Working Memory in Schizophrenia: Behavioral and Neural Evidence for Reduced Susceptibility to Item-Specific Proactive Interference

Christoph P. Kaller, Sandra V. Loosli, Benjamin Rahm, Astrid Gössel, Stephan Schieting, Tobias Hornig, Jürgen Hennig, Ludger Tebartz van Elst, Cornelius Weiller, and Michael Katzev

Background: Susceptibility to item-specific proactive interference (PI) contributes to interindividual differences in working memory (WM) capacity and complex cognition relying on WM. Although WM deficits are a well-recognized impairment in schizophrenia, the underlying pathophysiological effects on specific WM control functions, such as the ability to resist item-specific PI, remain unknown. Moreover, opposing hypotheses on increased versus reduced PI susceptibility in schizophrenia are both justifiable by the extant literature.

Methods: To provide first insights into the behavioral and neural correlates of PI-related WM control in schizophrenia, a functional magnetic resonance imaging experiment was conducted in a sample of 20 patients and 20 well-matched control subjects. Demands on item-specific PI were experimentally manipulated in a recent-probes task (three runs, 64 trials each) requiring subjects to encode and maintain a set of four target items per trial.

Results: Compared with healthy control subjects, schizophrenia patients showed a significantly reduced PI susceptibility in both accuracy and latency measures. Notably, reduced PI susceptibility in schizophrenia was not associated with overall WM impairments and thus constituted an independent phenomenon. In addition, PI-related activations in inferior frontal gyrus and anterior insula, typically assumed to support PI resistance, were reduced in schizophrenia, thus ruling out increased neural efforts as a potential cause of the patients' reduced PI susceptibility.

Conclusions: The present study provides first evidence for a diminished vulnerability of schizophrenia patients to item-specific PI, which is presumably a consequence of the patients' more efficient clearing of previously relevant WM traces and the accordingly reduced likelihood for item-specific PI to occur.

Key Words: Cognitive control, functional neuroimaging, prefrontal cortex, proactive interference, schizophrenia, working memory

Working memory (WM) impairments constitute a core deficit of cognition in schizophrenia (1,2), but remarkably little is known about the pathological effects on specific WM control processes. Current theories of WM stress mechanisms of interference control as an important source of interindividual variations in WM performance (3,4), which are also predictive for a broad range of other cognitive abilities (5–9). Item-specific proactive interference (PI) in WM occurs if processing of task-relevant information is influenced by lingering representations of previously activated but currently irrelevant WM contents (10). Efficient control mechanisms for protecting WM from item-specific PI may therefore be regarded as an important prerequisite for sustaining coherent lines of thought and action.

The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia consortium (11) suggested the recent-probes task (12) (Figure 1A) as a promising paradigm to investigate PI susceptibility in patients with schizophrenia (PSZ) (13,14). In healthy control subjects (HCS), reduced WM performance is associated with increased PI susceptibility (3,15). Given their well-documented WM deficits (2), PSZ might thus be expected to exhibit an increased vulnerability to PI effects. A similar expectation might be derived from studies suggesting a specific deficit of PSZ in the controlled selection from WM (16). However, item-specific PI can only arise from sufficiently stable representations of information in WM. If PSZ showed substantial deficits in WM performance, item-specific PI might therefore be less likely to arise from (unreliably maintained) previous WM contents. That is, assuming an inverted U-shaped relationship between WM performance and PI susceptibility (Figure 1B), the opposite prediction of a reduced PI susceptibility in schizophrenia would also be conceivable.

Besides the dependency of PI susceptibility on WM performance, demands on interference control might also be otherwise affected in schizophrenia. Theoretical frameworks on schizophrenia postulating a reduced influence of past experience on current information processing (17,18) would predict a reduced PI susceptibility in PSZ compared with HCS. However, as other aspects of inhibition-related control, such as restraining prepotent response tendencies, are known to be impaired in schizophrenia (19), one might also derive the opposite expectation that PSZ show an increased susceptibility

From the Department of Neurology (CPK, SVL, AG, TH, CW, MK), University Medical Center Freiburg, Freiburg; Freiburg Brain Imaging Center (CPK, SVL, AG, JH, LTvE, CW, MK), and Biological and Personality Psychology (SVL), Department of Psychology, University of Freiburg, Freiburg; Medical Psychology and Medical Sociology (BR), University Medical Center Mainz, Mainz; Center for Psychiatry (SS), Emmendingen; Department of Psychiatry (TH, LTvE), and Medical Physics (JH), Department of Radiology, University Medical Center Freiburg, Freiburg; and BrainLinks-BrainTools Cluster of Excellence (CPK, JH, CW), University of Freiburg, Freiburg, Germany.

Address correspondence to Christoph Kaller, Ph.D., University Medical Center Freiburg, Department of Neurology, Breisacher Str. 64, Freiburg 79106, Germany; E-mail: christoph.kaller@uniklinik-freiburg.de.

Received Aug 15, 2013; revised Mar 7, 2014; accepted Mar 11, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.03.012

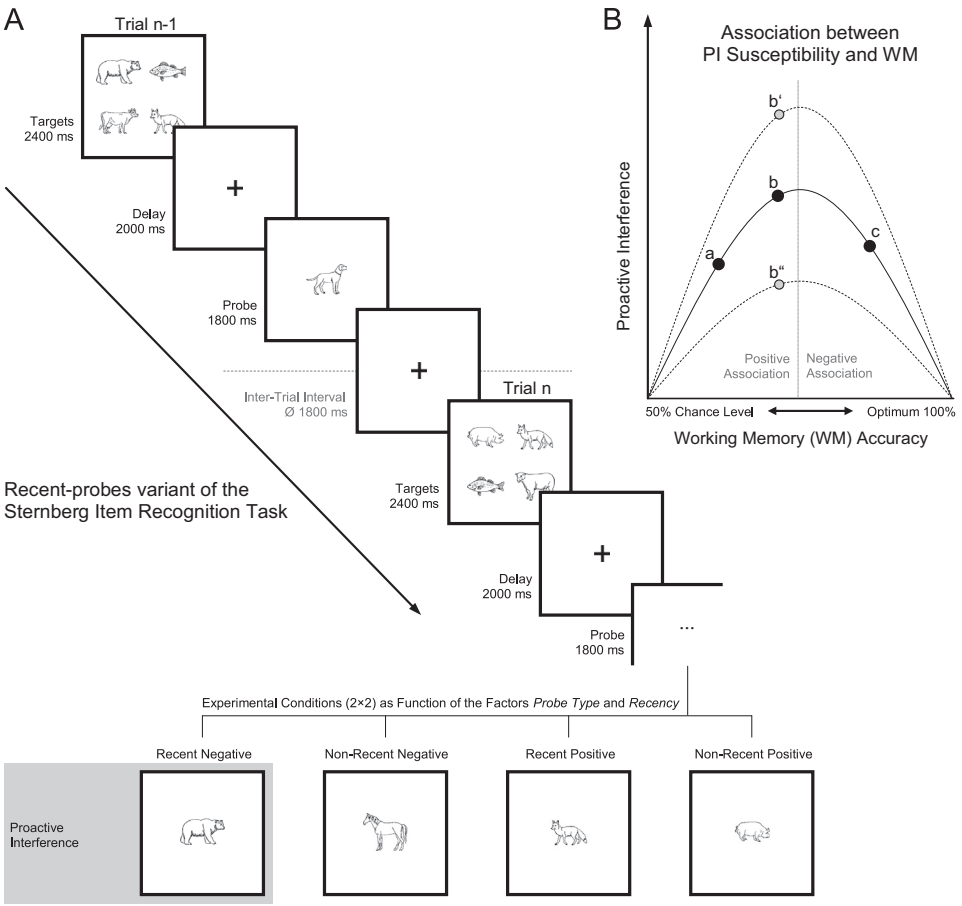

Figure 1. **(A)** Illustration of the recent-probes variant (12) of the Sternberg Item Recognition task (32). The Sternberg Item Recognition Task constitutes a delayed match-to-sample working memory (WM) paradigm. Target sets of items (here, four pictures of to-be-encoded animals) are presented for a short period of time after which they disappear. Following a delay, a probe item is presented requiring the subject to decide whether it was part of the target set or not. Commonly, one half of trials consist of positive probes matching one of the targets, whereas the other half of trials comprise negative nonmatching probes (factor probe type). In the recent-probes variant, matching of the probe is manipulated not only with respect to the current trial (*n*) but also with respect to the preceding trial (*n-1*) (10,12). In recent trials, the probe matches one of the targets in the preceding trial, whereas it does not match one of the targets in nonrecent trials (factor recency). The two factors probe type and recency are independently varied in a 2 × 2 factorial design. Item-specific proactive interference (PI) is specifically elicited in recent negative trials in which the probe was present as a target in the preceding but not the current trial, leading to false-positive decisions and increased response latencies (10). As illustrated, target and probe items in the present study were drawn from a pool of 12 achromatic line drawings of animals from the Snodgrass and Vanderwart (63) picture set (reprinted with permission, American Psychological Association). All animal pictures could be named with monosyllable German words. **(B)** Schematic illustration of the inverted U-shaped relationship between WM performance and PI susceptibility. In general, the occurrence of item-specific PI is highly dependent on the reliability of information representation in WM. Optimal WM representations, which are highly stably maintained representations of the present trial's target items, are unlikely to be confused with those from the previous trial when matched against the probe item. Likewise, if WM representation is at chance level, representations of the target items are too unstable and erratic and thus cannot interfere with the probe decision of the subsequent trial. In between these two extremes, item-specific PI inevitably arises as a function of WM performance, given that more or less reliably maintained representations of target items from the present trial compete with more or less reliably maintained representations of target items from the previous trial. That is, for moving from either extreme toward the other (WM representation at optimum vs. at chance), PI susceptibility consistently increases and eventually reaches its peak at a point where the stabilities of the competing representations of target sets trade off. Thus, the negative association with PI susceptibility reported for samples with normal to higher levels of WM performance (3,15) only partially reflects the actual bilinear/quadratic relationship, as a positive association with PI susceptibility necessarily results at lower levels of WM performance. As exemplified with the representative black dots on the solid line, schizophrenic patients compared with matched control subjects can thus be expected to have either an increased (e.g., dots b vs. a) or a decreased (c vs. b) or even a comparable susceptibility to item-specific PI (c vs. a), depending on the samples' respective positions on the inverted U-shape function. In addition, predictions become yet more complicated if one takes into account that the inverted U-shape function does not necessarily have an identical slope in patients and control subjects. For instance, the (passive) decay and/or (active) clearance of WM representations are other highly relevant factors influencing PI susceptibility across trials. For instance, slower versus faster decay should result in flatter versus steeper curvilinear relations (e.g., gray dots b′ and b″ on dashed lines).

to PI by responding impulsively to familiar stimuli. This assumption might be further supported by findings in healthy subjects that a higher susceptibility to PI is related to a higher incidence of unwanted intrusive thoughts (20).

Taken together, competing predictions of an increased versus a decreased PI susceptibility can be likewise postulated for WM performance of PSZ in the recent-probes task. Thus far, no empirical data are available to decide between these alternative hypotheses. The present study was set out to provide first insights into PI-related WM control functions in schizophrenia and to elucidate their neural underpinnings. Note that, unlike the processes of item-specific PI addressed here, effects of item-