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Building a Clinically Relevant Cognitive Task: Case Study of the AX Paradigm

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Tasks developed for basic cognitive neuroscience are often ill suited for experimental psychopathology. The development of the expectancy variant of AX continuous performance task to test theories about context processing in schizophrenia is used as an illustration of how this has been done in one research program. Four design principles are recommended: tasks should (1) have a foundation in existing literature and therefore stay as close as possible to an existing task; (2) be simple, which is frequently accomplished by paring down a task to evaluate the function of interest; (3) probe a mechanism of interest, with conditions that selectively manipulate this mechanism; and (4) have the potential to distinguish a specific deficit on the mechanism of interest from a generalized impairment. Data from a number of studies support several aspects of context-processing theory; however unpredicted results have also been reported. The development of the expectancy AX paradigm continues, and future developments that may enhance its usefulness are also described.

Key words: schizophrenia/testing/measurement/generalized deficit/translational research/behavioral tasks/context processing/executive processes

Developments in modern experimental psychopathology increasingly build upon a foundation of basic cognitive neuroscience. Both clinical and basic researchers stand to benefit greatly from this development, as do increasing numbers of patients, their families, and their caregivers. However, the path from basic cognitive neuroscience to its application in understanding disorders of the central nervous system has many challenges. It is sometimes quite difficult to determine whether a sophisticated test adopted from a basic science context provides any novel insight at all when applied to the study of a complicated mental disorder such as schizophrenia. Such disorders are heterogeneous and affect multiple cognitive systems. Reviewers of clinical grants and manuscripts at times scratch their heads and wonder why a promising new paradigm or procedure was prematurely brought to a study with patients.

The current article, like the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia initiative itself, grew from this experience. The aim in this case is to review a specific research program that has now spanned almost 2 decades, building in turn upon a half century of research conducted by others. This research program, initiated in the late 1980s by Jonathan Cohen and colleagues, highlights the understanding that can be gained by studying the context-processing deficits of patients with schizophrenia.[1–3] The workhorse of this program is a novel expectancy variant of the established AX continuous performance task (CPT).[4] For the purpose of providing an illustrative example of the development and validation of a clinically relevant cognitive task, I will use this paradigm as a kind of methodological case study. To this end, the article has the following structure: I will first review the state of knowledge about schizophrenia-related cognitive impairments at the time the context theory of schizophrenia was advanced. I will then review the strengths and limitations of the tasks available at that time and the design principles at work in determining how to modify them for the purpose of testing the theory. Finally, I will review subsequent developments that have contributed to the construct validity of the modified AX paradigm, informed the underlying theory, and increased the clinical applicability of the paradigm.

This selective focus on a single paradigm as applied to one disorder risks appearing as a self-congratulatory endorsement of a fixed perspective. It is therefore important to emphasize that this focus is not meant to advocate the use of the AX task per se or to advocate context-processing theory more generally. The AX task is certainly not the only, and may not even be the best, task to illustrate how one might translate a paradigm derived from cognitive neuroscience into use in clinical populations. Other deserving paradigms that have made a similar journey include surround contrast,[5] backward masking,[6,7] delayed response,[8,9] and a growing number of decision-making paradigms, just to name a few.

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Many Manifestations of a Single Deficit?

Novel hypotheses are judged by how well they account for a body of disparate results. While there may yet be compelling reasons to surrender to the abundant diversity of cognitive impairments in schizophrenia, 5 findings in the schizophrenia literature in that late 1980s were particularly amenable to an overarching explanation. First, a number of studies had found disturbances of attention in schizophrenia using CPTs[10–13] and shadow repetition tasks.[14] CPTs required participants to monitor a series of letters appearing one at a time and to respond according to a given rule. Shadow repetition required participants to monitor and repeat a series of words while being distracted by another voice. In addition, evidence from a variant of the digit span task with distractors[15,16] suggested a specific deficit in selective attention, the aspect of attention that requires focusing only on those stimuli relevant to the task at hand. Second, there was growing evidence of disturbances of inhibition in schizophrenia, as measured using a number of tasks such as the Stroop and Go/No-Go tasks.[17–19] In the Stroop task, for instance, participants responded to the ink color of a word while inhibiting the automatic response of reading a different color word (eg, RED printed in green, respond "Green"). Third, patients performed poorly on language tasks such as the cloze procedure.[20,21] In this procedure, participants infer which words are missing from a phrase using the constraints of the other words that are present. Finally, there was growing evidence for impairments in executive functioning and working memory, particularly as measured by perseverative errors on the Wisconsin Card Sorting Task (WCST).[22]

Was schizophrenia caused by an attentional impairment, compounded by dysinhibition, with inefficient language and executive processing? The literature was a mixed bag, with different tasks suggesting different core problems. However, the pioneering experimental work on the control of attention by Broadbent,[23] Treisman,[24] and others (eg, Shiffrin and Schneider[25], Norman and Shallice[26]) suggested a framework for thinking about these deficits that focused on basic mechanisms. This raised the possibility that superficially diverse disturbances reflected a core deficit in the ability to use information from the environment, ie, information about the immediate context, to guide controlled or underlearned behaviors. Thus, "context processing" was conceptualized as an aspect of cognitive control that represented and actively maintained task-relevant information in the face of competing stimuli or subsequent noise.[1,27] Task-relevant information was broadly construed and might include instructions or goals that must be abstracted and integrated to guide behavior and not merely memorized. Thus, context processing was more than mere storage, as in the phonological loop or visuospatial scratch pad of working memory.[28] Instead, it was conceptualized as a component of central executive functioning.

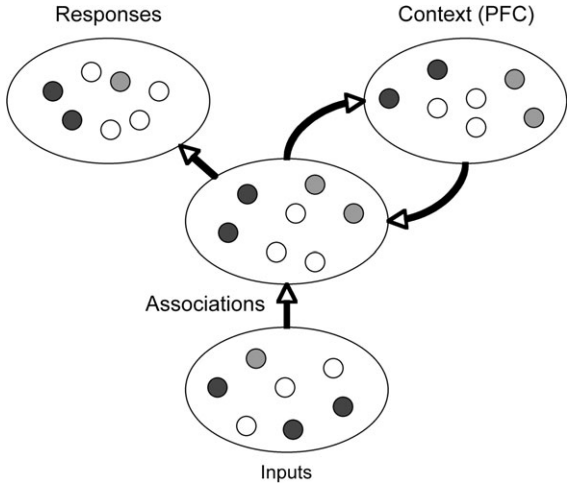


Fig. 1. Context-Processing Theory Implemented With a Connectionist Model. In this model, context information is stored in the prefrontal cortex (PFC), which provides top-down support for secondary or underlearned input-output mappings as indicated by current goal states (after Servan-Schreiber et al[43]).

Figure 1 illustrates the principles of the context-processing theory. According to this theory, goal representation or other contextual information relevant for guiding behavior is stored by units in the context layer of the model, identified with the prefrontal cortex (PFC). This stored information is then integrated with new inputs in the association layer. Imagine such a model was performing the Stroop task. If the current context was word reading, the context layer may not be necessary for accurate or efficient behavior. This is because the input layer and the output layer have strong, overlearned connections for this task. However, when color naming, the context units projecting downward into the association layer are crucial; they facilitate the processing of color-related information in the association layer, so these weaker connections produce a signal that is strong enough to overcome the automatic word-reading response. Indeed, the predictions about prefrontal activity have been computationally modeled as the capacity of prefrontal dopamine to distinguish signal from noise[1,29] and as described below have been empirically localized to PFC using functional imaging.[30,31]

From the perspective of context-processing theory, the 5 disparate findings from the schizophrenia literature fall into alignment.[3] Attentional selection relies on representation of context as a "template" for attention to the correct channel of information. Inhibition is the processing of task-relevant information to provide the "top-down" support needed to allow secondary responses to compete effectively with distracting information. Language processing involves the semantic disambiguation of lexical inputs. This disambiguation in turn requires the semantic

context of the current text. Working memory requires the active maintenance of context information in order to shape processing of subsequent stimuli. Finally, executive functioning is built upon the active maintenance of goal information as context for guiding complex behaviors. Thus, the representation and maintenance of context, 2 aspects of context processing, appeared to provide a framework for thinking about all these deficits. There remained a number of competing, albeit related, accounts that emerged around that same time (eg, Goldman-Rakic[22], Gray et al[32]). Thus, it was not enough to have explanatory power; the context-processing theory needed a task capable of testing the claims suggested by the model.

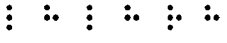
Evaluating Off-the-Shelf Tasks

Several tasks were growing in prominence in the late 1980s; lead among them was the WCST. While the propensity to make perseverative errors, the hallmark of WCST impairments, might be construed as an inability to use context (feedback from the previous trial) to sort the current card, the number of additional task demands—feedback integration, storage, strategy formation, and the role of chance—reduced the suitability of this task for the purposes of testing the context-processing theory. What about the Stroop task, then? This had been quantitatively modeled and the color-word incongruent condition (RED printed in green, say "Green") taxed context representations.[1] Unfortunately, the Stroop task was not appropriate, either. The Stroop effect (the difference between reaction times on incongruent compared with neutral or congruent trials) can be thought of as a specific measure of context processing. However, individual differences in the magnitude of this effect can be confounded by other cognitive processes. This is because impairments in any number of cognitive or affective processes (such as motivation, strategy, vigilance, etc) can result in selectively poorer performance on incongruent trials. This is called the generalized deficit confound, and this confound makes it difficult to interpret changes in the Stroop interference effect as a specific deficit in context processing or any other cognitive process.

The generalized deficit confound has been a perennial gremlin in the experimental psychopathology literature. Because it is a challenge that many tasks adapted from basic cognitive neuroscience face when used with clinical populations, it warrants a digression here. Fortunately, many aspects of this confound have already been described, so a short digression will suffice. The generalized deficit confound, originally brought to the attention of schizophrenia researchers by Chapman and Chapman,[33] is the result of an annoying property of tests: their sensitivity to individual differences in a cognitive process changes depending on the condition's difficulty (specifically changes in exposure to ceiling and floor effects) and reliability. That is why this problem is also known as the psychometric confound. This change in psychometric properties is important because it is the individual differences of each participant that contribute the overall group difference that is being measured. Thus, 2 tasks that have different degrees of difficulty are likely to have what the Chapmans called differential "discriminating power." *Differential discriminating power runs directly in the face of the standard methods of experimental cognitive psychology.* Tasks in experimental cognitive psychology are often designed to differ by a single process. This is particularly true for chronometric methods. For example, the difference in reaction times on the condition with the additional process is interpreted as the time required to accomplish that one additional process. However, the methodological habit of having the condition of interest also be the most difficult needs to be checked when approaching a clinical study. The additional demand of that condition of interest likely imbues it with different psychometric properties than the comparison condition. These psychometric properties give it more discriminating power, making it more sensitive to group differences that could occur for any reason, such as differences in motivation, task strategy, or personality. While these group differences affect all conditions of the task, these group differences will contribute to the biggest statistical effect of group on the condition with the most discriminating power. This confounds any attempt to interpret an impairment on that condition as caused by a deficit in the cognitive process of interest. In the case of the Stroop task, merely demonstrating that schizophrenia patients took relatively longer to respond on incongruent trials would be very weak support for the context-processing hypothesis. Because the incongruent condition is likely to have more discriminating power, such slowing might indeed be due to a context-processing deficit. But it might also result from any of a myriad other cognitive and affective differences between patients and controls. The impact of the generalized deficit on experimental cognitive psychopathology,[34,35] process-oriented approaches to the confound,[36–38] and limitations to some of these approaches[39,40] have been expounded at length elsewhere and await the interested reader.

If the Stroop task appeared unable to provide a strong test of the context-processing hypothesis, perhaps a variant of the CPT would serve? Table 1 describes some of the CPTs that had been used to date to study deficits in schizophrenia. As summarized in the table, there were a number of options offered with this literature, and some of the properties of these tasks were quite appealing. At it's simplest, the CPT is a series of stimuli that appear on a screen. Auditory variants that use a series of tones have also been used. Participants are instructed to respond selectively to the stimuli according to a rule. In the X-CPT,[4] the critical stimulus is fixed and participants

Table 1. Five Variants of the Continuous Performance Task Paradigm

Variant[citation]	Cue	Probe	Sequence	Features
X-CPT[4]	None	Fixed and rare	A **X** Q Q B **X**	Limited case of context processing, confounded with vigilance, no control for generalized deficits
IP-CPT[7]	Any	Any repeat	A X Q **Q** B X	Simple case of context processing, not optimally sensitive to context deficits (no competing response), no control for generalized deficits-
AX-CPT[4,6]	Fixed and rare	Fixed and rare	A **X** Q Q B X	Not optimally sensitive to context deficits (no competing response), no control for generalized deficits
Expectancy AX-CPT[3]	Fixed and common	Fixed and common	A **X** A **X** B X	Sensitive to context deficits (competing responses), control for generalized deficits (AY vs BX errors)
Dot pattern expectancy task[50]	Fixed and common	Fixed and common		Sensitive to context deficits (competing responses), parametrically manipulated stimuli increase demands on context representation, control for generalized deficits (AY vs BX errors)

Note: Targets in sequence are bold and underlined. CPT, continuous performance task; IP, identical pairs.

respond only when they see (or hear) that stimulus. Such a task seemed unsuitable because there was not a strong load on context processing, and there were no controls for either vigilance decrements or generalized deficits. A more difficult variant of the paradigm was the identical pairs (IP) or double CPT. In this variant, the critical stimulus was defined as any stimulus that matched the immediately preceding stimulus. Such a task had been used to great effect in high-risk studies to identify individuals likely to convert to schizophrenia.[12] However, while the task increased storage demands, it remained a simple case of context processing. Because all stimuli were equally likely to be targets, there were no competing responses, and therefore, it had low sensitivity to context-processing deficits. Also, like its simpler predecessor, it lacked control for generalized deficits. Another variant with a long history was the AX-CPT,[4] in which the critical stimulus was an X only if it followed an A. Like the IP-CPT, it lacked strong competition among responses or any control for generalized deficits and was therefore an unlikely candidate for testing the context-processing hypothesis. However, it provided a stronger manipulation of context than either the X or IP-CPTs because the cue stimulus needed to be evaluated under some conditions (following an A) but not under others (following any other letter). While no task existed that was optimal for testing the context-processing theory, this asymmetry inherent to the AX variant would prove to be the foundation upon which a new CPT would be built.

Designing a Theoretically Informed, Clinically Relevant Cognitive Task

Given that none of the off-the-shelf options appeared to be well suited, testing the context-processing theory would require significant modification to any existing task. While task development may be one of the most invigorating and creative aspects of our discipline, it is not to be undertaken lightly because it frequently requires years of piloting that as often as not ends in disappointment. Table 2 describes 4 design principles that emerged during the course of this process.[41] First, Cohen and a close colleague David Servan-Schreiber built upon the asymmetry of the context-processing demands of the AX-CPT paradigm. This increased the likelihood that patients would be impaired in a manner at least similar to that previously observed, which perhaps served to reduce piloting time in this case. It may have also facilitated integrating results with this task into the current literature. Second, the designers wanted to keep the

Table 2. Design Principles for Building a Clinically Relevant Cognitive Task[41]

	Desiderata:	Justification
1	A task should have a foundation in existing literature and therefore stay as close as possible to an existing task	Increase likelihood of building upon previous findings, decrease piloting time
2	A task should be simple, frequently accomplished by paring down a task to evaluate the function of interest	Increase interpretability in terms of cognitive mechanism, increase likelihood of computational modeling, may increase likelihood of animal model
3	A task should probe a mechanism of interest, with conditions that selectively manipulate this mechanism	Increase interpretability of pattern of performance, provides within-subject contrasts of interest
4	A task should be able to distinguish a specific deficit on mechanism of interest from a generalized impairment	Increase interpretability of individual differences in performance

task simple. This was done to increase the interpretability of the cognitive processes engaged and to maximize the parallelism between the task and any computational models that would be developed to understand it. Translational research across species is also facilitated by simple tasks. In this case, simplicity came from retaining the letter stimuli and conditional rule, changing only the proportions of trials and manipulating the interstimulus and intertrial intervals as described below. Third, these manipulations were designed to probe the mechanism of interest, in this case context processing. While this may seem obvious, it is important to recall that a manipulation must be compared with a condition that does not rely on the process of interest (or relies on it to differing degrees, as in a parametric manipulation). The AX paradigm has an inherent 2 × 2 structure (valid A vs invalid non-A cues, compared with generally valid X vs non-X invalid probes). This provided 4 conditions: a valid A followed by a valid X (AX condition), a valid A followed by an invalid non-X (AY condition), an invalid non-A followed by a generally valid X (BX condition), and an invalid-A followed by an invalid non-X (BY condition). These manipulations across conditions were chosen to have different degrees of sensitivity to context. Finally, as described above, a manipulation was chosen that would allow researchers to address the generalized deficit confound using a dissociation[42] or process-oriented approach.[38]

The expectancy manipulation of the AX task was the result of these considerations. In keeping with previous versions of the AX-CPT, in this task participants viewed a series of letters, one at a time, on a computer screen. For every X that followed an A, participants were instructed to make a "target" response (see table 1). Every other letter, of course including A's, was a nontarget that either required that a response was withheld[43] or that the participant make an alternative response.[44–46] What was different is that the expectation of an AX trial was introduced by making such sequences occur the majority (80% or 70%) of the time. This instilled a prepotent pattern of alternating nontarget then target responses. Under these circumstances, context processing was critical for invalidly cued BX trials. That is, the appropriate representation and maintenance of the non-A context made it easy to prepare a non-target response to the second stimulus even if it was an "X" (which usually required a target response). However, if this cue representation was lost due to poor context processing, then the generally valid "X" would be likely to cause a false alarm. In contrast to BX trials, AY trials (where Y is any non-X stimulus) were introduced as a general difficulty control condition. That is, the occurrence of "Y" following an "A" was difficult if one had already prepared the prepotent target response. Alternatively, it was easier to respond accurately to the "Y" if no prepotent response was prepared. BY trials were included as a general manipulation check to determine whether participants understood the instructions. Thus, the new expectancy variant of the AX paradigm had the potential to produce a double dissociation in performance: individuals with a context-processing deficit would show impaired performance on BX trials, whereas those with intact context processing would perform worse on AY trials. While this is all very well in theory, what is the likelihood that such a task would actually produce the predicted results?

The Development of the Expectancy AX Paradigm

An additional challenge that researchers face when translating paradigms from basic to applied domains of cognitive neuroscience is to ensure that the modifications made during this process do not change or weaken the construct validity of the paradigm. Thus, this simple reformulation of the AX-CPT has been used in the original study of schizophrenia patients compared with a psychiatric control group[43] and in at least 11 subsequent studies.[44–55] While all this work has incrementally expanded our understanding of context-processing deficits in schizophrenia, figure 2 compares a subset of these results to illustrate the basic pattern of findings across studies and to show some unexpected findings that have cropped up along the way.

The original study of the expectancy variant of the AX task compared 2 schizophrenia groups (medicated and unmedicated) with a group of psychiatric controls.[43] It

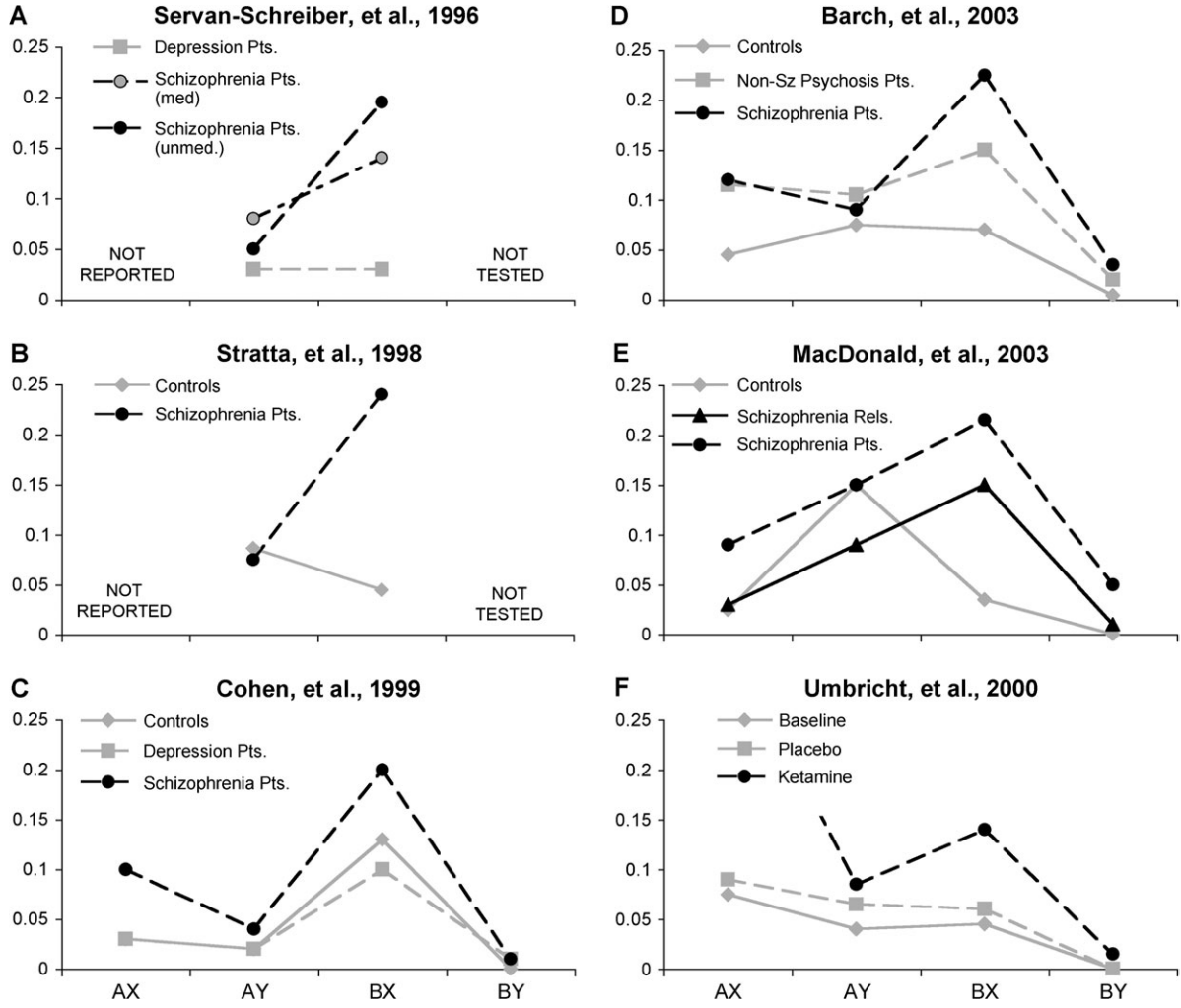


Fig. 2. Illustrative Results From 6 Studies Using the Expectancy AX Task. Y-axis shows proportion of errors. (A) Original study.[43] Eighteen unmedicated schizophrenia patients, 21 medicated schizophrenia patients, and 11 psychiatric controls with major depression. Long-delay performance illustrated. (B) Independent replication.[48] Fifteen schizophrenia patients and 15 healthy controls. Combined (short- and long-delay) performance illustrated. (C) Fifty-three schizophrenia patients, 25 psychiatric controls with major depression, and 31 healthy controls.[44] Combined performance illustrated. (D) Forty-nine schizophrenia patients, 30 patients with nonschizophrenia psychosis, and 72 healthy controls.[45] Combined performance at index hospitalization illustrated. (E) Twenty-four schizophrenia patients, 24 healthy siblings or patients, and 36 healthy controls.[46] Combined performance illustrated. (F) Twenty healthy volunteers undergoing pharmacological challenge. Combined performance in 3 manipulations illustrated. Pts., patients; med., medicated; unmed., unmedicated; Non-Sz, nonschizophrenia diagnoses; Rels., relatives.

was therefore an empirical test of the theory that had been already implemented in a quantitative model.[3] The task variant used in this original study was different from those that followed in part because it required no response to the cue (A or B) and it included no BY condition. This study focused on differences between AY and BX errors following a short compared with a long delay. As predicted, schizophrenia patients performed worse than controls on BX trials, especially after a delay (figure 2A). What is more, schizophrenia patients improved on AY trials following a delay, and it was this dissociation across delay and trial type that afforded the interpretation of a specific deficit. Thus, these findings were supportive not only of a context-processing deficit in schizophrenia but also the diagnostic specificity of that deficit. This basic pattern of findings was also independently replicated (figure 2B).

The next study to advance context-processing theory in schizophrenia involved showing the convergent nature of patient impairments on putative context-processing tasks.[44] This study was particularly important to the issue of establishing the construct validity of the expectancy AX task as a measure of context processing and not just as a global measure of working memory. In this study, chronic patients performed the AX task along with the Stroop task and a Lexical Disambiguation task. In this later task, participants viewed a cue sentence, such as "Jerry was surprised to find the mine tunnel deserted," followed by the letter string SH_FT. If the semantic context constrained the interpretation, participants

would complete with letter string "Shaft" (the nondominant response), whereas if the cue sentence did not constrain the letter string, they were more likely to make the dominant completion, "Shift." As predicted by the context-processing theory, Stroop color naming errors, the proportion of Lexical Disambiguation dominant responses and the proportion of BX were all elevated in schizophrenia patients, and the extent to which they were elevated was correlated (suggested that they all reflected a common, cognitive deficit). Furthermore, the extent to which patients expressed cognitive disorganization during a clinical interview correlated with their context-processing deficits but not other symptom dimensions. There were a few complications that occurred. In this study, the AY condition was easier than the BX across groups (see figure 2C), perhaps because of the lower proportion of AX trials (70% compared with 80% previously). It was also clear that schizophrenia patients were impaired on BX trials irrespective of the delay. Overall, however, the findings suggested not only that the AX task was capable to demonstrating impairments in patients but also that this deficit was related to deficits on other cognitive tasks and to the manifestation of disorganized symptoms.

Another aspect of establishing construct validity is to test the hypothesized links of the task to specific neural systems. In the case of the expectancy AX task, the theory predicted that the need to represent and maintain context should activate dorsolateral prefrontal cortex (DLPFC). Consistent with this hypothesis, the first imaging study of the expectancy variant of the AX task established that long-delay trials elicited greater activation of DLPFC than short-delay trials and that this effect could be dissociated from task difficulty.[30] Two neuroimaging studies of a sample of medication-naive first-episode schizophrenia patients then provided further evidence of the link between PFC dysfunction, poor performance on the AX task, and the symptoms of disorganization in patients with schizophrenia.[52,56] This imaging data illustrated that the requirement to maintain cue information lead to relatively decreased activity in DLPFC (Brodmann's Areas 9/46 and 9), respectively. It was also particularly useful to observe that the extent to which patients failed to activate PFC following a B cue, irrespective of delay, significantly correlated with their disorganization symptoms ($r = -.53$) but not to positive or negative symptoms.[52]

The next 2 studies used the AX task to address whether context-processing deficits might be causally related to schizophrenia. Barch et al[45] tested new psychiatric patients who were unmedicated at their first admission and then retested them 4 weeks later (figure 2D). The important result from this study was that patients who would eventually be diagnosed with schizophrenia showed context-processing deficits both during the acute (and unmedicated) stage of their illness and at the follow-up. In contrast, psychosis patients who went on to have other diagnoses showed context-processing deficits only at the acute stage of their illness. As before, there was a 3-way group by condition by trial–type interaction. The specifics of the changes with delay were generally consistent with the theory but differed from that observed in the original study. Most importantly the data showed that the context-processing deficits in schizophrenia appeared to be trait like and were detectable at the earliest stages of the illness.

The work of MacDonald et al[46] probed further into the etiology of schizophrenia by testing patients' nonpsychotic siblings. To do this, the AX task was modified to have a higher proportion of AX trials again so that AY and BX trials only occurred 8% of the time. This made AY trials again more difficult for controls, which was important for allowing an interpretable group-by-condition (AY vs BX) interaction. As predicted, both patients and their relatives showed significantly more impairment on the BX relative to the AY condition, whereas the opposite was true for controls (figure 2E). This pattern was observed irrespective of the delay interval. Thus, these data strongly implicated context-processing deficits in the unexpressed genetic liability to schizophrenia.

As should be the case, the expectancy AX paradigm can also be used to challenge the underlying theory. One important critique of the theory that context-processing deficits in schizophrenia reflect dopamine dysfunction examined the effect of ketamine, an N-methyl-d-aspartate antagonist, on task performance (figure 2F).[47] The investigators found that ketamine, whose mechanism of action is more directly linked to glutamatergic rather than dopaminergic functions, can induce in healthy volunteers schizophrenia-like deficits on BX trials without strongly affecting AY performance. (AX performance was also markedly degraded with ketamine.) This illustrates yet another principle: theory and the tools developed to test the theory do not always share the same fate.

Additional Challenges in Translating Paradigms for Use in Applied Settings

While the expectancy AX task had by now proved a workhorse for a number of studies across a number of independent investigators, its use had generally been limited to small sample size studies targeting the cognitive features or functional neuroanatomy of schizophrenia-spectrum pathology (for an exception, see MacDonald et al[54]). The task faced several challenges to more wide spread use. There were not yet studies to our knowledge that had published on the psychometric properties of the instrument, such as retest reliability or practice effects. In addition, it was arduous, taking as long as 45 minutes when employing both the short- and long-delay manipulations. This made it particularly difficult for low functioning patients to complete. Length also presented an opportunity cost to the investigator, who must therefore perforce study fewer constructs. Molecular genetic and

treatment studies where cognitive hygiene is not valued as highly as a short, off-the-shelf marker of individual differences in ability were therefore unlikely to include this task.

During my doctoral work, it became increasingly evident that a new variant of the expectancy AX paradigm might address a number of these challenges. In addition to concerns about length, a new variant might gain power by reducing ceiling effects in the AY and BX conditions observed in some studies,[44] increase interpretability by making the AY condition relatively harder than the BX condition, and increase tolerability and practicality by shortening the procedure. These considerations proved the impetus for the dot pattern expectancy (DPX) task.

The DPX is formally equivalent to the expectancy AX task (see table 1), in so far as it has a fixed common cue and a fixed common probe. However, rather than letters, these stimuli are configurations of dots. This serves to make the make-all conditions somewhat harder. Additionally, the cues are very distinctive (B's are distinctly different from A's), whereas the probes are more subtly different (Y's are rotated patterns of X's). This serves to increase the difficulty of AY trials for all groups, whereas BX trials are still quite easy for controls. Because the stimuli are not overlearned and their similarity is parametrically manipulated, errors across vulnerable trial types accumulate faster, thereby allowing the task to be compressed to as little as 15, or perhaps even 10, minutes.

While nowhere near as accomplished as the track record of the expectancy AX paradigm, the DPX is beginning to accumulate a series of replicated findings in its own right. The first challenge was to address whether the novel stimuli increased the role of other processes (perceptual imprecision, target sequence learning) to such a degree that they altered the interpretation of task. Thus, it was helpful to find that in a large general population sample, each condition of the DPX showed convergent validity with the corresponding conditions of the expectancy AX task.[57] Even so, further validation of this convergence is ongoing. Meanwhile, the DPX has also been used to demonstrate specific context-processing deficits in patients with schizophrenia in one published study,[57] and 2 further unpublished studies (J. Hurdelbrink, B.A., S. Sponheim, Ph.D., A.W.M., in preparation, 2008 J. Gold, Ph.D., personal communication, 2008). While the DPX has been shown to be sensitive to deficits associated with the genetic liability to schizophrenia in patients' nonpsychotic siblings,[57] it has also been shown to be sensitive to polymorphisms in the catechol-O-methyltransferase (COMT) genotype in the general population.[54] COMT is a gene thought to be associated with PFC function and the genetic liability to schizophrenia.[58]

The expectancy AX and the DPX tasks are unlikely to represent the final development of probes for context-processing impairments. For example, neither task is particularly well suited for cross-species translational applications. From the perspective of translation to animal models of schizophrenia, neither the letter nor dot pattern stimuli are optimal. Ongoing task development in our laboratory suggests that expectancies can be set up using spatial cues to obtain a similar pattern of errors. For clinical translation, efforts are underway to determine if sensitive and specific assessments of context-processing impairments can be obtained in shorter task variants. For example, efficiency of task administration might be gained by developing a variant of the task that is adaptive and proves able to titrate difficulty. Such an advance would further increase the tolerability of the task and facilitate its inclusion in future batteries of tests that evaluate a broad range of functions. In addition, item-response theory may play a role in evaluating such a task, which might also address some of the concerns that have been discussed about specific vs generalized deficits, eg, Coleman et al.[59]

Conclusions

The purpose of a retrospective focused on the history of the expectancy AX paradigm is to give an in-depth illustrative example of task development, not to advocate the underlying theory or petition for the paradigm's use. The example illustrates several steps, including (1) the basic, predicted group effect; (2) the relationship between performance and symptoms; (3) the relationship between deficits on the task and deficits on other tasks that putatively measure the same construct; (4) the relationship between context-processing deficits as measured by the AX task and PFC dysfunction; (5) the trait-related nature of the context-processing deficit in schizophrenia; and (6) the presence of context-processing deficits in patients' nonpsychotic siblings. Further adaptations have allowed the AX paradigm to be shortened while maintaining some of its desirable properties in the form of the DPX task. This task may be better tolerated by patients and easier to include in broader cognitive and neuropsychological batteries.

The story of the expectancy AX task also highlights the importance of maintaining controls for the generalized deficit confound. In the absence of such controls, we are constrained to very weak interpretations about the causes of any observed impairments in patient performance. By addressing these issues at the outset, one can preempt many of the difficulties on the journey from basic science to clinical application.

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