*Journal of the International Neuropsychological Society* (2003), **9**, 839–846.

DOI: 10.1017/S1355617703960036

# Working memory and relational reasoning in Klinefelter syndrome

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(Received December 11, 2001; Revised August 22, 2002; Accepted October 21, 2002)

**Abstract**

Klinefelter syndrome (KS) is a sex chromosome abnormality associated with male infertility and mild cognitive deficits. Individuals with KS have been reported to have impaired verbal ability, as well as deficits in executive function. To further understand the nature of their deficits, we assessed specific elements of frontal lobe function such as working memory and relational reasoning. Men with KS exhibited a deficit in a transitive inference task in which participants ordered a set of names based on a list of propositions about the relative heights of the people named. This deficit was present even for items in which the propositions were given in order, so a chaining strategy could be used. Men with KS are also impaired on the *n*-back task, which uses letters as stimuli. In contrast, these men performed as well as controls in nonverbal reasoning (Raven's Progressive Matrices). These results suggest that men with KS have intact nonverbal reasoning abilities, but that a difficulty in encoding verbal information into working memory may underlie their executive and linguistic impairments. (*JINS*, 2003, *9*, 839–846.)

**Keywords:** Klinefelter syndrome, Executive function, Sex chromosome abnormality, Working memory, Relational reasoning, Complexity

## INTRODUCTION

Klinefelter Syndrome (KS) is a sex chromosome abnormality affecting approximately 1 in 800 males (Mandoki et al., 1991). It is characterized by the presence of an extra X chromosome, and is accompanied by infertility and other signs such as tall stature, smaller genitals, hormonal imbalances at puberty, and gynecomastia (Rovet et al., 1996). KS is most often identified during late puberty or early adulthood, when patients present for endocrinological testing, but the syndrome can remain undetected over a lifetime.

For some time it has been known that KS causes learning disabilities in affected children. Primarily, these deficits have been shown to be verbal in nature, with early problems in expressive speech (articulation), phonemic processing, word retrieval (Bender et al., 1993; Graham et al., 1988; Netley & Rovet, 1984; Nielsen & Sorensen, 1984; Walzer et al., 1982), school-age impairments in reading and spelling, and subsequent problems in other areas (arithmetic, acquisition of generalized knowledge) in later school years. Rovet and colleagues (1996) reviewed evidence that boys with KS have shown impairments on many tasks that rely on auditory memory, language comprehension, or to a lesser extent, attention. As a result, older boys with KS in the Rovet et al.'s study showed not only verbal impairments, but also greater difficulties in nonreading-related areas such as logical and conceptual thinking. Rovet et al. hypothesize that KS deficits are primarily language related, and may stem from a base impairment in auditory temporal processing and working memory. Other researchers have found specific deficits in linguistic usage such as verbal abstraction and syntax production (Walzer et al., 1982), and Graham et al. (1988) characterized these difficulties as an essential impairment in accessing, retrieving, and applying linguistic information.

More recent research has suggested that KS may also result in frontal-executive deficits, although reports have been conflicting. Some researchers have found that men

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with KS exhibit attentional deficits such as distractibility (Rovet et al., 1996), hyperactivity (Theilgaard, 1984), and problems with concentration and short-term memory (Sorensen, 1992). In contrast, Nielsen and Sorensen (1984) and Stewart et al. (1986) found no evidence of attentional deficits in KS. Formal neuropsychological testing has also yielded mixed evidence of frontal dysfunction. Robinson et al. (1986) reported no impairments for KS patients in the Wisconsin Card Sorting Test (WCST), while Geschwind et al. (2000) found significant deficits in all measures of the test in adults with KS. By contrast, both groups found impairments in tests of attention shifting, and Geschwind et al. also found below-normal performance in tests of inhibition, figural fluency, and information-processing speed. More recently, Boone et al. (2001) found impairments in executive tasks that are verbal in nature, but none for nonverbal executive tasks.

Thus, the evidence on executive deficits in KS is so far inconclusive. An alternative approach to assessing this question is to test cognitive abilities that are known to be associated with frontal lobe function. Tasks involving working memory (Baddeley, 1986) and relational reasoning (Robin & Holyoak, 1995) are considered to require executive function, and have been shown in neuroimaging studies to activate frontal lobe areas. Tests of working memory can focus on two aspects of processing: capacity of the memory buffer (how many items can be stored simultaneously) and executive control (how many items can be manipulated competently while stored in memory) (Baddeley, 1986). In the current study, we used the *n*-back task to test the capacity of the working memory buffer, as well as manipulation of buffer contents. The *n*-back task has been used in imaging studies to explore working memory, and results have consistently shown that dorsolateral prefrontal cortical areas become active as load levels increase (e.g., Cohen et al., 1994, 1997; Smith et al., 1996; Smith & Jonides, 1998).

The current study also used relational reasoning tasks to test working memory. These tests emphasize the number of *relations* that can be manipulated at one time, rather than the number of items. A relation is the mental representation of the relationships between objects or events. Reasoning involves the manipulation of relations in order to solve a problem. Relational integration, the simultaneous manipulation of relations that share an argument (i.e., an object in a specific role), is considered by many researchers to be the fundamental executive function common to all working memory and reasoning tasks (Halford et al., 1998; Hummel & Holyoak, 1997; Waltz et al., 1999). For example, Waltz et al. proposed that relational integration is the essential component in such diverse reasoning abilities as logical inference, drawing analogies, problem solving, planning, and goal/subgoal management.

The relational approach to reasoning allows problem complexity to be quantified (Halford et al., 1998), and offers a possible index of working-memory capacity (Hummel & Holyoak,1997). There is also suggestive evidence that brain areas associated with working memory (especially dorsolateral prefrontal cortex, or DLPFC) may be the locus of relational abilities as well. Imaging studies that have manipulated relational complexity (in reasoning paradigms) have consistently shown that activation in DLPFC rises and falls in concert with complexity level (e.g., Christoff et al., 2001; Kroger et al., 2002; Prabhakaran et al., 1997). In addition, studies with neurological patients have revealed a severe drop in performance for frontal patients on problems entailing multiple (rather than single) relations (Waltz et al., 1999). These studies provide further support for the view that relational integration is fundamental to higher reasoning, and that relational abilities may indeed be tied to prefrontal cortex.

The present study administered both a traditional working-memory test (the *n*-back task), and two relational reasoning tasks to men with KS. The relational tasks used were a transitive inference test (deductive inference) and a matrix task (inductive inference) similar to the Raven's Progressive Matrices. Both tasks allow for straightforward manipulation of relational complexity. Our prediction was that if men with KS have frontal executive problems, these deficits should be reflected in both impaired working memory and impaired relational processing. Specifically, in the latter case, we should find that for zero- or one-relation problems, which do not require relational integration, patients should perform comparably to controls. By contrast, when the relational level rises above one, so that integration of multiple relations is required, control participants should continue to perform competently, while the men with KS will show impairments. In contrast, if the KS deficit is fundamentally verbal in nature, rather than a general deficit in relational processing, then men with KS will be selectively impaired in verbal tasks at all complexity levels.

## METHOD

### Research Participants

Participants were 21 men with KS, and 20 men with no known genetic or neurological abnormalities who served as controls. The men with KS were recruited through an endocrinology clinic, where most had appeared for help with fertility or hormone treatments. They were matched on age and education with control participants, and independent *t* tests revealed no significant differences between ages or educational levels for the two groups ($p > .50$ for both comparisons). Table 1 gives characterizing data for both groups. Patients with a history of major head trauma or neurological disease were excluded, as were those who were XXY mosaics. About half of the men with KS were diagnosed only in adulthood, whereas the other half received their diagnosis during adolescence. All but two of them were being treated with testosterone replacement therapy, and at the time of testing had been on these treatments consecutively for at least 4 months. One participant with KS refused to take the *n*-back test, and data from two par-

**Table 1.** Age, education, and IQ for men with KS and controls

| Participants | *N* | Age | Education | VIQ[a] | PIQ[b] | FSIQ[a] |
|---|---|---|---|---|---|---|
| Men with KS | 21 | 35.4 (3.1) | 13.7 (.43) | 97.9 (4.6) | 100.7 (3.5) | 98.7 (3.8) |
| Controls | 20 | 37.6 (2.9) | 14.1 (.34) | NA | NA | NA |

*Note*. Values shown are means and standard errors. NA = not applicable.
[a]$n = 14$.
[b]$n = 15$.

ticipants with KS were lost for the matrix task due to computer error. Four of the men with KS and all of the control participants were paid for their participation.

## Materials and Procedure

Participants performed all tests in a fixed order, beginning with transitive inference, then the matrix task, and finally the *n*-back task. All testing was done in a single session, which lasted an hour and a half.

### *N-back task*

In this task, the participant views letters presented on a computer screen, one at a time. At $n = 1$, the participant's task is to view each letter and compare it to the immediately preceding letter. If the two letters are the same, the participant says "same"; otherwise, he says "different". When the next screen appears, the participant compares the new (third) letter to the most recent (second) one. Thus, for $n = 1$, the participant is always remembering a single letter at any given time. At the second level ($n = 2$), the participant compares the currently displayed letter with the letter two positions back, and so must store two letters at a time. Likewise, at the hardest level ($n = 3$), the participant must compare the currently displayed letter with the third letter back (see Figure 1). All participants were requested to give their answer verbally, and the experimenter entered responses by pressing a "same" or "different" key. Participants were given practice trials at each *n*-back level to make sure they understood the task. Performance was measured by the percentage of trials correct.

This test was presented to the participant on a Macintosh G3 laptop, using the MacProbe programming language to display the stimuli. Each letter displayed had a 50% chance of matching its target letter, and the 50% that did not match were generated randomly. All letters were presented in upper case. Stimulus duration was 900 ms, followed by a 4500-ms interstimulus interval. If the participant did not respond in that time interval, an error was recorded. Individual trials were presented in blocks of five (i.e., six letters for $n = 1$, and eight letters for $n = 3$), with five blocks presented at each *n*-back level.

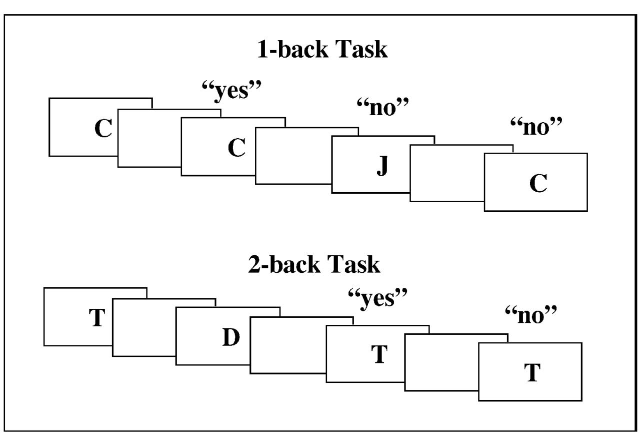


**Fig. 1.** The *n*-back task: a possible sequence of trials.

### *Transitive inference task*

This task was performed using a set of 3″ × 5″ index cards that were each printed with the name of a person. For each trial, the participant was given 3, 4, or 5 such cards, and a display specifying the relative heights of the people named on the cards. This information was presented in the form of binary relations (e.g., "Jim is taller than Bob" and "Bob is taller than Tom"), always one proposition less than the number of cards given. Thus when given three cards (Tom, Jim, and Bob), the participants' task was to arrange the cards on the table in order of tallness (e.g., Jim—Bob—Tom). The taller-than sentences always presented a relationship between two people who were adjacent in the correct ordering.

At the one-relation level, relations were presented in order of actual tallness (as in the example above), so that the participant could use a simple chaining strategy to add the new name to the list already built. He only needed to consider the relation between the new name and the name most recently added to the series. However, if the height information was scrambled (e.g., "Jim is taller than Bob" and "Tom is taller than Jim."), new names would need to be added either to the beginning or the middle of the list. This is a two-relation problem, because participants cannot merely chain onto the end of the list. The person at the end of the first proposition (Bob) is not even mentioned in the second proposition. Participants must integrate both relations in order to get the correct answer. Although the requirement to add a card at the front of the list may not seem significantly harder than adding to the end, Halford (1984) have shown that children under 5 years of age cannot solve the two-relation version consistently, while they can perform well on the chained version.

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In three-relation problems, participants get two relations in a row in which no common names are used: “Jim is taller than Bob,” “Tom is taller than Mike,” and “Bob is taller than Tom.” In this sequence, the participant must first order Jim and Bob, and then Tom and Mike separately, since the first two propositions do not convey how the two subseries relate to each other. To handle the third proposition, all three relations must be considered at one time. Thus, the ordering of the propositions could present a group of names as a one-, two-, or three-relation problem.

The participant sat with a large binder in which cards and displays of taller-than information were kept. For each trial, the participant spread the cards out on the table so they were easily visible. He then turned the page to read the taller-than information, and as he turned it, the experimenter started a timer. The participant then slid the cards around on the table until satisfied that he had the correct ordering. (The taller-than information was visible throughout; the participant was not required to remember it.) He then said “done,” and the experimenter stopped the timer, noting response time and accuracy of the answer. The test included trials with two propositions (three names), three propositions (four names), and four propositions (five names). All possible orderings of propositions were presented, so that there were two two-proposition trials, six three-proposition trials, and 24 four-proposition trials. Thus a total of 32 problems were administered, with three at level 1 complexity, ten at level 2, and 19 at level 3. The trials were presented to all participants in a fixed order. Participants worked without a specified time limit.

### *Matrix task*

The Raven’s Matrices are a widely used set of problems, and performance on them is more strongly correlated with intelligence or generalized cognitive skill than are many other executive tasks (Carpenter et al., 1990; Raven, 1941). We administered a group of matrix problems that resembled Raven’s Matrices, but used a simpler set of relations. The matrices spanned three levels of complexity: zero-relation, one-relation, and multirelation (the latter category included problems with two or more relations). All problems were presented in the top half of a computer display, and the possible answers were displayed in the bottom half. The participants’ task was to inspect the problem, and choose the answer from below that correctly solved the problem.

The zero-relation problems consist of a visual pattern presented inside a rectangle (see Figure 2A). Participants pressed a number key to indicate their answer choice. The zero-relation matrices require visual pattern completion, but no integration of relational information. One-relation problems involved matrices consisting of $2 \times 2$ or $3 \times 3$ sets of figures (see Figure 2B). Scanning across a row, or down a column, some transformation was applied to each figure that changed its visual appearance. The participant had to choose the answer that applied the corresponding transformation. A multirelation problem (see Figure 2C for a two-relation example) applied two or more operations at once, either across the rows, down the columns, or both. To solve such a problem, the participant must do true relational integration: he must choose the answer that applies only to the needed operations, and no others.

For this test, 32 problems were presented, seven at level 0, six at level 1, and 19 at levels 2 and higher. These problems were presented in a fixed order, beginning with level 0, then level 1, then level 2, and higher. Participants worked at their own pace, without a time limit. The matrices were presented to participants on a Macintosh G3 laptop, using the SuperLab program to display the problems.

## RESULTS

### *N*-Back Task

Results for the *n*-back task showed that men with KS have a deficit in manipulating verbal material in working memory (Figure 3A). A mixed analysis of variance revealed a main effect of group on percent correct, $F(1,38) = 9.44$, $p < .01$, with the KS group making more errors than con-

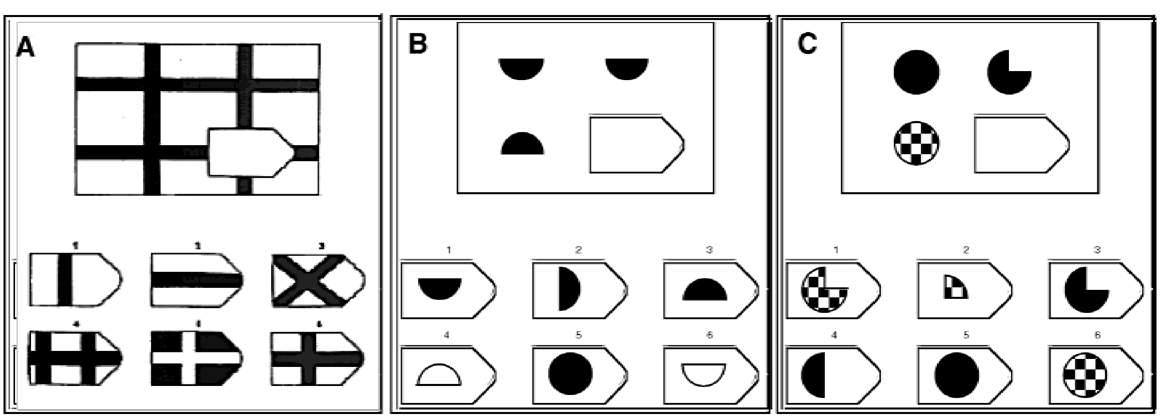


**Fig. 2.** The matrix task: sample problems used for (A) a zero-relational problem, (B) a one-relational matrix, and (C) a multirelational matrix. The multirelational matrix contains two relations.

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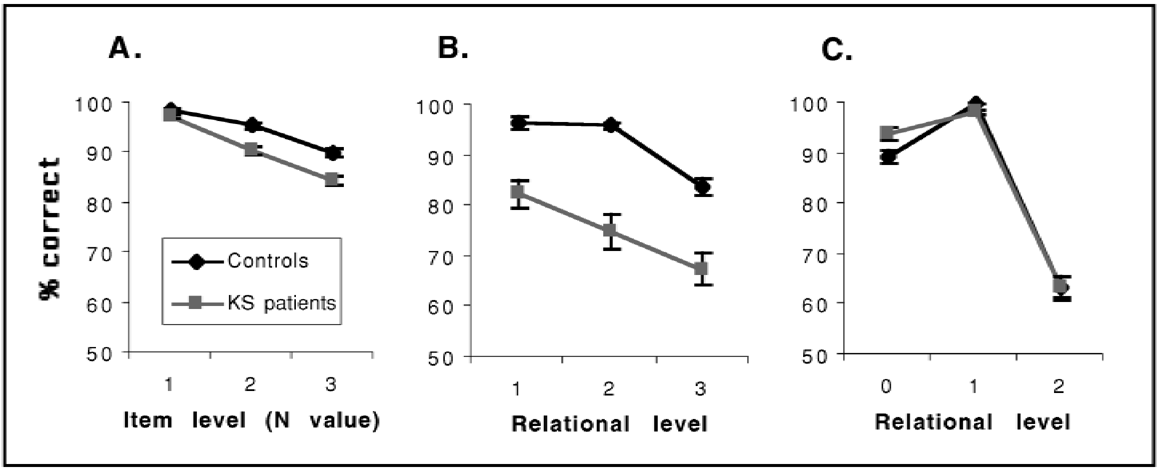


**Fig. 3.** Mean percent of problems performed correctly in (A) the *n*-back task, (B) the transitive inference task, and (C) the matrix task. Error bars show standard error.

trols (9.2% *vs.* 5.1%). A main effect of *n*-back level was also found, $F(2,76) = 37.78$, $p < .01$, with difference contrasts showing more errors at level 3 than at level 2, $F(1,38) = 17.79$, $p < .001$, and more at level 2 than level 1, $F(1,38) = 20.43$, $p < .001$. No significant interaction was found, ($p > .1$).

## Transitive Inference Task

Results for the transitive inference task showed that men with KS ($N = 21$) made more errors than controls ($N = 20$) at every complexity level (Figure 3B) (overall mean of 28.7% errors for the KS group *vs.* 11.3% for controls). An analysis of variance revealed a main effect of group on percent correct, $F(1,39) = 10.24$, $MSE = .90$, $p < .01$, and a main effect of relational level, $F(2,78) = 7.62$, $p < .01$, with higher levels resulting in more errors. Difference contrasts showed that percent correct was not significantly different for levels 1 and 2 ($p > .1$), but contrasts comparing levels 2 and 3 did find a significant difference, $F(1,39) = 15.26$, $p < .001$. There was no interaction between group and complexity level ($F < 1$). Men with KS were consistently impaired at the transitive inference problems, but not disproportionately so at higher complexity levels.

For men with KS, mean response times (± SEM) for the 1-, 2-, and 3-level problems were 13.8 ± 1.1 s, 15.5 ± 1.1 s, and 20.2 ± 3.1 s, respectively, while for the control participants, the reaction times were 11.2 ± 1.1 s, 13.7 ± 1.2 s, and 16.8 ± 1.5 s for the three complexity levels. Response times for the two groups were not significantly different ($F < 1$), but there was a significant difference between levels, $F(2,74) = 11.05$, $MSE = 428.08$, $p < .001$. Difference contrasts found significant response-time differences between levels 1 and 2, $F(1,37) = 5.49$, $p < .05$, and between levels 2 and 3, $F(1,37) = 9.752$, $p < .01$. There was no group × relational level interaction ($F < 1$).

## Matrix Task

Results for the matrix task showed that men with KS performed normally compared to controls (Figure 3C). Percent of trials correct for KS participants was numerically better overall than for controls (76.6% correct for the KS group *vs.* 76.1% for controls), but the main effect of group was not significant ($F < 1$). A significant effect of relational level on percent correct was found, $F(2,74) = 107.24$, $MSE = 13699.85$, $p < .001$, such that level 2 was the most difficult level, $F(1,37) = 145.4$, $p < .001$, and level 0 (pattern completion) was more difficult than the 1-relation level, $F(1,37) = 15.2$, $p < .001$. There was no interaction between group and relational level ($F < 1$).

For men with KS, mean reaction times (± SEM) were 6.1 ± 0.6 s, 5.3 ± 0.4 s, and 17.3 ± 2.5 s for the zero-relation, one-relation, and multirelation problems, respectively, while the corresponding mean reaction times for controls were 6.2 ± 0.7 s, 5.0 ± 0.2 s, and 13.9 ± 1.1 s. There were no significant group differences in response times ($F < 1$). There was a significant effect of level on response time, $F(2,74) = 66.79$, $MSE = 1.298E{+}09$, $p < .001$, with no interaction between group and level ($F < 1$).

## DISCUSSION

The men with KS in this study presented a mixed profile in terms of frontal executive abilities: they showed deficits in the *n*-back and the transitive inference tasks, but none in the matrix task. This pattern of deficits does not appear to be due to task difficulty *per se*, since men with KS performed normally on the difficult multirelation matrix problems. The *n*-back results suggest that KS does cause a deficit in verbal working memory. However, the results in the two reasoning tasks argue against a general impairment in relational reasoning. Instead, we interpret the lower performance on the transitive inference task as a possible outgrowth of a verbal

https://doi.org/10.1017/S1355617703960036 Published online by Cambridge University Press

working-memory deficit. We do not view the transitive inference result as reflecting an executive deficit because our patients exhibited general impairment, but not disproportionate impairment for multirelation *versus* single-relation problems. In addition, their relatively good performance on the matrix task suggests that men with KS do not have reasoning impairments when the test materials are presented in nonverbal form.

The verbal working-memory deficit observed in the present study is consistent with prior findings showing KS deficits in verbal tests, and supports other research showing that childhood verbal disabilities are carried over into adulthood (Boone et al., 2001). The present conclusion regarding relational reasoning, however, does not support the hypothesis that men with KS have reduced executive function. Both reasoning tasks used in the present study have been shown to be sensitive to frontal damage (Waltz et al., 1999), and the matrix task in particular has been shown to activate prefrontal cortex as levels of relational complexity increase (Christoff et al., 2001; Kroger et al., 2002; Prabhakaran et al., 1997). Thus, the present results do not support the hypothesis that men with KS exhibit a general prefrontal dysexecutive syndrome. Nor do the present results support the possibility that adults with KS are impulsive or exhibit global deficits in attention. Reaction times were similar (in terms of means and variance) for KS patients and controls in our study. If men with KS tended to respond impulsively, we might expect to have observed shorter reaction times for this group, and if they were easily distracted from the task we might expect to have observed longer reaction times.

A working-memory deficit might impair performance in the verbal tasks (*n*-back and transitive inference) in several possible ways. *Maintenance* of information in working memory is thought to involve a storage buffer and rehearsal processes that keep buffer contents in an active state. *Manipulation* of this data is governed by an executive component (Baddeley, 1986; Norman & Shallice, 1986) that includes functions such as the relational operations discussed previously. Performance on the *n*-back task entails both maintenance and manipulation of items in working memory. In the transitive inference task, taller-than relations must be encoded and manipulated. For individual relations, encoding must take place in order to bind arguments to their relations, while for higher relational levels, relations must be both encoded and integrated. Impairments might result from deficient encoding and maintenance of the material, deficient manipulation, or both. In the transitive inference case, the presence of an impairment even at the single-relation level (where no integration is required) strongly suggests an encoding deficit. Since we found no disproportional impairment for KS participants at the higher relational levels (that is, no group by level interaction), the evidence for KS deficits in relational integration is not compelling.

Findings from the current study thus argue for the view that if executive impairments exist in KS, they are relatively mild. Previous mixed findings on executive dysfunction in KS may be an artifact of strategy differences across participants. For example, in the Wisconsin Card Sorting Test, many participants tend to subvocalize while performing the task. If men with KS are verbally impaired, then a strategy of subvocalizing may provide less help, or be unavailable in some patients. Alternatively, the mixed findings may signal the existence of subgroups within the Klinefelter population, some of whom may show executive differences, and some not. Boone et al. (2001), using a sample of men with KS that included most of the current participants, have found evidence for such subgroups. A third possibility (discussed below) is that hormone replacement may alleviate cognitive deficits in some cases, particularly in the areas of working memory and attention. Finally, executive function as a construct may be more fruitfully divided into modality-specific domains (verbal and nonverbal). Thus, any executive dysfunction shown by KS participants may be limited to the verbal domain, and may be largely a result of defective verbal encoding. This notion is consistent with findings of Boone et al. (2001), which showed KS executive deficits on tasks that used verbal material, but not on tasks using nonverbal material.

Overall, a finding of working-memory deficits without executive dysfunction may be consistent with other findings on cognitive deficits found in KS. It is important to note that our patient group was relatively small ($n = 21$) and the KS participants we studied were considered high functioning. Most were diagnosed with KS after presenting with hypogonadism or infertility rather than language or cognitive deficits. Also, all but two were receiving testosterone at the time of testing, which may have attenuated cognitive deficits in this group. Nevertheless, significant deficits were found in verbal working memory, suggesting that this deficit is reliably present in men with KS.

This pattern of findings echoes research on individuals with other sex chromosome abnormalities, and is consistent with a role for sex steroids in cognitive function. Most notably, Turner syndrome (TS), characterized by a missing or malformed X chromosome, is often compared with KS as representing a mirror-image set of cognitive deficits (e.g., Geschwind et al., 2000). Females with TS show related or opposite physiological symptoms (e.g., short stature rather than tall), as well as cognitive deficits that appear to affect right-hemisphere rather than left-hemisphere functions. Specifically, women with TS show no verbal impairments, but do show visuospatial deficits in perception, in motor abilities, and in nonverbal memory. They also show other deficits hypothesized to affect men with KS, particularly attention and executive abilities (Ross et al., 2000b). For both disorders, researchers have postulated a role for genes on the pseudoautosomal region (PAR) of the X chromosome. The expression of these genes is thought to lead to cognitive deficits in both KS and TS, as well as signs of anomalous cerebral laterality found in both syndromes (Geschwind et al., 1998; Ross et al., 2000b). In the case of TS, the neurocognitive phenotype has been mapped to the distal Xp region of the PAR1 (Ross et al., 2000a), but a region for KS has not been identified. Thus, a gene-dosage effect is postulated to explain the existence of verbal learning deficits in KS and other trisomies (XXY, XXX, XYY), and of visuospatial deficits in TS (monosomy X) (Geschwind et al., 2000; Netley & Rovet, 1984; Ross et al., 2000b). According to this theory, the presence of an extra X chromosome (three copies of the PAR, instead of the normal two) could lead to abnormal development of left-hemisphere structures, while the right hemisphere is preserved. By contrast, the presence of only a single X chromosome (single copy of the PAR) could result in abnormal development of right-hemisphere structures, while the left hemisphere remains intact. These developments would result in anomalous architecture, possibly leading to the language (left-sided) or visuospatial (right-sided) deficits seen in KS and TS.

If that is the case, then we predict that the tests used in the current study should show the mirror-image results among women with TS: deficits in visuospatial working memory (using a spatial *n*-back task) and the matrix task, but not in the transitive inference or verbal *n*-back task. But how could the hypothesized anomalous architecture result in the deficits seen in either syndrome? What areas, within either hemisphere, should be affected? While adults with KS appear to perform normally on a nonverbal task dependent on prefrontal cortex (PFC), their deficit in verbal working memory implicates dysfunction in circuitry involving prefrontal cortex and the connecting posterior cortex. The left inferior frontal gyrus, left dorsolateral prefrontal gyrus, and left posterior parietal cortex have been strongly associated with verbal working memory (D'Esposito et al., 2000; Smith & Jonides, 1998). The chromosomal abnormality in KS may influence the development of this circuitry. Researchers in working memory (D'Esposito et al., 2000; Smith & Jonides, 1998) have presented evidence that the left inferior frontal gyrus (Brodmann area 44, Broca's area) may support maintenance functions of verbal working memory (that is, rehearsal). By contrast, dorsolateral prefrontal cortex (or DLPFC, area 46) appears to support both maintenance and manipulation, and the parietal areas (Brodmann areas 40 and 7) may be the substrate for an actual storage buffer. Accordingly, we hypothesize that, in men with KS, the areas involved in encoding and maintaining verbal material (Broca's area and parietal areas) and/or the connections between them may be compromised.

The lack of an interaction between group and complexity level suggests that DLPFC regions are not specifically involved in KS. Both Smith & Jonides (1998) and Cohen et al. (1997) have reported sharp increases in activation of left DLPFC as *n*-back performance moves from $n = 1$ to $n = 2$. This activation is held to reflect recruitment of special processing for higher *n*-back levels, and suggests that in men with KS, who show no additional impairment at higher levels, DLPFC may be functioning normally. Neuroimaging studies of matrix task performance also support the hypothesis that DLPFC may be spared in KS. Imaging studies of relational reasoning have consistently found right-sided or bilateral DLPFC activation during performance of matrix tasks (Christoff et al., 2001; Kroger et al., 2002; Prabhakaran et al., 1997). Figural pattern matching (such as used in the zero-relation matrices in this study) seems to activate right-sided DLPFC, while matrices requiring relational integration (two relations or more) result in bilateral DLPFC activation. While none of these studies demonstrate the necessity of DLPFC for doing matrix problems, they strongly suggest that this is an area integrally involved in relational reasoning, and that may in fact be necessary for it. It is reasonable to hypothesize that areas so prominently active during matrix tasks are likely to be intact in men with KS.

The picture that emerges from the present study and previous work suggests two hypotheses: (1) men with KS may have differences in the neural circuitry associated with maintenance of verbal material, but (2) the areas mediating relational integration, especially for nonverbal reasoning, may be spared. We thus hypothesize that KS patients have neuroanatomical differences in the left inferior frontal gyrus and/or left parietal circuitry, but no differences in left or right DLPFC. Importantly, this study provides strong evidence that the working-memory deficits seen in men with KS are not global. Instead, our results support the view that working-memory deficits can be domain specific, and that men with KS are impaired only in verbal working memory. Findings such as these demonstrate the potential usefulness of cognitive tasks and neuroimaging results in eludicating the neurocognitive phenotype of genetic disorders.

## ACKNOWLEDGMENTS

We thank four anonymous reviewers for valuable comments on earlier drafts of this paper. This research was supported by the National Science Foundation under Grant SBR-9729023. A version of this material was presented at the 8th Annual Meeting of the Cognitive Neuroscience Society in New York City in March, 2001.

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