psychol* 116:30–42.
13. Heerey EA, Robinson BM, McMahon RP, Gold JM (2007): Delay discounting in schizophrenia. *Cogn Neuropsychiatry* 12:213–221.
14. Herbener ES (2009): Impairment in long-term retention of preference conditioning in schizophrenia. *Biol Psychiatry* 65:1086–1090.
15. Williams LM, Das P, Harris AW, Liddell BB, Brammer MJ, Olivieri G, *et al.* (2004): Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. *Am J Psychiatry* 161:480–489.
16. Tanabe J, Crowley T, Hutchison K, Miller D, Johnson G, Du YP, *et al.* (2008): Ventral striatal blood flow is altered by acute nicotine but not withdrawal from nicotine. *Neuropsychopharmacology* 33:627–633.
17. Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE (2008): A single dose of nicotine enhances reward responsiveness in non-smokers: Implications for development of dependence. *Biol Psychiatry* 63:1061–1065.