Pediatric Sports-Related Concussion Produces Cerebral Blood Flow Alterations
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Pediatric Sports-Related Concussion Produces Cerebral Blood Flow Alterations

WHAT’S KNOWN ON THIS SUBJECT: The pathophysiology of pediatric sports-related concussion (SRC) is largely unknown. Studies of concussed adults have identified neuronal and axonal injury and time-limited metabolic disruptions. An experimental animal model has also demonstrated physiologic perturbations, including reduced cerebral blood flow (CBF).

WHAT THIS STUDY ADDS: Using MRI techniques, we found no evidence of neuronal, axonal, or metabolic disruptions in 12 children with SRC. However, when compared with controls, statistically significant alterations in CBF were defined and frequently persisted beyond 30 days after injury.

OBJECTIVE: The pathophysiology of sports-related concussion (SRC) is incompletely understood. Human adult and experimental animal investigations have revealed structural axonal injuries, decreases in the neuronal metabolite N-acetyl aspartate, and reduced cerebral blood flow (CBF) after SRC and minor traumatic brain injury. The authors of this investigation explore these possibilities after pediatric SRC.

PATIENTS AND METHODS: Twelve children, ages 11 to 15 years, who experienced SRC were evaluated by ImPACT neurocognitive testing, T1 and susceptibility weighted MRI, diffusion tensor imaging, proton magnetic resonance spectroscopy, and phase contrast angiography at <72 hours, 14 days, and 30 days or greater after concussion. A similar number of age- and gender-matched controls were evaluated at a single time point.

RESULTS: ImPACT results confirmed statistically significant differences in initial total symptom score and reaction time between the SRC and control groups, resolving by 14 days for total symptom score and 30 days for reaction time. No evidence of structural injury was found on qualitative review of MRI. No decreases in neuronal metabolite N-acetyl aspartate or elevation of lactic acid were detected by proton magnetic resonance spectroscopy. Statistically significant alterations in CBF were documented in the SRC group, with reduction in CBF predominating (38 vs 48 mL/100 g per minute; \( P = .027 \)). Improvement toward control values occurred in only 27% of the participants at 14 days and 64% at >30 days after SRC.

CONCLUSIONS: Pediatric SRC is primarily a physiologic injury, affecting CBF significantly without evidence of measurable structural, metabolic neuronal or axonal injury. Further study of CBF mechanisms is needed to explain patterns of recovery. Pediatrics 2012;129:28–37

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KEY WORDS: concussion, pediatrics, MRI, cerebral blood flow, magnetic resonance spectroscopy

ABBREVIATIONS:
- CBF—cerebral blood flow
- Cr—creatinine and phosphocreatine
- CT—computed tomography
- DTI—diffusion tensor imaging
- °H-MRS—proton magnetic resonance spectroscopy
- LA—lactic acid
- MR-PCA—magnetic resonance phase contrast angiography
- MRS—magnetic resonance spectroscopy
- NAA—N-acetyl aspartate
- RT—reaction time
- SRC—sports-related concussion
- SWI—susceptibility weighted imaging
- TBI—traumatic brain injury
- TSS—total symptom score

The authors of this work met the following criteria for authorship: Drs Maugans, Farley, Altaye, Leach, and Cecil contributed substantially to the conception and design, acquisition of data, and analysis and interpretation of the data. Drs Maugans and Cecil drafted the article and revised it critically for important intellectual content. Dr Maugans approved the final version to be published.

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Funded by the National Institutes of Health (NIH).
Pediatric sports-related concussion (SRC) is an important individual and public-health issue.1–7 Despite its high incidence, the pathophysiology of SRC is not well understood. Symptoms and neuropsychological alterations of SRC have been well characterized8–19; however, the biological substrate has been studied limitedly, largely in adults and focusing on structural injury patterns.20–25 Physiologic perturbations detected in the concussed rodent brain26 include altered neurotransmitters and ions, production of lactic acid (LA), and reduction in cerebral blood flow (CBF). Although most abnormalities resolved within minutes to hours, CBF remained altered for >1 week postinjury.

In this preliminary investigation, we examined the pediatric brain for structural and metabolic alterations associated with SRC. Through a prospective, case-control approach using MRI methodologies, we examined brain structure, selected metabolite alterations, and total CBF in a small group of children who experienced SRC. We hypothesized that (1) structural changes detected by diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) techniques are minimal; (2) time-limited reductions in N-acetyl aspartate (NAA) concentrations by proton magnetic resonance spectroscopy (1H-MRS) occur as demonstrated in three adult SRC studies27–29; and (3) CBF values determined by magnetic resonance phase contrast angiography (MR-PCA) are reduced immediately after SRC with improvement to control levels within a 14-day follow-up, analogous to an experimental animal model.26

**PATIENTS AND METHODS**

**Study Approval**
The study protocol was reviewed and approved by the institutional review board of the Cincinnati Children’s Hospital Medical Center. Parents completed informed consent procedures upon referral to the study. Participants provided assent before study procedures.

**Participants**
The concussed group comprised children between the ages of 11 and 17 years who had sustained a single concussion during participation in an organized athletic event. Recruitment occurred through a referral network of certified athletic trainers, sports medicine physicians, and emergency departments. The diagnosis of concussion was made by a single licensed healthcare professional, using the definition advanced by the consensus group of the Third International Conference on Concussion in Sport held in Zurich, November 2008.30 Exclusion criteria included other injuries, focal neurologic deficits, pathology on clinical neuroimaging, or use of prescription medications for neurologic or psychiatric illness. A healthy control population matched by age and gender was recruited after enrollment of the concussed participants.

Each concussed participant underwent ImPACT (ImPACT Applications, Inc, Pittsburgh, PA) neurocognitive testing and MRI investigations at 72 hours or less, 14 days, and 30 days or more days postconcussion (Fig 1). Exact timing of the final testing session was predicated upon symptom resolution, return to normal physical activity, and logistics of scheduling the studies. An identical series of examinations were performed on the control group during a single session.

**Neurocognitive Assessment**
ImPACT was employed to quantify SRC and to assess clinical recovery. The standard online test (version released in 2007) was administered to all study participants.

**Image Acquisitions, Data Processing, and Analyses**
A Philips 3T Achieva (Philips Medical Systems, Cleveland, OH) magnetic resonance system with an eight-channel phased array head coil was used to acquire T1-weighted anatomic images, SWI, DTI, single-voxel 1H-MRS (three regions of interest: anterior cingulate gyrus, left dorsolateral prefrontal white matter, and left thalamus), and MR-PCA studies. DTI studio31 was used for evaluations of the genu, splenium and body of the corpus callosum, and anterior and posterior limbs of the bilateral internal capsules. 1H-MRS data were processed quantitatively (concentration levels using LCModel, Guelph, Ontario, Canada) and semiquantitatively (ratios using Philips scanner software, Cleveland, Ohio), assessing NAA, creatine (Cr), and...
choline, and LA. CBF data were determined by quantitative flow (Q-FLOW) software (Philips Medical Systems), adjusted for brain volume for each participant. Detailed protocols are described in the Supplemental information.

The data were reviewed and analyzed by participant case number, without knowledge of clinical factors including concussion history.

**Statistical Analysis**

A power analysis based on previous magnetic resonance spectroscopy (MRS) studies of traumatic brain injury (TBI) and psychiatric disorders conducted in our laboratory indicated that a sample size of 12 participants per group would show statistical significant differences between concussed and control groups. Vagnozzi et al. demonstrated statistically significant H-MRS results in 13 adults with SRC and five control participants.

All analyses were performed by using the SAS system (version 9.2, SAS Institute, Cary, NC). Comparisons between concussed and carefully matched control participants were examined by paired t-test or a Wilcoxon signed rank test, depending on the distribution of the outcome measure considered. Temporal data were examined by paired t test. Correlations between total CBF values and total symptom score (TSS) and reaction time (RT) were examined by using Spearman rank correlation. A P value <0.05 was considered significant.

**RESULTS**

The concussion group comprised nine boys and three girls, ages between 11 and 15 years. Nine patients completed studies at all three time points. Three patients completed studies at the first two time points only. One patient did not complete a third testing session due to severe postconcussion symptoms requiring medical attention. Two participants did not respond to invitations to

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<th>Gender</th>
<th>Weight, kg</th>
<th>Number of Previous Concussions</th>
<th>Loss of Consciousness, Days</th>
<th>Sport</th>
<th>Time Postconcussion to First Testing Session</th>
<th>Initial TSS</th>
<th>Control Initial RT Composite Score</th>
<th>Final TSS</th>
<th>Control Final RT Composite Score</th>
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<td>0.64</td>
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**TABLE 1** Characteristics of SRC Participants With Control Comparisons

**Downloaded from pediatrics.aappublications.org by guest on February 9, 2013**
arrange a final follow-up visit. Twelve age- and gender-matched controls completed testing. One control underwent two testing sessions to serve as an internal control for the testing methodologies. Table 1 summarizes the concussed participants and presents RT composite scores and TSSs from ImPACT testing for each concussed participant and his or her appropriate age- and gender-matched control.

**Clinical Assessment**

Two participants experienced loss of consciousness. Three participants had previous SRCs, all more than 12 months prior. One child experienced very brief (minutes) transient quadraparesis followed by severe concussive symptoms (confusion, severe headache, and vomiting). He underwent emergency MRI of the brain, spinal cord, and cervical vessels. These studies were normal, effectively ruling out structural spinal cord or brainstem injuries and cerebral arterial dissections. Within the concussed group, mean arterial blood pressure was normal in all participants at the time of enrollment (mean = 84 mm Hg; SD = 2.1).

**ImPACT Testing**

Table 2 presents ImPACT TSS and RT for each concussed participant and his or her appropriate age- and gender-matched control.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Session</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
<th>P*</th>
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<td>SRC</td>
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<td>27.83</td>
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<td>SRC</td>
<td>2</td>
<td>11.17</td>
<td>4.41</td>
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<td>3.78</td>
<td>1.24</td>
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<td>0.03</td>
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<td>0.0580</td>
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<tr>
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<td>0.02</td>
<td>12</td>
<td>0.13</td>
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</tbody>
</table>

* Paired t-test result comparing SRC to control groups.

Initial postinjury RT composite scores were significantly higher (connoting longer RTs during timed tests) in the concussed group (mean = 0.73 seconds versus 0.59 seconds; \( P = 0.0049 \)), persisted at 14 days after injury (mean = 0.68 vs 0.59; \( P = 0.25 \)), and reached control levels by the final testing session (mean = 0.66 vs 0.59; \( P = 0.58 \)). Additional univariate and multivariate analyses did not reveal statistically significant differences between the concussed and control groups for other subtests (verbal memory, visual memory, visual motor speed, or impulse control).

**DTI**

There were no significant differences in the diffusion metrics (fractional anisotropy, trace, axial diffusivity, and radial diffusivity) over time for any of the regions of interest (bilateral anterior limb of the internal capsule [ALIC] and posterior limb of the internal capsule [PLIC], genu, body and splenium of the corpus callosum) in the concussed patient group. There were no group differences in the diffusion metrics for any region of interest at the initial study time-point comparing the concussed with the control participants.

**1H-MRS**

Quantitative and semiquantitative analyses of the 1H-MRS data revealed no significant changes in the concentration of NAA or NAA:Cr ratio levels for three regions sampled over time for the concussed participants (see Tables 3 and 4). There were no group-related differences when comparing the initial study time-point concentration of NAA or NAA:Cr ratio levels for the SRC and control participants. No elevated LA levels were demonstrated in the SRC participants.

**CBF**

Detailed CBF values for the SRC and controls participants are presented in Table 5. The CBF values for Participant 8 were excluded from the analysis due to gross motion during the data acquisition for CBF determination. On the initial postinjury study, statistically significant differences in mean total CBF values were demonstrated between the two groups (38.0 mL/100 g per minute concussed versus 48.0 mL/100 g per minute control; \( P = 0.0274 \)). All but one concussed participant demonstrated...
The 2 youngest concussed participants demonstrated increased immediate postinjury CBF values compared with matched control value. Nine participants demonstrated decreased immediate postinjury CBF values versus control mean (mean difference = 20.9 mL/100 g per minute). Average difference in initial postinjury CBF values versus control mean was 21% with a maximum of 60% (Participant 4).

Three (27%) concussed participants reached CBF values of ±10% of their matched control at 14 days after injury, whereas seven (64%) concussed participants did so by time for final follow-up. However, when comparing the two groups, a statistically significant difference in CBF values persisted at final testing (mean = 39.2 vs 48.0; \( P = .019 \)).

Participant 4 demonstrated the lowest CBF value and the most dramatic clinical presentation: transient quadriparesis and severe concussive symptoms. His CBF value of 19 mL/100 g per minute and was based on low flow through the basilar and left internal carotid arteries.

**Correlation Analyses**

No statistically significant correlations between CBF and ImPACT scores were demonstrated in this small sample. The Spearman correlation coefficient between TSS and total CBF for the whole sample (ie, both case and control at all-time points) was –0.08 (\( P = .59 \)) and –0.07 (\( P = .64 \)) between RT and total CBF.

**DISCUSSION**

Defining the pathophysiology of pediatric SRC is paramount, given the high incidence of this injury,1–6,40 considerable recent lay press attention, and the potential for short- and long-term impact on health and well-being.13,16,41–47

To study similarities and differences between pediatric and adult SRC, we evaluated a small cohort of children with SRC and healthy controls, using ImPACT neurocognitive testing and MRI measures of brain structure, metabolism, organization, and blood flow. Based on the findings of previous investigations, we hypothesized that (1) structural changes would be minimal by conventional MRI with DTI and SWI; (2) \(^1\)H-MRS would demonstrate a time-limited reduction in NAA and absence of lactate; and (3) CBF would be reduced immediately after SRC with improvement to control levels by 14-day follow-up.

Using TSS and RT composite data, ImPACT testing results substantiated the clinical diagnosis of SRC in our study group. This well-validated software program has become a prevalent tool used in the diagnosis and management of SRC in the youth, scholastic, collegiate, and professional sporting worlds. It has also emerged as an important research tool.8,10,12,14,48–50 Our concussed children responded similar to many previous reports in the literature, with significant symptom reduction in the first 2 weeks after concussion.2,14,15,19,47,51–56

As predicted, we did not demonstrate findings of gross structural injury by anatomic MRI, DTI, or SWI.20–25 Although others have demonstrated such injury patterns in adults after SRC,20,22,23,25 it is possible that the mechanisms of injury (head to head, body to head, or head to ground) and the different energy and forces (related to body mass and velocity) involved in pediatric SRC would make it less likely that major structural injury would occur. Although the pathogenesis of chronic post-traumatic encephalopathy has yet to be fully elucidated, our findings suggest that a single pediatric SRC does not produce structural injury that may represent a substrate for development of this devastating condition.57–80

Analysis of the \(^1\)H MRS data revealed incomplete support of our hypotheses. As expected, we did not observe elevated LA in any of the SRC participants, consistent with the MRI findings suggesting a mild pattern of trauma. Surprisingly, the data did not support our hypothesis of an expected decrease in NAA. We did not identify significant differences in
NAA concentrations or ratios when comparing concussed participants, individually or as a group, to matched controls. This differs from work of Vagnnozzi et al\textsuperscript{28} who examined 13 adult athletes with SRC, demonstrating an 18.5% reduction in NAA:Cr ratio values compared with control values at 3 days after injury, persistent at 15 days after injury (despite symptom resolution), and returning to control values by 30 days. In an expanded study, the same group\textsuperscript{27} demonstrated identical findings in 40 concussed older adolescent and adult athletes, proposing that a reduction in NAA concentration by MRS is a robust “noninvasive biomarker” of the metabolic injury inflicted during concussion.

We believe that our negative findings may represent an important difference between adult and pediatric SRC pathophysiology. There were no known technical limitations that prevented an accurate acquisition and analysis of \textsuperscript{1}H-MRS data in the concussed population, led by an expert magnetic resonance spectroscopist (Dr Cecil) with extensive experience using this methodology to study central nervous system pathologies, including TBI.\textsuperscript{32–37,61–69}

Our third hypothesis, pertaining to time-limited alterations in total CBF, was also partially supported by the data. As predicted, we observed CBF differences >10% of matched control values in all but one of our concussed participants immediately after injury. Comparing the SRC and control groups’ mean CBF values, a statistically significant difference was also demonstrated. Regarding our hypothesis that resolution would occur within 2 weeks, however, we found that only 27% of the participants recovered to within 10% of control mean CBF at the 2-week post-injury evaluation point, and 64% by final testing 30 days or more after injury.

The dominant pattern of initial alteration in CBF after concussion was decreased values compared with individually matched and group control values. Decreased CBF has been noted in several adult\textsuperscript{71–81} and pediatric\textsuperscript{82–85} TBI studies and shows a strong correlation with poorer outcomes; however, these studies have focused largely on adults with moderate and severe injuries. No published investigations have described quantitative CBF values in concussed children.

The pathophysiologic mechanisms of decreased CBF after TBI have not been fully elucidated. Possibilities include alterations in cerebral autoregulation, reduction of large artery caliber (ie, vasospasm), or extensive regional perfusion perturbations.\textsuperscript{72,75,81,86–90} Although loss of autoregulation (during which reduced CBF becomes dependent on mean blood pressure) was observed in 2 of 10 patients with mild TBI in a previous investigation,\textsuperscript{91} we did not observe altered mean blood pressure in any of our patients. Based on the methodology we employed for determining CBF by using phase contrast angiography data, the calibers of the internal carotid and basilar vessels were influential. Therefore, alteration in arterial tone that affects caliber and vascular capacity is a possible pathophysiological mechanism worthy of further investigation. Alterations in regional blood flow after SRC have been demonstrated by using functional MRI techniques\textsuperscript{92–94}; however, the combination of large regional blood flow alterations with total CBF impairment has not been demonstrated. This represents another hypothesis that could be tested by using arterial spin labeling MRI techniques.

Regardless of its etiology, we believe that altered CBF contributes to SRC-related symptom generation and altered neurologic and neuropsychiatric function as measured by ImPACT testing. One concussed study participant strongly supports this concept. After a violent takedown, a 13-year-old male wrestler presented with several minutes of dense quadriaparesis and protracted severe symptomatology of concussion. At 26 hours after injury, CBF was assessed at 19 mL/100 g per minute presenting a 60% reduction from mean control values, placing the patient into the range of cerebral ischemia.\textsuperscript{71} He had markedly diminished flow through his basilar and left internal carotid arteries. It is possible that reduced blood flow through the posterior circulation created the transient quadriaparesis. At 2 weeks after injury, his CBF value improved by 50% but remained 35% below control mean value. He remained extremely symptomatic and exited the study for medical treatment.

Not all subjects evidenced reduced CBF values. The youngest two concussed children, 11 and 12 years of age, presented with the highest initial CBF values, averaging 28% above the mean control CBF value and above their individual controls. Although little can be concluded from such a small number of subjects, one hypothesis worthy of exploration is that initial hyperemia is a CBF-alteration pattern in younger children. Certainly symptoms
CBF perturbations have been identified as a protracted timeframe for resolution. CBF values with a variable and possibly physiologic process resulting in altered physiologic activity, or experiences a second SRC, symptoms and neuropsychological testing deficits frequently worsen. Investigators have demonstrated measurable biological indicators of this vulnerability in animals and human adults. Furthermore, catastrophic outcomes such as the second impact syndrome (death resulting after a second concussive type injury) have been attributed to probable loss of cerebral autoregulation. Therefore, our results reinforce the concept that a protracted state of physiologic abnormality exists for some young athletes. This substantiates the need for further investigations and circumpect management of the concussed pediatric athlete. These data also have important implications for the management of pediatric SRC. Many medications presently prescribed for severe postconcussive symptoms have known effects on CBF, including stimulants, β blockers, calcium channel blockers, and triptans. Additionally, the prescription of “cognitive rest” has become commonplace and is based on the concept of reducing cerebral metabolic demand. In patients with reduced CBF, this strategy is physiologically sound.

Taken together, these CBF data suggest that pediatric SRC produces a pathophysiologic process resulting in altered CBF values with a variable and possibly protracted timeframe for resolution. CBF perturbations have been identified in experimental models as the cause of a “metabolic mismatch” between supply and demand for oxygen and glucose. Neurons under such a state of physiologic stress function abnormally and become more susceptible to secondary injury. Considerable clinical evidence suggests a period of vulnerability after SRC, even after symptom resolution. If a concussed child returns too quickly to strenuous physical activity or experiences a second SRC, symptoms and neuropsychological testing deficits frequently worsen. Investigators have demonstrated measurable biological indicators of this vulnerability in animals and human adults. Furthermore, catastrophic outcomes such as the second impact syndrome (death resulting after a second concussive type injury) have been attributed to probable loss of cerebral autoregulation. Therefore, our results reinforce the concept that a protracted state of physiologic abnormality exists for some young athletes. This substantiates the need for further investigations and circumpect management of the concussed pediatric athlete. These data also have important implications for the management of pediatric SRC. Many medications presently prescribed for severe postconcussive symptoms have known effects on CBF, including stimulants, β blockers, calcium channel blockers, and triptans. Additionally, the prescription of “cognitive rest” has become commonplace and is based on the concept of reducing cerebral metabolic demand. In patients with reduced CBF, this strategy is physiologically sound.

A small sample size and confined follow-up period are the primary limitations of this preliminary investigation. Recruitment occurred from many organizations and scholastic institutions making it impossible to acquire baseline (preinjury) ImPACT and imaging studies. Three participants completed only two postinjury evaluations, limiting the later-recovery period CBF data set available for analysis. We also had two outliers that require discussion. Participant number 8 reported an extremely high TSS. He had previously sustained a SRC, which may have increased his sensitivity to concussion symptoms; however, his first SRC occurred more than 1 year before, making it difficult for us to assert a plausible biological mechanism that connects these two events. Alternately, he may have simply felt “severely” symptomatic, since the TSS Likert scales are entirely subjective.

Participant number 6 had a long interval between her second and third testing sessions. She was an early enrollee but was not successfully recruited back for her final visit until late in the study due to logistical factors. For this reason, we did not include her data in the calculation of mean follow-up interval presented in Table 5. Finally, it is acknowledged that ImPACT represents one of many validated commercially available tools for the assessment of concussion. Our decision to use this tool does not imply its superiority in the evaluation and management of SRC.

Future investigations should enroll larger numbers of participants, followed for longer periods of time, and stratify by age over a broader range. Single versus repeat SRC events require investigation as well.

CONCLUSIONS

Our investigation suggests that a single pediatric SRC produces a state of physiologic disruption rather than structural or metabolic injury. In a small group of children, we demonstrated no evidence of structural or metabolic injury by MRI and 1H-MRS, differing from investigations of adult SRC. Statistically significant alterations in CBF values were observed, with reduced CBF values predominating. Despite evidence of clinical improvement by ImPACT testing, recovery toward CBF control values was temporally variable, extending in 36% of participants beyond 30 days after injury. Although larger investigations conducted over longer time periods are required, our findings suggest an important role of CBF alterations in the pathophysiology of pediatric SRC.

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REFERENCES


37. Cecil KM, Lenkinski RE, Gur RE, Gur RC. Proton magnetic resonance spectroscopy in the frontal and temporal lobes of neurolologic naive patients with schizophrenia.


Hlatky R, Contant CF, Diaz-Marchan P, Valadka AB, Robertson CS. Significance of...
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*Pediatrics* 2012;129;28; originally published online November 30, 2011;
DOI: 10.1542/peds.2011-2083

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