Emotional Memory in Schizophrenia

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Emotional memories play an important role in our day-to-day experience, informing many of our minute-to-minute decisions (eg, where to go for dinner, what are the likely consequences of not attending a meeting), as well as our long-term goal setting. Individuals with schizophrenia appear to be impaired in memory for emotional experiences, particularly over longer delay periods, which may contribute to deficits in goal-related behavior and symptoms of amotivation and anhedonia. This article reviews factors that are known to influence emotional memory in healthy subjects, applies these factors to results from emotional memory studies with individuals with schizophrenia, and then uses extant neurobiological models of emotional memory formation to develop hypotheses about biological processes that might particularly contribute to emotional memory impairment in schizophrenia.

Key words: anhedonia/amotivation/biological mechanisms/episodic memory/emotional memory

Individuals with schizophrenia typically have normal emotional responses to stimuli at the moment of consumption or exposure (consummatory pleasure) but often do not appear to use these positive experiences to guide their decisions to engage in similar activities in the future.1,2 Anticipatory pleasure, or the expectation that an upcoming event will provide pleasure, is strongly influenced by memories of past positive experiences. From this perspective, impairment in the ability to establish long-term memories of positive experiences would be expected to significantly decrease an individual’s anticipation of pleasure from repeated engagement in such activities.3

It is well known that individuals with schizophrenia demonstrate significant impairment in episodic memory; further, meta-analyses assessing relative deficits in different aspects of cognitive functioning in schizophrenia have indicated that episodic memory is one of the areas of greatest impairment in individuals with schizophrenia4-5 with effect sizes varying between 0.78 and 1.20.6-7 Deficits in episodic memory are strongly associated with poor outcome5 including significant impairment in both functional and clinical spheres.8-12 Although research on emotional memory in schizophrenia is limited, past studies have particularly noted a relationship between emotional memory deficits and negative symptoms.2,13,14 Neurobiological research on processes involved in establishing episodic memories and the emotional modulation of these memories may help to clarify the specific processes that are impaired in individuals with schizophrenia and thus could help to identify effective interventions.

Late long-term potentiation (LTP), which is generally believed to be the biological substrate for long-term memory, is modulated by activity from brain regions involved in detection and assessment of emotional stimuli. Particularly, there is significant evidence for the modulation of hippocampal activity by the amygdala15-18 and/or by prefrontal cortex (PFC) and the ventral striatum.19,20 Arousing characteristics of stimuli appear to particularly elicit modulatory processes via the amygdala, while ventral striatal modulation appears to reflect additional salience characteristics.21 By integrating data on impairments in emotional memory and neurobiological models of mechanisms underlying emotional memory, it may be possible to initiate a move beyond description to explanation of these deficits.

This article begins with a brief review of psychological and biological factors that have been shown to influence emotional memory performance in healthy subjects. Next, studies on emotional memory performance in schizophrenia are reviewed in the context of these factors in order to identify areas of specific impairment. This is followed by a brief review of neurobiological processes contributing to short- and long-term memory and emotional memory and an evaluation of the fit between these models and the pattern of emotional memory impairments found in schizophrenia. Next, the context of the larger literature on abnormalities in brain function in individuals with schizophrenia is used to further refine hypotheses and identify priorities for future studies of emotional memory in schizophrenia.
Definitions

Emotion

In the current review, emotion is defined in terms of valence and arousal. Valence is considered a dimensional construct characterized by endpoints of “very unpleasant” and “very pleasant.” Arousal is also considered a dimensional construct, with low levels of arousal including experiences of calmness and dullness while high levels of arousal can reflect excitement or agitation.22 Notably, there are other systems of parsing emotional experience, such as considering positive and negative emotion as independent constructs23,24 or focusing on differential effects of specific emotions within the negative or positive valence domains (e.g., sadness vs anger vs fear); however, these systems have rarely been used in studies of emotional memory in schizophrenic subjects to date and thus cannot be easily applied to the available data.

Long-Term Episodic Memory

Given the focus of the current article on integrating behavioral and neurobiological data on emotional memory, definitions of short- and long-term episodic memory are based in the neurobiological rather than the psychological literature. Long-term memory is thus defined as episodic memory following a delay of 24 hours or greater including sleep.25–28 “Long term” is defined in this way because such delay periods provide sufficient time for biological mechanisms that are believed to support lasting memory (e.g., late LTP) to become active.27,28 This 24-hour delay period is admittedly quite different from the delays typically considered to be representative of long-term memory in most psychology studies.

However, such long-term emotional memories may be particularly important in guiding decision making and supporting motivation. For example, Wirtz et al.29 tested the relative impact of emotional experience reported during a vacation (using an experience sampling method) in contrast to memories reported a month after the vacation on future vacation plans. They found that memories of a vacation assessed a month after return from the vacation were not significantly associated with future plans. In explaining this result, Wirtz et al.29 note that experiences reported “in the moment” were more likely to include emotionally neutral moments (e.g., brushing teeth before bed, driving to a restaurant for dinner) while long-term memories of the vacation were more strongly influenced by the most salient experiences occurring during the vacation. Long-term emotional memories, because they are biased to include strongly salient experiences, are the best predictors of future choices. Further, memory for emotionally salient experiences is not simply a category of long-term episodic memory; rather, as indicated by the neuro-biological models of memory described later in the article, the salience of stimuli or experiences is one of the important factors determining whether long-term memories are established.

Factors Contributing to Emotional Episodic Memory

Psychological Factors

Both short- and long-term memory are enhanced for emotional relative to neutral stimuli.16,30–39 A number of psychological mechanisms have been proposed to support this enhancement, including (a) increased attention to emotional or distinctive stimuli at encoding and associated enhanced perceptual or higher level processing,30,40–43 (b) increased engagement of higher cognitive processes at encoding or recall including utilization of the semantic relatedness of emotional word stimuli44,45–47 or more frequent postencoding processing or rumination about emotional in contrast to neutral stimuli, and (c) effects of mood congruency.48 In addition, methodological factors, such as differences in types of stimuli (verbal vs pictorial), outcome variables (recognition vs recall), and delay period, are known to significantly affect memory performance.

Biological Factors

Physiological arousal has been shown to modulate both short- and long-term memory.40,49,50 In general, negative stimuli more strongly influence cognitive processes than positive stimuli, even when arousal characteristics are balanced across valences.51 Further, it appears that emotional arousal more strongly influences memory for negative than positive stimuli in short-term memory studies: Talmi et al.40 found that memory for negative stimuli was strongly supported by arousal levels at encoding, while memory for positive stimuli was dependent on attentional processes. Kensinger52 similarly suggested that valence characteristics of stimuli engage conscious encoding strategies and elaboration, while arousal characteristics may influence memory via engagement of the amygdala and physiological arousal.

Studies of long-term memory indicate that memory for emotional stimuli may be modulated by a number of different mechanisms.15,19 The majority of studies assessing the modulation of long-term episodic memory by emotional content have focused on the influence of negative in comparison to neutral stimuli (cf 39,53–56). However, negative and neutral stimuli differ in both valence and arousal, and thus, it has not been clear what aspect of emotional experience accounts for enhanced memory for negative stimuli. Notably, several emotional memory studies in healthy individuals have used both positive and negative stimuli,17,57,58 with inconsistent results: 2 have reported no significant difference in enhancement of recall for positive in contrast to negative stimuli, while
one\textsuperscript{57} found significantly greater enhancement of memory for negative than positive stimuli in healthy individuals. The relative effects of valence and arousal on long-term memory are not clear at this point.

**Table 1. Performance in Emotional Memory Studies of Individuals with Schizophrenia in Comparison to Healthy Subjects**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample (N)\textsuperscript{a}</th>
<th>Delay\textsuperscript{b}</th>
<th>Stimulus Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh et al Peterson (1976)</td>
<td>18 SZ 19 HC</td>
<td>30 s</td>
<td>Pleasant, Neutral, and Unpleasant Words</td>
<td>1a: Recall: SZ = HC; 1b: Recog: SZ = HC 2: Recog: SZ = HC</td>
</tr>
<tr>
<td>Calev and Edelist (1993)</td>
<td>14 SZ 14 HC</td>
<td>1a: Im; 1b: 2 days</td>
<td>Pleasant, Neutral, and Unpleasant Words</td>
<td>1a: Im Recall: HC &gt; SZ 1b: Delayed Recall: HC &gt; SZ</td>
</tr>
<tr>
<td>Danion, Kazes, Huron and Karchouni, 2003</td>
<td>24 SZ 24 HC</td>
<td>15 m</td>
<td>Pleasant, Neutral and Unpleasant Words</td>
<td>Recog R/K/G: HC &gt; SZ</td>
</tr>
<tr>
<td>Matthews and Barch, 2004</td>
<td>27 SZ 28 HC</td>
<td>Im</td>
<td>Pleasant and unpleasant high and low arousal words, neutral words</td>
<td>1a: Recall: HC &gt; SZ, 1b: Recog: HC = SZ</td>
</tr>
<tr>
<td>Neumann, Philippot and Danion, 2007</td>
<td>24 SZ 24 HC</td>
<td>1 day</td>
<td>Neutral pictures pleasant and unpleasant Words</td>
<td>R/K/G Recog: HC &gt; SZ</td>
</tr>
<tr>
<td>Neumann, Blairy, Lecompte and Philippot, 2007</td>
<td>20 SZ 20 HC</td>
<td>1 day</td>
<td>Pleasant and Unpleasant High and low arousal pictures</td>
<td>RecogniR/K/G: HC &gt; SZ</td>
</tr>
<tr>
<td>Horan, Green, Kring and Nuechterlein (2007)</td>
<td>30 SZ 31 HC</td>
<td>4 hours</td>
<td>Pleasant and Neutral Foods and films; Subject rated arousal</td>
<td>Recall: SZ = HC</td>
</tr>
<tr>
<td>Hall, Harris, McKirdy, Johnstone, and Lawrie (2007)</td>
<td>20 SZ 20 HC</td>
<td>1a: 10 m 1b: 21 days</td>
<td>Pleasant and Unpleasant pictures matched on arousal, Neutral Pictures</td>
<td>1a: 10 m Recall: HC &gt; SZ 1b: Delayed Recall: HC &gt; SZ 1e: Recog: HC &gt; SZ</td>
</tr>
<tr>
<td>Herbener, Rosen, Khine and Sweeney, 2007</td>
<td>33 SZ 28 HC</td>
<td>1 day</td>
<td>Pleasant and Unpleasant pictures matched on arousal, Neutral Pictures</td>
<td>Recog: HC &gt; SZ</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Treatment: FGA = first generation antipsychotic medication; SGA = second generation antipsychotic medication. Subjects are assumed to be outpatients unless otherwise specified. Koh et al, 1976: 11 FGA, 7 unmedicated inpatients; Koh et al, 1981: Studies 1 and 2: 11 FGA, 5 unmedicated, Study 3: 9 FGA, 7 unmedicated; all inpatients; Calev and Edelist: FGA inpatients; Danion et al, 2003: FGA or SGA outpatients; Matthews and Barch, 26 medicated with FGA or SGA, 1 unmedicated; Neumann, Phillipot et al: 12 FGA, 8 SGA; Neumann, Blairy et al, 4 FGA, 14 SGA, 2 unmedicated; Horan et al, 25 SGA, 5 FGA; Hall et al, 10 SGA, 7 FGA, 3 FGA + SGA, 7 inpatients; Herbener et al: 26 SGA, 4 FGA, 3 unmedicated.

\textsuperscript{b}Im = immediate (specific time not specified), s = seconds, m = minutes

Emotional Memory in Schizophrenia

An overview of the studies conducted on emotional memory in schizophrenia, to date, is shown in table 1. Many of the emotional memory studies reviewed included several tasks, and specific tasks may have included assessment of both recognition and recall. Each specific outcome variable is considered as a separate outcome; thus, when multiple outcomes from a single study are referenced, the task and outcome measure (shown in table 1) will also be indicated.

Do Schizophrenia Subjects Differ From Healthy Subjects in Their Attention or Response to Emotional Stimuli at Encoding?

Individuals with schizophrenia demonstrate unusual scan patterns to visual stimuli\textsuperscript{59,60} that might suggest differences in attention. However, in multiple studies assessing self-reported emotional responses to visual emotional stimuli at the time of encoding, including the emotional memory studies included in this review, no difference in
the intensity of emotional response to stimuli has been found in comparisons of schizophrenic and healthy subjects (cf 2,6). Further, a study62 assessing ratings of responses to both valence and arousal characteristics of a large number of visual stimuli indicated very similar responses across healthy and schizophrenic samples (valence \( r = 0.98 \), arousal \( r = 0.95 \)). Similarly, ratings of affective responses to verbal stimuli (cf 14,63) indicate minimal differences between groups. Although emotional response to stimuli may reflect processes other than attention, these data do suggest that healthy and schizophrenic subjects demonstrate similar comprehension of the valence and arousal characteristics of emotional stimuli.

Do Schizophrenia Subjects Demonstrate Impairment in Effective Use of Self-initiated Encoding Strategies in Comparison to Healthy Subjects During Emotional Stimulus Encoding?

There is significant evidence that individuals with schizophrenia are impaired in independently initiating effective strategies for encoding stimuli, such as increasing depth of processing, although they do demonstrate significantly enhanced memory performance when they are prompted to use such strategies.64,65 As shown in table 1, studies have varied in their use of incidental in contrast to intentional encoding. In general, healthy subjects would be expected to increase their use of encoding strategies when they are aware that their memory will be tested, while individuals with schizophrenia would be expected to have greater difficulty in self-initiating such strategies. Thus, if use of such strategies significantly influences performance, we would predict that healthy subjects would show superior performance in comparison to schizophrenic subjects particularly in studies involving intentional encoding paradigms.

Koh et al63 directly assessed the effects of incidental vs intentional encoding in a single group of schizophrenia and healthy subjects but did not find any differences in memory performance in relation to diagnosis. In other emotional memory studies with schizophrenia subjects, there were not direct comparisons of incidental and intentional encoding. However, overall, studies using intentional encoding indicated impaired memory in schizophrenic in comparison to healthy subjects in 5 out of 7 tasks (66: 1a, 1b; 67–69 vs 63: 2; 70: 3) while studies using incidental encoding indicated impaired memory in 5 of 10 tasks (13: 1a, 1b, 1c; 14: 1a; 61: vs 2; 63: 1a, 1b; 70: 2a, 2b). The pattern of results suggests, at most, a moderate effect of intentional in contrast to incidental encoding on emotional memory performance.

These results are consistent with, but suggest, a somewhat more modest effect of intentional encoding processes than studies of memory for neutral stimuli (cf 71,72). The limited effect of intentional vs incidental encoding in emotional memory studies may be due to a stronger impact of emotional stimuli on other processes, such as attention or arousal, which may decrease the importance of conscious encoding strategies. Further, the studies included in the current analysis vary significantly in methodology, and the total number of studies is quite small, and thus, it is also possible that there was not sufficient power to detect the effects of conscious encoding strategies on emotional memory performance.

Do Mood Congruency Effects Differentially Influence Emotional Memory Performance in Healthy and Schizophrenic Subjects?

There is a significant literature in healthy and mood-disordered individuals demonstrating effects of mood congruency or mood dependence on memory performance. Buchanan48 suggests that one biological mechanism potentially supporting enhanced mood-congruent memory is an overlap in the brain regions that are active at the time of memory retrieval and initial encoding. Reactivation of the same brain region may act as a memory cue and thus facilitate retrieval of mood-congruent memories.

Several of the emotional memory studies conducted in individuals with schizophrenia included assessments of baseline mood or emotional state. Horan et al2 assessed emotional state using the Emotional Experience Scale prior to encoding and after each stimulus presentation. Their recall task, completed 4 hours later, focused specifically on the ability of subjects to accurately recall the emotions they had reported in response to the stimuli at the initial assessment. Baseline emotional state did not differ between healthy and schizophrenic subjects in terms of pleasant emotions or high activation emotions, but schizophrenic subjects did report significantly higher levels of negative emotion than healthy subjects. However, this difference in baseline mood did not significantly influence the accuracy of their recall of their past positive, negative, or activated emotional state.

Three studies have included assessment of symptoms of depression; in 2 studies, no relationship was found between depression as assessed using the Positive and Negative Syndrome Scale (PANSS)13 or the Beck Depression Inventory68 and memory performance. Matthews and Barch14, however, did find that higher levels of depression (based on PANSS ratings) were associated with less enhancement of memory for negative high arousal and positive low arousal words in comparison to neutral words. Decreased enhancement of memory for positive low arousal words is consistent with the mood congruency model. Deficits in recall of high arousal negative words are more difficult to interpret; however, interactive effects of valence and arousal, discussed later in this article, may help to explain this finding. Overall, the data from emotional memory studies conducted with schizophrenic subjects, to date, do not indicate a consistent impact of mood effects on memory for mood-congruent stimuli, but again the number of studies assessing this factor is quite small and certainly not definitive.
Does Stimulus Type (Words Vs Pictures) Differentially Influence Emotional Memory Performance in Schizophrenia and Healthy Subjects?

In a meta-analysis of the literature on memory in schizophrenia, Pelletier et al. reported that individuals with schizophrenia are more severely impaired in recognition memory for visual in contrast to verbal stimuli and noted that the effect size $d$ for visual stimuli is 1.00, in contrast to an effect size $d$ for verbal stimuli of 0.71. Consistent with this report, in all 6 tasks assessing emotional memory using pictorial stimuli (1a, 1b, 1c; 64, 68, 69), individuals with schizophrenia demonstrated impaired memory in comparison to healthy control subjects, while in studies using verbal emotional stimuli, no differences due to diagnosis were found in 7 out of 12 tasks (3, 14, 1b, 63, 1a, 1b, 1c; 70, 2a, 2b; vs 14, 1a; 65, 1a, 1b, 67, 70, 1). Thus, consistent with data on neutral memory, emotional memory appears to be more impaired for pictorial emotional than verbal emotional stimuli in individuals with schizophrenia.

Does Assessment Using Recognition Vs Recall Tasks Differentially Influence Emotional Memory Performance in Schizophrenia and Healthy Subjects?

Recall requires initiation of retrieval mechanisms that are not required in recognition memory, and recall is typically more impaired than recognition memory in individuals with schizophrenia (cf. 5). In addition, tasks assessing recall of visual stimuli and verbal stimuli are likely to involve different cognitive processes. Specifically, recall of verbal stimuli requires retrieving a specific word that was encoded, while recall of visual stimuli typically requires not only retrieval but also the ability to describe the image in a way that differentiates it from all other encoded images. Pelletier et al. thus suggest that recognition tasks may be able to more selectively target memory processes, while recall tasks may assess a combination of memory and executive abilities.

In studies using verbal stimuli, healthy subjects demonstrated better recall than schizophrenic subjects in 4 out of 6 tasks (14, 1a; 66, 1a, 1b; 70, 1; equal: 63, 1a; 70, 2a) and better recognition memory than schizophrenics in 2 out of 7 tasks (67, 69 vs 3, 14, 1b; 63, 1b, 2; 70, 2b). In the 6 tasks using pictorial stimuli, however, healthy subjects showed better recall and recognition performance in all tasks (2 recall, 4 recognition: 13, 1a, 1b, 1c; 61, 68, 69). Thus, schizophrenia subjects were impaired in both recognition and recall of emotional stimuli, but their recall performance was more impaired than recognition performance, particularly for pictorial stimuli.

Do the Arousal Characteristics of Stimuli Differentially Influence Emotional Memory in Schizophrenia and Healthy Subjects?

Arousal characteristics of emotional stimuli were not reported prior to 2004 article of Matthews and Barch, but the number of studies available to assess arousal effects is quite limited. Further, although arousal levels of pictures were varied in Neumann et al., the effect of arousal variation on memory was not reported. However, of the remaining studies, arousal characteristics of stimuli had similar, enhancing, effects on memory in both schizophrenia and healthy subjects in 2 studies, but more limited effects in 3 other studies. Hall et al. found greater impairment in memory for highly arousing negative images in schizophrenic subjects in comparison to healthy subjects, while Hall et al. did not find this effect. In post hoc analyses, Hall et al. found that their schizophrenic subjects demonstrated significantly impaired memory only for the very high arousal images; further, this effect was apparent already at the 10-minute delay, suggesting that characteristics of the high arousal negative stimuli impaired either encoding or early memory consolidation rather than long-term memory consolidation. The difference in results between studies conducted by Hall et al. and Neumann et al. thus appears to be due to differences in definitions of high arousal and related differences in selection of stimuli.

Studies of the effects of emotional arousal on memory do indicate that arousal, up to a certain level, enhances memory, while arousal beyond this optimal point impairs memory. Many individuals with schizophrenia demonstrate abnormalities in autonomic arousal, often in the direction of higher tonic levels of arousal. In such individuals, highly arousing images may increase arousal to a level that impairs rather than enhances emotional memory.

Effects of Valence Characteristics of Stimuli

All the studies in this review included stimuli of more than one valence, but not all studies reported statistical tests regarding the relative effect of valence on memory performance in different diagnostic groups. Table 2 provides a summary of data from the 7 studies that tested differential effects of valence on memory. Numbers in the table refer to the study in which the result was found. The top half of the table is a summary of results for schizophrenia subjects, and the bottom half is the summary of results for healthy subjects in the same studies.

Emotional memory studies in healthy subjects have pretty consistently indicated that positively and negatively valenced stimuli are more memorable than neutral stimuli. As indicated in the 2 leftmost data columns of table 2, schizophrenia subjects demonstrated enhanced memory for positive in comparison to neutral stimuli in 2 tasks and enhanced memory for negative in comparison to neutral stimuli in 3 tasks. The comparable rates for healthy subjects were enhancement of memory for positive in contrast to neutral stimuli in 5 tasks and enhancement for negative in contrast to neutral stimuli in 4 tasks. The next 2 columns compare relative enhancement for negative in contrast to positive stimuli. Here, schizophrenics showed
better memory for positive than negative stimuli in one task, in comparison to healthy subjects showing this pattern in 4 studies. The reverse pattern, i.e., better memory for negative than positive was found for schizophrenics in 3 tasks but never occurred for the healthy subjects. Neutral stimuli were better remembered than positive or negative stimuli in 3 tasks for schizophrenics and 2 tasks for healthy subjects. Finally, emotional valence showed no statistically significant effect on memory in 6 tasks for schizophrenia subjects and 3 tasks for healthy subjects. An interesting, but obviously tentative, pattern does emerge from these comparisons, such that schizophrenia subjects more frequently demonstrated a lack of enhancement of emotional in contrast to neutral stimuli (9 times in comparison to 5 times for healthy subjects) and also showed better memory for negative than positive stimuli in 3 out of 4 tasks, while healthy subjects showed the reverse pattern of better memory for positive than negative stimuli in 4 out of 4 tasks.

**Effects of Delay Period**

Based on the definitions of short- and long-term memory defined earlier, schizophrenic subjects demonstrated impaired performance on 5 of 13 short-term memory tasks (13: 1a; 14: 1a; 66: 1a; 67: 1b; 70: 1 vs 63; 1a, 1b; 2; 70: 2a, 2b; 3; 14: 1b; 2) but in all 6 tasks assessing long-term memory performance (61: 66; 1b; 68; 69; 13: 1b, 1c). Differences in the mechanisms that underlie “short”- and “long”-term memory are discussed in the next section.

There do appear to be important interactions of delay period and valence on memory performance. Specifically, in studies assessing memory performance following a 24-hour delay healthy subjects demonstrated the normative pattern of enhanced memory for emotional in contrast to neutral stimuli on 3 tasks (13: 1b; 1c; 66: 1b) and better memory for positive than negative stimuli on one task. In contrast, schizophrenics showed no differentiation between positive, negative, and neutral images in one task (13: 1c) and better memory for negative than positive stimuli in 2 tasks (61: 66; 1b). They demonstrated the normative pattern of better memory for positive and negative than neutral information only in one study. These results suggest abnormalities not only in long-term memory but also in emotional enhancement of long-term memory, specifically reflected by a decrease in enhancement of emotional in contrast to neutral stimuli in individuals with schizophrenia.

Overall, consistent with studies on memory performance using neutral stimuli, individuals with schizophrenia demonstrated greater impairment when (a) pictures vs verbal material needed to be remembered and (b) recall rather than recognition was tested. In addition, this review suggests that other factors that significantly and differentially influence emotional memory performance in schizophrenic in comparison to healthy subjects are (a) the arousal intensity of stimuli to be remembered, (b) the valence of stimuli to be remembered, and (c) whether the delay period is shorter or longer than 24 hours. These are discussed below in the context of the neurobiological processes underlying long-term emotional memory.

**Neurobiological Mechanisms Underlying Memory**

It is important to start with a caveat that this review certainly cannot do justice to the full literature on the neurobiology of memory, but rather is necessarily simplified, and probably inaccurate at points, as any overview will fail to account for the true complexity of any field.

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**Table 2. Summary of Study Results on Effects of Valence on Memory Performance in Schizophrenia and Healthy Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Pos &gt; Neut</th>
<th>Neg &gt; Neut</th>
<th>Pos &gt; Neg</th>
<th>Neg &gt; Pos</th>
<th>Neut &gt; Neg</th>
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<tr>
<td>Recognition</td>
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<td>1</td>
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<td>Pictorial</td>
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<td>4</td>
<td></td>
<td>5</td>
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<tr>
<td>Recall</td>
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<td>2, 6, 7</td>
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<tr>
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<td>6</td>
<td>6</td>
<td>6</td>
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<td>2, 6, 7</td>
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<tr>
<td><strong>Healthy subjects</strong></td>
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<td>2, 6, 7</td>
</tr>
</tbody>
</table>

*Note: 1 = Koh et al63; 2 = Koh et al70; 3 = Calev and Edelist66; 4 = Matthews and Barch14; 5 = Herbener et al61; 6 = Hall et al13; 7 = Neumann et al68. Pos, positive; Neut, neutral; Neg, negative.*

*aResults from Danion et al67 and Neumann et al69 not reported because these studies do not assess total memory performance in relationship to valence characteristics of stimuli. Results from Horan et al (2007) are not included because their stimuli did not fit this categorization.*
However, an attempt to map questions from psychiatry and psychology onto mechanisms understood by neurobiology is an essential translational step that may promote insight into biological factors contributing to the pathophysiology of schizophrenia.

Current neurobiological models of memory suggest that there is significant, although not conclusive, data indicating that LTP processes are the biological substrate of memory. There is also significant evidence that biological processes that are engaged at, or soon after, the encoding of stimuli help to differentiate whether information will be solely represented in short-term memory or will be represented in long-term memory. Early LTP, which consolidates between 5 and 30 minutes after induction, is based on a reorganization of the actin cytoskeleton within postsynaptic spines. Specifically, significant depolarization of the spine results in the influx of calcium ions through voltage-sensitive N-methyl-D-aspartate receptors. This calcium influx, in turn, activates calcium-sensitive protein kinases and protease calpain, which, by disassembling proteins (spectrin, actinin, Arc) that typically stabilize actin filaments, support changes in the postsynaptic density of the spine. In addition, during this process, additional alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors are added to the spine, which increases its response to glutamate. Thus, early LTP appears to specifically involve changes in the postsynaptic spine, increasing the availability of glutamate receptors and thus providing increased sensitivity to presynaptic neuron activity.

Late LTP involves the activation of additional processes. Specifically, in late LTP calcium ion entry into the neuron activates cell signaling cascades, including cyclic adenosine monophosphate, and associated increases in activation of regulatory proteins (such as protein kinase A, mitogen-activated kinases, extracellular signal-regulated kinases) that in turn modulate cyclic AMP-response element binding protein (CREB)-related gene expression. There are regional variations in the availability of different protein kinases, but they similarly act to modulate gene expression and protein synthesis. Reymann and Frey note that late LTP is dependent on the availability of plasticity-related proteins (PRPs). Although some PRPs are already available in neurons, this cache is typically depleted after about 8 hours; the availability of PRPs after 8 hours is dependent on initiation of CREB cycles to support gene expression in order to create additional PRPs. Modulatory neurotransmitters, such as dopamine or norepinephrine, appear central to the initiation of this additional process. Reymann and Frey specifically note that there is significant evidence of D5 receptors in the CA1 region that may act to support late LTP via dopaminergic effects on glycoprotein processing within these neurons and that similar effects are found for noradrenergic activity and glycoprotein activity in the dentate gyrus. Thus, induction of late LTP, in contrast to early LTP, requires heterosynaptic inputs, such as the activation of glutamatergic and dopaminergic receptors in area CA1 or glutamatergic and noradrenergic or muscarinic receptors in the dentate gyrus.

**Impact of Emotion on LTP**

As noted above, neurotransmitters and neuroendocrines, which increase in response to emotional stimuli, such as norepinephrine, dopamine, and glucocorticoids, have significant effects on late LTP via their impact on glycoprotein processing. Studies that have manipulated neurotransmitter or neuroendocrine responses to emotional stimuli have demonstrated specific impairment in long-term memory but not short-term memory (cf 82).

**Neuroscience Models of the Effect of Emotion on Long-term Episodic Memory**

Moving up a level of analysis, this next section focuses on connecting psychological factors to changes at the neurobiological level. Cahill and McGaugh are largely responsible for initially demonstrating how emotional arousal influences long-term episodic memory in humans (cf 15,18,33,38,39,53). Their model proposes that emotionally arousing stimuli increase amygdala activity, initiating a cascade of events including release of norepinephrine, which in turn influences release of glucocorticoids, which attach to glucocorticoid receptors in the hippocampus and ultimately enhance late LTP. Data based on this model have demonstrated a significant correlation between amygdala activity during encoding and long-term memory for emotionally arousing in contrast to neutral stimuli.39,53–56 Additional studies have demonstrated that autonomic system arousal in response to emotional stimuli, in addition to amygdala activity, is a necessary component of this process.83,84

Another model of the effects of emotion on long-term memory is based on the salience of stimuli. In this model, hippocampal activity indicating novelty activates the ventral tegmentum, and the tegmentum, in turn, uses convergent information from limbic and prefrontal regions indicating the goal-related importance of incoming information to determine its salience and value. If new information is determined to be salient, the ventral tegmentum sends dopaminergic bursts to the hippocampus to support late LTP. This model is supported by studies demonstrating that dopaminergic activity in hippocampal regions has been consistently associated with enhanced late LTP. Further, several functional imaging studies have provided support for the role of ventral striatal regions in the enhancement of memory. For example, Wittmann et al reported significant relationships between higher activity in a region, including the ventral tegmental area (probably indicative of higher dopaminergic activity), and better recall of reward-related stimuli. Similarly, Hamann et al found that...
nucleus accumbens and anterior cingulate activity during exposure to positive images was significantly correlated with long-term recognition memory of those images. There are strong bidirectional interconnections between orbitofrontal cortex and the amygdala, striatum, and hippocampus that support prioritized processing of salient information. Further, Hurlemann et al found that valence effects on memory could be observed even when arousal effects were eliminated with a pharmacological intervention, suggesting some independence between valence and arousal modulatory effects on memory.

Implications of Neurobiological Models for Emotional Memory in Schizophrenia

Salience Model. Given the significant disruptions in dopaminergic signaling in schizophrenia, it would be expected that the effectiveness of the “salience” route to enhanced emotional memory would be impaired. Studies assessing the effects of dopamine agonists and antagonists on memory performance in healthy individuals certainly support this view. Several researchers have assessed differences in long-term memory for unpleasant and neutral images in healthy subjects who had taken a placebo or amisulpride, a dopamine D2/D3 antagonist, and neutral images in healthy subjects who had taken amisulpride, a dopamine D2/D3 antagonist, on memory performance in healthy individuals. Further, Hurlemann et al found that valence effects on memory could be observed even when arousal effects were eliminated with a pharmacological intervention, suggesting some independence between valence and arousal modulatory effects on memory.

Arousal Model. From the perspective of the arousal model, there are a number of reasons why individuals with schizophrenia could demonstrate impaired long-term emotional memory, including abnormalities in amygdala response to stimuli and abnormalities in physiological activity in response to signals from the amygdala. There is significant evidence of abnormalities in amygdala volume and responsiveness to emotional stimuli in individuals with schizophrenia, including less change in activity in the amygdala in response to
emotional stimuli in individuals with schizophrenia (cf.\textsuperscript{110,111}). Thus, impaired memory for emotional stimuli could reflect decreased modulatory input from the amygdala.

However, functional imaging studies reporting decreased amygdala response to emotional in contrast to neutral stimuli in individuals with schizophrenia have often used subtraction methods, which do not take into account differences in baseline levels of activity. Thus, amygdala activity may not be reduced in individuals with schizophrenia but rather may demonstrate less change in response to emotional characteristics of stimuli. Consistent with this idea, Taylor et al.\textsuperscript{110} reported high tonic activity in the amygdala in individuals with schizophrenia. Further, multiple studies have indicated that individuals with schizophrenia experience abnormalities in autonomic arousal, including more prolonged autonomic responses after the termination of stressful stimuli,\textsuperscript{112} enhanced sensitization and decreased habituation to acoustic startle stimuli,\textsuperscript{113,114} and increased physiological responsivity to threat and negative affect.\textsuperscript{115–117} It is not clear that these higher levels of autonomic activity are due to higher tonic levels of amygdala activity. However, a higher baseline level of autonomic activity could put individuals at greater risk for exceeding levels of arousal that would optimally enhance memory. Further, this arousal effect would be expected to occur more strongly with negative than positive emotional stimuli because increases in unpleasantness are more strongly associated with increasing arousal than increases in pleasantness are associated with increasing arousal.\textsuperscript{23,24} Thus, it may be that the impairments in memory specifically for negative high arousing stimuli such as shown in study of Hall and colleagues\textsuperscript{13} study is due to such overarousal.

**Future Research**

**Salience**

The salience model highlights the importance of involvement of ventral PFC and ventral striatum and the essential role of dopaminergic activity in the modulation of long-term emotional memory. Obviously, it will be important to continue to assess the impact of antipsychotic medications on abnormalities in long-term memory for valence characteristics of stimuli. However, it is also important to note that ventral prefrontal regions can significantly modulate both hippocampal and amygdala activity; thus, it would be useful to expand our research focus to include assessment of relationships between ventral prefrontal regions and structures in the medial temporal lobe during studies of memory for emotional stimuli.

**Arousal**

Data from the arousal model particularly point to the possibility that the optimal level of arousal for enhancing memory in individuals with schizophrenia may be lower than that for healthy individuals. This information may be useful in refining cognitive remediation strategies so that material is presented in a way that supports optimal learning. For example, educational computer programs that resemble video games can be very engaging and helpful learning tools; at the same time, if such tools raise arousal to a point beyond that for optimal learning in individuals with schizophrenia, their use will be counterproductive. It is likely that there is individual variation in the optimal arousal level for learning; it thus may be useful to assess individual arousal response to different stimuli in order to refine treatments to the level of arousal that best supports learning for each individual.

As a methods issue, relative effects of valence and arousal are difficult to disentangle particularly given the stronger relationship between unpleasantness and arousal in contrast to pleasantness and arousal. This may be due to a stronger evolutionary emphasis on the potential impact of negative in contrast to positive stimuli. However, data indicating a stronger relationship between negative emotion and arousal than positive emotion and arousal may also be influenced by the stimuli we are using to represent positive and negative situations. Studies of the impact of emotion on experience or cognitive processes have often taken advantage of the availability of standardized stimuli, such as images from the International Affective Picture System (IAPS). However, given that norms for the valence and arousal characteristics of these stimuli are often based on reports from college populations, it is possible that factors that might influence valence or arousal in postcollege adults are not optimally tapped. For example, stimuli that are considered very positive and highly arousing by young adults are not optimally tapped. For example, Takahashi et al.\textsuperscript{105} found that their healthy and schizophrenia subjects showed similar categorization (eg, 80% or higher matching) of unpleasant and neutral images to the IAPS norms but concurred with IAPS norms for only 50%–60% of the pleasant pictures. It appears that the qualities associated with positive affect is more difficult than identification of stimuli that elicit negative affect. It may be useful to give further thought to how pleasure might be differently defined as individuals mature, and if so, how these changes might influence our development or interpretation of emotion tasks.

**Delay**

As noted above, individuals with schizophrenia were not only more impaired in their memory performance over...
a long delay but also appear to demonstrate less enhancement of emotional in contrast to neutral stimuli over this delay period. Potential contributors to this abnormality, such as decreased effectiveness of modulatory neurotransmitters or neuroendocrines on hippocampal LTP, or decreased effective signaling via typically modulatory brain regions (ventral PFC, amygdala) related to structural or functional abnormalities in these regions were identified.

Generally, these results suggest that it may be useful to assess activity in more brain regions and at different points in the memory consolidation process in order to really understand how emotion effects long-term memory. For example, Takashima et al.120 assessed brain activity during recognition memory tasks completed at various times across a 3-month follow-up interval and reported increases in ventral medial prefrontal activity strongly correlated with decreases in hippocampal activity over time. Perhaps there is more to learn about abnormalities in emotional memory in schizophrenia by expanding both the time period and the brain regions we investigate.

Emotional memories play an important role in our day-to-day experience, informing many of our minute-to-minute decisions, as well as our long-term goal setting. Further, models of sense of self often suggest that our autobiographical memories are important in supporting a sense of self-continuity. Thus, impairment in the ability to use emotion to effectively modulate memory strength has important implications for multiple aspects of experience and may significantly contribute to the clinical presentation and functional difficulties of individuals with schizophrenia.

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References
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pathophysiologcal link in schizophrenia. *Brain Res Rev.* 2007;54:92–112.


