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Evidence for a deficit in procedural learning in children and adolescents with autism: Implications for cerebellar contribution

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Abstract

To examine the hypothesis that abnormalities in those cognitive functions for which cerebellar components have been implicated contribute to the pathophysiology of autism, tests of judgment of explicit time intervals and procedural learning were administered to 11 participants with autism and 17 age-and-IQ-matched controls. Results indicated that the group with autism demonstrated significant impairments in procedural learning compared with the group of controls. No significant difference in judgment of explicit time intervals was found. The data suggest that deficits in procedural learning may contribute to the cognitive and behavioral phenotype of autism; these deficits may be secondary to abnormalities in cerebellar–frontal circuitry. (*JINS*, 2000, *6*, 752–759.)

Keywords: Autism, Procedural learning, Motor learning, Timing, Cerebellum, Cognition

INTRODUCTION

Autism is a syndrome characterized by impairments in social relatedness and communication as well as a pattern of repetitive behavior and a restricted range of interests. Recent reports estimate the prevalence to be as high as 1:1,000 (Gilberg & Wing, 1999). Despite this, the neurologic basis of the disorder remains unclear. One brain region that has been implicated is the cerebellum.

Investigations utilizing histopathological and morphometric magnetic resonance imaging (MRI) techniques have led to suggestions that abnormalities in the cerebellum may contribute to the behavioral and cognitive phenotype of autism. The cerebellum is one of the few brain regions in which consistent abnormalities are described on neuropathologic examination (Bailey et al., 1998; Bauman & Kemper, 1994; Ritvo et al., 1986; Williams et al., 1980). There is a diffuse decrease in Purkinje cell numbers that involves the vermis and hemispheres with a lesser degree of granule cell loss. The changes are most prominent in the posterior inferior neocerebellar cortex and the adjacent archicerebellar cortex. There is no associated glial cell hyperplasia, which suggests an onset in early prenatal development at a time when Bergmann's glia cells are not able to proliferate (Bauman & Kemper, 1994).

Using positron emission tomography (PET), investigators have observed alterations in serotonin synthesis in the frontal cortex and thalamus and contralateral dentate nucleus in autistic boys, suggesting that abnormalities in a dentatothalamocortical circuit may underlie the disorder (Chugani et al., 1997). Structural MRI studies have revealed abnormalities in the cerebellar vermis (Ciesielski et al., 1997; Courchesne et al., 1994; 1988; Hashimoto et al., 1993; 1995; Kates et al., 1998) and hemispheres (Murakami et al., 1989), although these reports conflict with others that have not shown these abnormalities (Garber & Ritvo, 1992; Holttum et al., 1992; Kleiman et al., 1992; Piven et al., 1997).

Over the past several years there has emerged evidence for a role of the cerebellum in cognitive function, based on observations of the effects of lesions and on functional imaging studies of adults (Allen et al., 1997; Appollonio et al., 1993; Botez et al., 1989; Fiez et al., 1992; Gao et al., 1996; Grafman et al., 1992; Kim et al., 1994; Mostofsky et al.,

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1998). Specific cognitive functions for which cerebellar contributions have been implicated include judgment of explicit time intervals and tasks involving implicit learning including classical eyeblink conditioning and visual–motor procedural learning.

Judgment of explicit time intervals is a cognitive domain for which cerebellar circuits may be critical. Ivry and colleagues have found that, compared to individuals with cerebral cortical lesions and those with Parkinson's disease, adults with cerebellar lesions perform worse on tasks involving judgment of duration (Ivry & Keele, 1989). In a PET study investigators utilized a similar task; cerebellar activation that included the vermis was observed supporting the findings of Ivry and colleagues (Jueptner et al., 1995). Judgment of duration was also found to be impaired in children and adolescents with ataxia–telangiectasia, a disorder with onset in early childhood in which the most consistent and predominant neuropathologic finding is diffuse degeneration of the Purkinje cell and granular cell layers of the cerebellar cortex (Mostofsky et al., 2000).

There is some conflicting evidence for a contribution of the basal ganglia to judgment of short-duration intervals. While Ivry did not find individuals with Parkinson's disease to be impaired in judging explicit time intervals (Ivry & Keele, 1989), another investigation of adults with Parkinson's disease revealed deficits in judgment of durations in the 50-ms range (Rammsayer & Classen, 1997). It has been proposed that the cerebellum may be critical for extracting temporal information and for learning to produce a precisely timed response whereas the frontal lobe and basal ganglia may be more important in implementing the motor response (Penhune et al., 1998) which includes holding the temporal information in working memory (Mangels et al., 1998).

The cerebellum has also been implicated in nondeclarative (implicit) learning. Lesion studies in both animals and humans have found the cerebellum to be critical for certain forms of implicit learning including classical conditioning and procedural learning (Daum et al., 1993; Lye et al., 1988; Mostofsky et al., 1999; Solomon et al., 1989; Thompson et al., 1997; Topka et al., 1993; Woodruff-Pak, 1997; Woodruff-Pak et al., 1996). Procedural learning refers to the process by which motor skills and actions are acquired through repeated exposure to a task. In contrast to declarative learning, acquisition of procedural knowledge, as reflected by improvement in performance of the task, is not linked to a conscious memory (Squire, 1986).

In studies utilizing the Serial Response Time Task (SRTT), a visual–motor procedural learning task, investigators reported adults with cerebellar lesions to be impaired in implicit learning of the sequence (Gomez-Beldarrain et al., 1998; Molinari et al., 1997; Pascual-Leone et al., 1993). In contrast, individuals with PD were not impaired (Pascual-Leone et al., 1993). Nonetheless, there is evidence from other studies supporting roles played by the basal ganglia and frontal lobes in procedural learning (Ackermann et al., 1996; Gabrieli et al., 1997; Gomez-Beldarrain et al., 1999; Saint-Cyr et al., 1988; Vakil & Herishanu-Naaman, 1998). Within the frontal lobes, the supplementary motor area (SMA) and prefrontal regions have been implicated in lesion studies (Ackermann et al., 1996; Gomez-Beldarrain et al., 1999). Investigations utilizing functional imaging have been somewhat less well sublocalized, implicating these areas as well as premotor and primary sensory motor cortices (Grafton et al., 1992; Hazeltine et al., 1997; Honda et al., 1998; Jenkins et al., 1994).

The differential roles played by the frontal lobes, basal ganglia and cerebellum (or more plausibly frontal–striatal and frontal–cerebellar circuits) in procedural learning remains unclear. Observations of dual afferent systems of climbing fibers and mossy fibers coupled with synaptic plasticity of the long-term depression type in Purkinje cells has led to the hypothesis that the cerebellum provides adaptive-learning capabilities to systems controlling motor behavior (Ito, 1990). In a review of functional imaging of procedural ("skill") learning, Doyon (1997) concluded that findings from several studies (Flament et al., 1994, 1995; Grafton et al., 1994; Seitz et al., 1994) suggest that these cerebellar systems may play a critical role in the early acquisition stages of motor and visuomotor skill learning. The findings also suggest that the *neuronal representation* (engram) of the learning is not stored in the cerebellum, but may be mediated by cerebral cortical–subcortical (basal ganglia) systems.

In another review of investigations of the cerebellum in motor skill learning, Hallett and Grafman (1997) concluded that the cerebellum appears to play a principal part in adaptation learning; while its role in skill learning is less clear, evidence from studies using the SRTT and tasks with serial finger movements suggest that the cerebellum may be critical when sequencing is important.

Based on findings from a study of rotary pursuit in patients with Parkinson's disease, Haaland et al. (1997) hypothesized that the role of the basal ganglia during procedural learning may be in planning and executing motor sequences that require switching (or selecting) among multiple motor programs. Consistent with this hypothesis are findings from a PET study utilizing the SRTT in which the time course of blood flow changes suggested that the ventral striatum is responsive to novel information (Berns et al., 1997). Alternatively, Gabrieli proposed that closed-skill loop learning involving continuous external visual feedback about movement errors is dependent upon the cerebellum. Open-loop skill learning involving the planning of movements and delayed feedback about errors is dependent upon the basal ganglia (Gabrieli et al., 1997).

In order to investigate possible cerebellar contributions to the cognitive phenotype of autism, judgment of explicit time intervals (using a task similar to the one described by Ivry) and procedural learning (using the SRTT) were studied in participants with autism and age-and-IQ-matched controls. It is recognized that cerebellar circuits may not be unique as a neural basis for these tasks; however, based on evidence for a cerebellar contribution in performance of these tasks and evidence for cerebellar abnormalities in autism, it

was hypothesized that performance on both tasks would be impaired in individuals with autism.

METHODS

Research Participants

Twenty-eight individuals participated in this study. There were 11 individuals with autism (6 male and 5 female) with a mean age of 13.3 years (range 6.8–17.8 years) and a mean full-scale IQ (FSIQ) of 101 (range 81–132). Individuals with autism were recruited as outpatients. The 17 individuals without autism (6 male and 11 female) had a mean age of 12.5 years (range 8.3–16.7 years) with a mean of FSIQ of 105 (range 80–133). For all participants with autism, diagnosis was based on DSM–IV criteria and was confirmed by a trained researcher using the Autism Diagnostic Interview (ADI; Lord et al., 1997) and the Autism Diagnostic Observational Schedule (ADOS; Lord et al., 1989). None of the participants with autism had a history of seizures and in no participant was there evidence of any other neuromedical disorder.

FSIQ was determined using the Wechsler Intelligence Scale for Children III (WISC–III) or the Wechsler Adult Intelligence Scale–Revised (WAIS–R). One of the participants with autism received only part of the WISC–III; a Performance IQ estimate of 102 was derived and used to estimate FSIQ in this case. IQ testing was not available for 5 of the control group. Of these, 3 were normal sibling controls in studies of fragile X syndrome, Turner's syndrome, and ataxia-telangiectasia. Two were normal volunteers. All of these participants had clinical histories and/or evaluations consistent with at least normal intelligence. The sibling controls in studies of Turner syndrome and ataxia-telangiectasia showed clinical profiles that were not consistent with these diagnoses; controls, including sibling controls, from studies of fragile X had genetic testing to rule out the diagnosis.

Among the participants with autism, all 11 received the SRTT; 10 received the Judgment of Timing Test. All 17 controls received both the SRTT and the Judgment of Timing Test.

Judgment of Timing

All participants were tested on a 33-MHz PC Warehouse desktop computer. Judgment of explicit time intervals was studied using a duration ("perceptual timing") task based on previous work by Ivry and Keele (Ivry & Keele, 1989). As was the case in other reported studies, a contrasting auditory perception task was included to control for the possibility of a general auditory processing deficit. In this case a judgment of pitch ("frequency perception") was used. Both tasks used a threshold procedure known as parameter estimation by sequential testing (PEST) to determine perceptual ability (Taylor & Creelman, 1967).

For the judgment of duration (perceptual timing) task, participants compared successive time intervals generated by two pairs of tones that were 73 dB, 50 ms in duration, and at a frequency of 1000 Hz. The first tones were separated by 550 ms; the second pair (presented 1 s after the first pair) were separated by a variable interval that was either longer or shorter in duration than 550 ms. Participants were asked to say "shorter" or "longer" as appropriate. (The examiner then pushed "s" on the keyboard if the participant responded "shorter" and "l" if the subject responded "longer.") For half of the trials, test intervals varied so as to estimate the lower threshold (the point at which the participant correctly responded "shorter" on approximately 90% of the trials); the remaining trials were used to estimate the higher threshold (the point at which the participant correctly responded "longer" on approximately 90% of the trials). The closer the thresholds were to the standard interval of 550 ms, the better the performance. For example, a lower threshold of 500 ms would indicate that the participant could reliably distinguish an interval of 500 ms from 550 ms; whereas, a lower threshold of 530 ms would indicate a better performance in that the participant could reliably distinguish an interval of 530 ms from 550 ms. Overall scores were based on the difference between the higher and lower thresholds, with lower scores indicating better performance.

For the control task (judgment of pitch) participants compared a test pair of tones (73 dB, 50 ms in duration, separated by 550 ms) that varied in pitch to a pair of tones with a standard pitch (1000 Hz). This task was performed in a fashion entirely analogous to the duration task described above. Participants were asked to say "higher" if the frequency of the second pair of tones was perceived as being higher than the first; they were asked to say "lower" if the frequency of the second set of tones was perceived as being lower than the first. (The examiner then pushed "h" on the keyboard if the participant responded "higher" and "l" if the participant responded "lower.") For half of the trials, the pitch of the second pair was chosen to estimate the lower threshold (the point at which the participant correctly responded "lower" on approximately 90% of the trials); the remaining trials were used to estimate the higher threshold. Scores were based on the difference between the higher and lower thresholds with lower scores indicating better performance.

Both the judgment of timing and judgment of pitch tasks were preceded by a practice session with 10 trials. Participants needed to answer correctly on at least 7 of the 10 trials before proceeding with the actual task.

Procedural Learning (Serial Response Time Task)

Procedural learning was investigated using a variation of the Serial Response Time Task (SRTT) designed by Nissen and Bullemer (1987). Participants were seated in front of a computer screen with four open circles arranged horizontally; the preferred hand responded using four buttons laid

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out in horizontal fashion, aligned with the circles on the computer screen. Each time a circle illuminated (was filled in) the participant had to press the corresponding button. The circle remained filled in until a button was pushed, upon which the next stimulus would appear after a 1500-ms delay. Each test consisted of five blocks of 80 trials. During Blocks 1 and 5, the sequence of circles was random. During Blocks 2 through 4, there was a 10-trial sequence that repeated eight times. Participants were not told about the repeating sequence. Acquisition of procedural knowledge was measured by the shortening of response time over Blocks 1 through 4 and a rebound in response time from Block 4 to Block 5. Response time was defined as the interval between the appearance of the stimulus (the circle lighting up) and the pushing of a response button.

Statistical Analyses

For the duration and frequency perception tasks, scores were not normally distributed; therefore nonparametric analyses (Mann–Whitney *U* tests) were used to compare performances between the group with autism and the controls.

For the SRTT, the shortening of response time over Blocks 1 through 4 was measured within each group using a repeated measures ANOVA. A Mann–Whitney *U* test was used to compare rebound in response time from Block 4 to Block 5 between the control group and the autism group. For all analyses, a significance level was set at $p < .05$.

RESULTS

Preliminary Analyses

There was no statistical difference in age or FSIQ between the group of individuals with autism and the control group.

Table 1. Judgment of Duration and Pitch scores in groups of participants with autism and controls

	Group			
	Autism ($n = 10$)		Control ($n = 17$)	
Score	*M*	*SD*	*M*	*SD*
Judgment of Duration ("duration score")	37.2	16.7	32.7	17.2
Judgment of Pitch ("frequency score")	3.9	3.4	4.7	5.5

Note. Differences between groups were not significant for either the judgment of duration or judgment of pitch scores.

Primary Analyses

Judgment of timing

Results for the two groups on the judgment of duration and pitch tasks are displayed in Table 1. There was no significant difference between the two groups in performance on the judgment of duration task ($p = .3$; see Figure 1) or the judgment of pitch task ($p = .9$; see Figure 2).

Procedural learning (Serial Response Time Test)

Overall, control participants were faster than participants with autism during all five blocks of trials.

As displayed in Figure 3, on the SRTT, the control participants demonstrated a significant reduction in the response time over the first four blocks of trials ($p = .0003$), whereas the participants with autism did not ($p = .7$). In addition, rebound in response time from Block 4 to Block 5

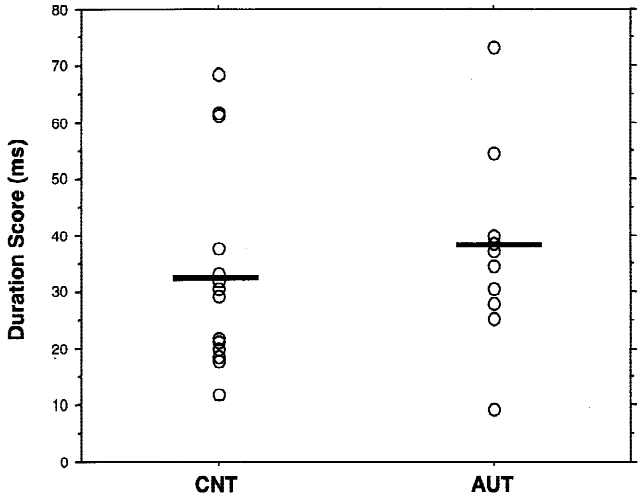

Fig. 1. Scattergram showing the distribution of scores from the judgment of duration task ("duration scores") in participants with autism (AUT) and control participants (CNT).

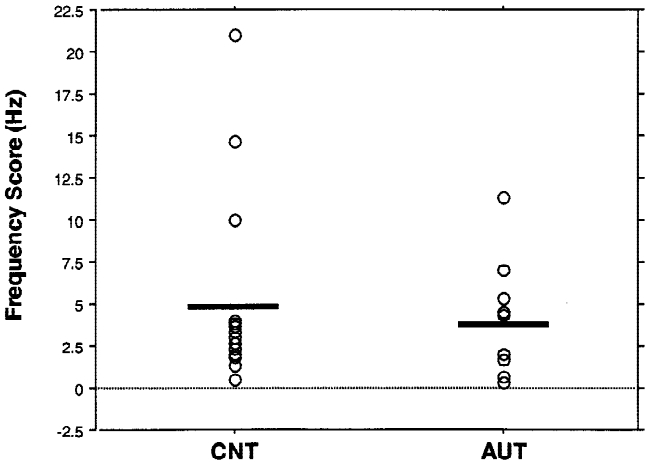

Fig. 2. Scattergram showing the distribution of scores from the judgment of pitch task ("frequency scores") in participants with autism (AUT) and control participants (CNT).

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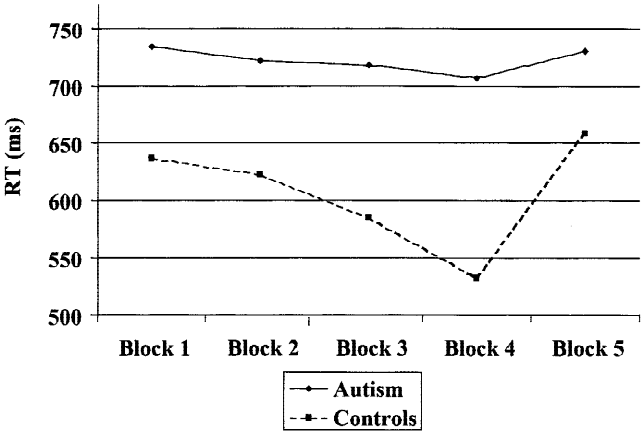

Fig. 3. Plot of the mean reaction time (milliseconds) over the five blocks of trials in the Serial Response Time Task (SRTT) in participants with autism and control participants.

was significantly greater in the control group compared with the autism group ($p = .02$).

DISCUSSION

Data from this study confirmed one of our hypotheses; participants with autism had impaired ability to acquire procedural knowledge based on a lack of significant reduction in response time over the first four blocks of trials of the SRTT and a significantly lower rebound in reaction time from Block 4 to Block 5 compared with controls. On the other hand, the participants with autism demonstrated normal ability to judge explicit time intervals.

In previous studies, acquisition of procedural knowledge on the SRTT has been shown to be impaired in adults with diffuse cerebellar degeneration and focal cerebellar lesions (Gomez-Beldarrain et al., 1998; Molinari et al., 1997; Pascual-Leone et al., 1993). Results from functional imaging studies also provide evidence that the cerebellum is one of the structures important in acquisition of procedural knowledge (Flament et al., 1994, 1995; Grafton et al., 1994; Jenkins et al., 1994; Krebs et al., 1998; Seitz et al., 1990; 1994; Seitz & Roland, 1992) and suggest that a dentatothalamocortical circuit may be critical in this process. Relevance to autism is supplied by a PET study of boys with autism in which abnormalities of serotonin uptake were found in a similar circuit involving frontal regions and the thalamus and the contralateral dentate of the cerebellum (Chugani et al., 1997).

When compared with what is known about the cerebral cortex, little is known about functional localization within the cerebellum. For competence in the judgment of time intervals, studies of individuals with cerebellar lesions have primarily implicated lateral cerebellar regions (Ivry et al., 1988); whereas, a functional imaging study using a similar task found activation in both the cerebellar vermis and lateral cerebellar regions (Jueptner et al., 1995). It may be that in autism, specific cerebellar regions are affected that result in abnormalities in procedural learning but not judgment of time intervals.

Recent PET results suggested a "supramodal" role of the cerebellum in timing, so that the role of the cerebellum in timing is not as a clock or counter but simply as the structure that provides the necessary circuitry for the sensory system to extract temporal information and for the motor system to learn to produce a precisely timed response (Penhune et al., 1998). Motor timing was not tested in our study. Considering our findings of deficits in procedural learning, it could be that deficits would be observed in motor timing, reflecting a difficulty with learning the precise motor response, but not in perceptual timing.

Alternatively, frontal lobe and basal ganglia have also been reported to be involved in procedural and other forms of implicit learning (Ackermann et al., 1996; Gabrieli et al., 1997; Gomez-Beldarrain et al., 1999; Saint-Cyr et al., 1988; Vakil & Herishanu-Naaman, 1998), so that, with respect to the SRTT, it is certainly possible that our findings could be secondary to abnormalities in frontal–striatal rather than frontal–cerebellar circuits.

When considering the probabilities as to the most fundamental level of involvement of the procedural learning circuit in autism, it may be helpful to note that there is no reported lesion in adults that results in autistic behavior. This suggests that autism is truly a *developmental* disorder. In other words, autism may not be due to a "lesion" in the brain that results in a specific skill deficit, but rather, may be due to an early lesion that impairs the ability to acquire or develop specific skills. Evidence from neuropathological examinations of individuals with autism lends support to this hypothesis. Observed cerebellar abnormalities in autism, including decreased Purkinje cell numbers, are not associated with hyperplasia of glial tissue and therefore likely occur early in prenatal development (Bauman & Kemper, 1994). Purkinje cells, through mechanisms involving long-term depression, provide the cellular mechanism necessary for learning. Purkinje cell abnormalities present early in gestation could negatively affect the capacity for motor and other forms of procedural learning during early infant development.

Several investigators have reported deficits in motor imitation and praxis in individuals with autism (DeMyer et al., 1972; Hammes & Langdell, 1981; Hertzig et al., 1989; Loveland et al., 1994; Ohta, 1987; Rogers et al., 1996; Rogers & Pennington, 1991; Sigman & Ungerer, 1984). Based on these observations, Rogers and Pennington posited that the core deficits in autism may be due to abnormalities in motor imitation, suggesting that this impeded early affective, social, and communicative development (Rogers & Pennington, 1991). Deficits in procedural learning might result in difficulty in developing or learning the sequence of motor movements necessary to perform skilled tasks, including those tasks utilized in studies in which individuals with autism were found to have deficits in motor imitation and pantomime.

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When taken in conjunction with previous findings of abnormalities in motor imitation and praxis, the findings from this study suggest that deficits in procedural learning may contribute to the core behavioral and cognitive deficits of autism. It appears that much of the behavior involved in social interaction is learned through procedural, rather than declarative, means. In addition, deficits in procedural learning might also account for the limited repertoire of motor activities observed in autism. Finally, some of the abnormalities in communication observed in autism might be accounted for by deficits in procedural learning as well. In examining the type of language deficit in many individuals with autism it appears that there is a characteristic difficulty with propositional language (e.g., a conversation) *versus* scripted, nonpropositional language (e.g., reciting the Pledge of Allegiance). Development of propositional language may depend upon procedural learning as suggested by recent connectionist (neural network) theories (Elman et al., 1996).

In conclusion, the data from this study suggest that in individuals with autism acquisition of sequential visual–motor procedural knowledge is impaired. This deficit, which may be secondary to cerebellar dysfunction, could result in impaired implicit learning of social interactions and nonpropositional forms of communication, thus contributing to autistic behavior. This study was limited by small sample size and replication with larger groups of individuals with autism will be needed to confirm this hypothesis. In addition, examination of other procedural learning tasks, such as rotary pursuit and mirror reversed tracking, will be helpful in determining whether the observed deficit is specific to sequential procedural learning tasks, such as the SRTT, or whether it is more generalized. Finally, functional imaging using the SRTT and other procedural learning tasks may be useful in showing where the brain of autistic persons may be different.

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