Original Research

Effect of Concussion on Reaction Time and Neurocognitive Factors: Implications for Subsequent Lower Extremity Injury

Tyler Ray[1 a], Daniel Fleming[1], Daniel Le[2], Mallory Faherty[3], Carolyn Killelea[3], Jeffrey Bytomski[3], Tracy Ray[4], Larry Lemak[5], Corina Martinez[3], Michael F. Bergeron[6], Timothy Sell[7]

[1] Duke Doctor of Physical Therapy Program, [2] Michael W. Krzyzewski Human Performance Lab, Department of Orthopedic Surgery, Duke University Medical Center, [3] Department of Orthopedic Surgery, Duke University, [4] Piedmont Orthopedic Sports Medicine, [5] Lemak Sports Medicine, [6] WTA Performance Health and Sport Sciences & Medicine, WTA Women's Tennis Association, [7] Atrium Health Musculoskeletal Institute

Keywords: athletic injuries, injury prevention, postural balance, sport injuries

https://doi.org/10.26603/001c.36648

International Journal of Sports Physical Therapy

Vol. 17, Issue 5, 2022

Background

Recent evidence has demonstrated that athletes are at greater risk for a lower extremity injury following a return-to-sport (RTS) after sport-related concussion (SRC). The reason for this is not completely clear, but it has been hypothesized that persistent deficits in neurocognitive factors may be a contributing factor.

Hypothesis/Purpose

This study assessed simple reaction time, processing speed, attention, and concentration in a group of athletes, post-concussion upon clearance for RTS for potential deficits that may result in slower reaction time, processing speed, attention, and concentration. The researchers hypothesized that the concussion group would demonstrate worse scores on both assessments compared to a sex-, age-, and sport-matched cohort.

Study Design

Case-controlled study

Methods

Twelve participants who had suffered a SRC and eight healthy individuals who were matched to the concussed group by age, sex, and sport were evaluated. Those with a concussion had been cleared for RTS by a licensed healthcare provider. Each participant underwent neurocognitive tests that included a simple reaction time test (SRT) and the King-Devick Test (K-D). Independent t-tests were performed to compare the groups with significance set a priori at $p<0.05$.

Results

There was a significant difference ($p = 0.024$) between groups for SRT with the concussed group demonstrating a better SRT than the control group. There were no significant differences ($p = 0.939$) between the groups for the K-D.

Conclusion

With no significant differences between groups in the K-D assessment and, surprisingly, the concussed group having a better SRT compared to the healthy group, our hypothesis was not supported.

a **Corresponding author:**
Tyler Ray, PT, DPT, CSCS.
Duke Doctor of Physical Therapy Program, Durham NC, USA
434-660-7748
raytw30@gmail.com

Clinical Relevance

These specific measures, compounded with extensive post-concussion time lapse until RTS clearance, may have limited capacity in revealing potential persistent deficits in relevant neurocognitive characteristics.

Level of Evidence

Level of Evidence 3

INTRODUCTION

Sport-related concussions (SRC) continue to be a rising and prominent global concern in contact and non-contact related sports, especially in youth. According to the 2017 Youth Risk Behavior Survey (YRBS) conducted by the Centers for Disease Control and Prevention (CDC), out of all the student athletes in the United States (U.S.), "15.1% of students (about 2.5 million) reported having at least one concussion related to sports or physical activity, and 6% reported having two or more (about 1 million students)."[1] In a study across 20 high school sports during the 2013-2014 to 2017-2018 school years, 9,542 concussions were reported for an overall rate of 4.17 per 10,000 athlete exposures (AE) (95% CI: 4.09 to 4.26). In this sample, 64% occurred during competition and the rest during practice.[2]

Recent evidence suggests that athletes who have suffered a concussion may be at a greater risk for a lower extremity (LE) injury following a return to sport (RTS). The association between increased instantaneous relative risk of LE injury in the 365 days after incurring a concussion in Division I college athletes has been demonstrated across 15 sports.[3] In a military population, a greater risk of musculoskeletal (MSK) injury post-concussion was demonstrated in U.S. Army soldiers, which remained elevated for more than a year.[4] This has been corroborated in a recent systematic review indicating that athletes who had a concussion had two times greater odds of sustaining a MSK injury than athletes without having incurred a concussion (OR, 2.11; 95% CI, 1.46 -3.06).[5] Whereas there may be observed differences in gait strategy, this study and others suggest than an underlying prominent contributing factor may be persistent deficits in neurocognitive factors.[6,7]

Impaired neuromuscular control in these post-concussion scenarios may be evidenced through deficits in cognitive performance, including via measured reaction time, processing speed, and verbal and visual memory.[8] As a diagnostic tool, the King Devick (K-D) test has been successfully utilized in detecting SRC.[9] The K-D test may also be effective in identifying witnessed and unwitnessed episodes of SRC in youth sports, as demonstrated in junior rugby over continuous seasons.[10] Additionally, because K-D test performance may be influenced by attention, concentration, reaction time, and processing speed, it may provide valid insight to these same overlapping domains that can inhibit an athlete's neuromuscular control.[11] A test of simple reaction time (SRT) has also been utilized in those who have suffered a concussion, with this straightforward metric of clinical reaction time (RT_{clin}) showing close alignment and validity to computerized measured reaction time (RT_{comp}) in athletes.[12] Clinical reaction time (RT_{clin}) also reveals an athlete's ability to protect one's head in a lab-simulated athletic environment demonstrating functional relevance.[13] Notably, prolonged reaction time is one of the most sensitive indicators of neurocognitive change following concussive injury, and thus this utility is incorporated in many concussion evaluation instruments.[14] For example, simple reaction time (SRT) is a featured metric in the Automated Neuropsychological Assessment Metrics (ANAM) commonly used to evaluate concussions in the U.S. military.[15] In military cadets recovering from a concussion, a prolonged increase in SRT did not return to baseline upon return to active duty.[16] Further practical benefits of the K-D and RT_{clin} include being able to administer these uncomplicated tests to a large group of athletes in a comparatively small amount of allotted time with minimal cost and no requirement for highly trained and certified testers. Accordingly, the convenient, practical, and valid K-D and RT_{clin} tests were utilized for this study to measure reaction time and indirectly reveal potential deficits in attention, concentration, and processing speed as potential contributing factors that can hinder neuromuscular control in a post-concussion population, thus leading to higher risk of LE injury. These observed changes in neuromuscular control and MSK injury risk challenge physicians and other providers when attempting to screen post-concussion patients easily and effectively and identify when athletes are ready to return to sport.

The evident connection between SRCs and the subsequent impact on musculoskeletal injury risk underscores a practical clinical concern regarding athletic readiness and the decision to clear an athlete for RTS – competition and/or training. Therefore, the present study assessed simple reaction time, processing speed, attention, and concentration in a group of athletes, post-concussion upon clearance for RTS for potential deficits that may result in slower reaction time, processing speed, attention, and concentration. The purpose of this research was to examine the effects of SRC on neurocognitive and neuromuscular performance by utilizing the K-D test and a simple reaction time assessment after clearance for RTS. The researchers hypothesized that the concussion group would demonstrate measurable deficits on both assessments compared to a sex-, age-, and sport-matched healthy cohort. These findings should provide new perspective into the relationship between concussion and LE MSK injury and the utility of these two assessments during RTS decision-making which may help provide additional tools for clinicians who must assess clinical readiness for safe RTS. The practical utility of these readily accessible, easily assessable, and cost-effective neurocognitive and reaction time metrics could also be instrumental in screening and identifying athletes who are more likely to experience a LE MSK injury following a SRC.

METHODS

PARTICIPANTS

Twelve participants (7 boys, 5 girls; age: 16.1 ± 1.4 years; height: 172.3 ± 11.3 cm; weight: 65.7 ± 15.3 kg) who had suffered a sports-related concussion and eight healthy (no concussion history) individuals (4 boys, 4 girls; age: 16.5 ± 2.1 years; height: 172.2 ± 10.9 cm; weight: 67.9 ± 15.4 kg) were matched by age, sex, and sport. Participants were voluntarily recruited through the university's concussion clinic. Each participant had been cleared for RTS (60.9 ± 54.0 days following concussion) by a licensed healthcare provider. The evaluated subjects played a range of sports including soccer, basketball, volleyball, and football. Each subject under the age of 18 required a parent's or guardian's informed voluntary assent to enroll in the study. Subjects at or over the age of 18 signed a written informed voluntary consent form as well. The study protocol and consent forms utilized in this study were approved through Duke University Office of Research Support Institutional Review Board committee. Individuals who reported a history of surgery or any injury (concussions excluded for the concussion group) within the prior six months were excluded from the study. Each subject underwent neurocognitive tests that included a King-Devick Test (K-D) and simple reaction time test (SRT).

KING-DEVICK ASSESSMENT

The King-Devick assessment (K-D) is a timed rapid number naming assessment that assesses saccadic eye movements, attention, and processing speed. In a large sample of collegiate athletes across 16 sports, the K-D test was reliable from trial to trial (ICC=0.888) and when taking the test between years (ICC=0.827).[17] Furthermore, the test can help in assessing ocular and cognitive effects of concussion. After being cleared for RTS by a licensed healthcare provider, each subject was scheduled for testing individually. The K-D test was given to each individual study participant to challenge the athlete's attention and eye movement in a rapid manner. Each participant was given standardized instructions and asked to read aloud a series of single-digit numbers from left to right on three test cards. The participant was then given one demonstration card for practice, followed by the three test cards that were used for recording scores. The three tests became progressively more challenging as testing continued. Targets on test card 1 are separated with guide lines. On test card 2, these guide lines are removed, and the numbers are spread out; and, on card 3, vertical crowding of number targets occurs.[18] Before reading from left to right as quickly as possible, each participant was informed to read as fast as possible without making any mistakes. The participants were also informed that they could go back and correct any mistake. If this was done, the error was not recorded. The amount of time to read from the three test cards and the number of errors made while reading were recorded by a member of the study team. The test administrator had an answer sheet during the test to catch any errors. This test was repeated a second time and an average of the two trials was calculated.

REACTION TIME

Clinical Reaction Time (RT_{clin}) was measured by having participants attempt to grasp a falling small apparatus as quickly as possible. The participant sat with his or her non-dominant forearm resting on a table and with the dominant hand held over the table's edge in an open position. An examiner held the apparatus (80-cm inflexible stick wrapped in friction tape attached to a rubber disc) directly above the participant's outstretched, dominant hand. The participant's dominant hand enclosed the rubber disc without touching it while the attached stick portion was held vertically above the rubber disc lying perpendicular to the plane of the outstretched hand. After waiting a preset delay time of two to five seconds, the examiner released the stick and the participant then tried to catch it as quickly as possible by closing his or her dominant hand around the rubber disc. After each trial, an RT_{clin} value reported in milliseconds (ms) was calculated, using the formula for a falling body affected by gravity or d=0.5gt. The distance the device fell measured in centimeters was utilized in the formula for d and used to calculate the reaction time or *t* for each individual trail. A total of eight trials were collected and scores averaged.

STATISTICAL ANALYSIS

Descriptive data including means, minima, maxima, and standard deviations were calculated for all variables. Normality of both variables were assessed utilizing a Shapiro-Wilk test. A two-sample Wilcoxon rank-sum test was used to examine differences between the two groups if data did not demonstrate a normal distribution. Independent t-tests were utilized to examine group differences when the data were normally distributed. Significance was set *a priori* at p<0.05 for all statistical tests. All statistics and analyses were performed with Stata Statistics Data/Data Analysis software (version 14.2, StataCorp, College Station, TX).

RESULTS

Descriptive statistics for the key outcome metrics are presented in Table 1. The results of the Shapiro-Wilk assessment of normality indicated that SRT was normally distributed; whereas the K-D scores were not normally distributed. The statistical significance of the group comparisons is also presented in Table 1. There was a significant difference (*p*=0.024) in SRT between groups with the concussed group (14.6 ± 4.2 cm) demonstrating a better SRT than the control group (18.7 ± 2.5 cm). No difference (*p*= 0.939) was observed between groups for the K-D test (concussed = 46.7 ± 18.2 seconds; healthy = 43.8 ± 6.6 seconds).

DISCUSSION

This study provides new perspective into the relationship between concussion and LE MSK injury risk and the practical utility of these two simple oculomotor and reaction time assessments during RTS decision-making. Notably, average K-D time among the concussed population was a little

Table 1. Key Metrics and Group Comparisons

	Concussed			Healthy			p-value
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	
Simple Reaction Time (seconds)	14.6 (4.2)	6.10	19.80	18.7 (2.5)	15.0	22.8	0.024
King-Devick (seconds)	46.7 (18.2)	22.70	98.50	43.8 (6.6)	34.2	52.5	0.939

slower compared to the healthy group, but not statistically significant. This suggests possible lingering oculomotor and related neurocognitive deficits post-concussion, even after being cleared for RTS, which can arguably bias affected athletes to a potential greater LE injury risk. However, with no distinctive between-group differences in K-D and SRT values (in fact, the concussed group had a better SRT compared to the healthy group), the hypothesis was not supported. Accordingly, any (if they existed) lingering oculomotor and related neurocognitive deficits and/or poorer reaction time following a SRC after being cleared for RTS were either resolved or were not detectable using these tests.

The lack of difference between the two groups in K-D scores may be attributable to the extensive time elapsed between concussion and clearance for RTS which was, on average, two months following the concussion. In a national database of high school athletes, the average time for concussion symptoms to resolve was seven days or less with, generally, an additional 8-11 days before RTS; whereas when the recovery period was 14 or 28 days, the affected athletes tended to RTS almost immediately after their symptoms were no longer present.[19] Moreover, these specific measures in our study may not be sensitive and/or specific enough to reveal other potential persistent deficits in neurocognitive capacities that may place an individual at greater risk for MSK injury following RTS. Previous literature has supported recent concussion being related to risk of LE injury in an athletic population.[3,8,20,21] However, the proposed contributing factors for greater LE injury risk included potential neuromuscular control deficits, postural control being altered, or general LE stiffness which would be beyond the expected capability of our SRT or K-D tests to reveal.[21–23] Although, to date, the addressable clinical features aligned with these proposed LE injury risk contributing factors remain unclear.

Whereas clinicians typically utilize a broad array of neurocognitive test batteries to assess SRC patients, we chose to measure the expected lingering neurocognitive effects post-concussion with SRT and the K-D test, because of their ease of administration, quick results, and overall cost effectiveness. K-D has also been utilized to identify athletes without traditional symptoms of concussion.[24,25] Poor oculomotor function caused by concussion is one of the strongest predictors of mild traumatic brain injury present within 65-90% of patients experiencing some form of mild traumatic brain injury.[25] This prolonged RT is one of the most common signs post-concussion. Accordingly, RT is featured as a component in nearly all computerized neurocognitive test battery assessments for concussion, because of its high sensitivity for detecting concussion. Whereas RT is measured through a computerized application in most of these assessments, there is supporting evidence in the ability of our manual SRT to differentiate between concussed and non-concussed athletes and to determine a concussed athlete's level of recovery by cognitive RT.[26–28] Previous findings also indicate that post-concussion SRT assessments consisting of simple finger or hand movement in a static setting do not accurately assess functional, sport-like reaction time needed for optimal and safe sport performance.[29]

Prior relevant research on athletes who were involved in combative sports, such as boxing and Mixed Martial Arts (MMA), had significantly higher post fight K-D scores for those with head trauma during the match.[30] Whereas others observed that using the RT_{clin} method for measuring SRT in a concussed population appeared to distinguish concussed and non-concussed athletes with similar sensitivity and specificity to other commonly used concussion assessment tools.[14]

LIMITATIONS

The primary limitations to this study are the small sample size and time to RTS varying highly among individuals. Accordingly, the unexpectedly better SRT scores in the concussed group may be due to biased sampling in the small cohorts. The widely varying RTS resolution time among individuals could have led to better performance for some on the RT_{clin} and K-D testing. Thus, with more participants, several narrower specific ranges for RTS could have been utilized in assessing and more clearly revealing these potential contributing factors to LE injury risk following clearance. Screening patients prior to and after incurring a concussion using the Vestibular/Ocular-Motor Screening (VOMS) testing that analyzes ocular smooth pursuits, saccades horizontal and vertical, convergence, and Vestibular Ocular Reflex (VOR) horizontal and vertical could further assist in detecting prior ocular motor deficits and clarifying any injury-induced changes. For future studies, these considerations and having a more precise inclusion and exclusion criteria would likely be beneficial in controlling for practical confounding variables that can hinder K-D and SRT utility in detecting related potential deficits and LE injury risk. Finally, the researchers did not examine subsequent MSK injury in the participants, so direct inferences cannot be made from the results of this study and future injury risk in concussed athletes who have been cleared for RTS.

CONCLUSION

This study provides new perspective on post-concussion MSK injury risk and the utility of the K-D and SRT assessments during RTS decision-making. The concussed group performed the K-D test a little slower, however, this difference was not statistically significant. At the same time, the concussed group had a significantly better SRT compared to the non-concussed group. Both results suggest that any neurocognitive and reaction time deficits potentially resolved, or detection was confounded by other influencing factors. These findings also spotlight the possibility that any lingering affected neurocognitive and/or reaction time deficits after being cleared for RTS are not detectable using these tests, even in the potential presence of neuromuscular control deficits, postural control being altered, and/or general LE stiffness contributing to greater risk of LE injury after a SRC.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

Submitted: August 03, 2021 CDT, Accepted: May 04, 2022 CDT

REFERENCES

1. DePadilla L, Miller GF, Jones SE, Peterson AB, Breiding MJ. Self-reported concussions from playing a sport or being physically active among high school students - United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(24):682-685. doi:10.15585/mmwr.mm6724a3

2. Kerr ZY, Chandran A, Nedimyer AK, Arakkal A, Pierpoint LA, Zuckerman SL. Concussion incidence and trends in 20 high school sports. *Pediatrics*. 2019;144(5). doi:10.1542/peds.2019-2180

3. Fino PC, Becker LN, Fino NF, Griesemer B, Goforth M, Brolinson PG. Effects of recent concussion and injury history on instantaneous relative risk of lower extremity injury in division I collegiate athletes. *Clin J Sport Med*. 2019;29(3):218-223. doi:10.1097/jsm.0000000000000502

4. Kardouni JR, Shing TL, McKinnon CJ, Scofield DE, Proctor SP. Risk for lower extremity injury after concussion: a matched cohort study in soldiers. *J Orthop Sports Phys Ther*. 2018;48(7):533-540. doi:10.2519/jospt.2018.8053

5. McPherson AL, Nagai T, Webster KE, Hewett TE. Musculoskeletal injury risk after sport-related concussion: a systematic review and meta-analysis. *Am J Sports Med*. 2019;47(7):1754-1762. doi:10.1177/0363546518785901

6. Oldham JR, Howell DR, Knight CA, Crenshaw JR, Buckley TA. Gait performance is associated with subsequent lower extremity injury following concussion. *Med Sci Sports Exerc*. 2020;52(11):2279-2285. doi:10.1249/mss.0000000000002385

7. Herman DC, Zaremski JL, Vincent HK, Vincent KR. Effect of neurocognition and concussion on musculoskeletal injury risk. *Curr Sports Med Rep*. 2015;14(3):194-199. doi:10.1249/jsr.0000000000000157

8. Brooks MA, Peterson K, Biese K, Sanfilippo J, Heiderscheit BC, Bell DR. Concussion increases odds of sustaining a lower extremity musculoskeletal injury after return to play among collegiate athletes. *Am J Sports Med*. 2016;44(3):742-747. doi:10.1177/0363546515622387

9. King D, Brughelli M, Hume P, Gissane C. Concussions in amateur rugby union identified with the use of a rapid visual screening tool. *J Neurol Sci*. 2013;326(1-2):59-63. doi:10.1016/j.jns.2013.01.012

10. King D, Hume P, Gissane C, Clark T. Use of the King–Devick test for sideline concussion screening in junior rugby league. *J Neurol Sci*. 2015;357(1-2):75-79. doi:10.1016/j.jns.2015.06.069

11. Clugston JR, Houck ZM, Asken BM, et al. Relationship between the king-devick test and commonly used concussion tests at baseline. *J Athl Train*. 2019;54(12):1247-1253. doi:10.4085/1062-6050-455-18

12. Eckner JT, Kutcher JS, Richardson JK. Pilot evaluation of a novel clinical test of reaction time in national collegiate athletic association division I football players. *J Athl Train*. 2010;45(4):327-332. doi:10.4085/1062-6050-45.4.327

13. Eckner JT, Lipps DB, Kim H, Richardson JK, Ashton-Miller JA. Can a clinical test of reaction time predict a functional head-protective response? *Med Sci Sports Exerc*. 2011;43(3):382-387. doi:10.1249/mss.0b013e3181f1cc51

14. Eckner JT, Kutcher JS, Broglio SP, Richardson JK. Effect of sport-related concussion on clinically measured simple reaction time. *Br J Sports Med*. 2014;48(2):112-118. doi:10.1136/bjsports-2012-091579

15. Norris JN, Carr W, Herzig T, Labrie DW, Sams R. ANAM4 TBI reaction time-based tests have prognostic utility for acute concussion. *Mil Med*. 2013;178(7):767-774. doi:10.7205/milmed-d-12-00493

16. Warden DL, Bleiberg J, Cameron KL, et al. Persistent prolongation of simple reaction time in sports concussion. *Neurology*. 2001;57(3):524-526. doi:10.1212/wnl.57.3.524

17. Breedlove KM, Ortega JD, Kaminski TW, et al. King-Devick test reliability in National Collegiate Athletic Association Athletes: A National Collegiate Athletic Association-Department of Defense concussion assessment, research and education report. *J Athl Train*. 2019;54(12):1241-1246. doi:10.4085/1062-6050-219-18

18. Dhawan PS, Leong D, Tapsell L, et al. King-Devick Test identifies real-time concussion and asymptomatic concussion in youth athletes. *Neurol Clin Pract*. 2017;7(6):464-473. doi:10.1212/cpj.0000000000000381

19. Bergeron MF, Landset S, Maugans TA, et al. Machine learning in modeling high school sport concussion symptom resolve. *Med Sci Sports Exerc*. 2019;51(7):1362-1371. doi:10.1249/mss.0000000000001903

20. Guskiewicz KM, Ross SE, Marshall SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. *J Athl Train*. 2001;36(3):263-273.

21. Herman DC, Jones D, Harrison A, et al. Concussion may increase the risk of subsequent lower extremity musculoskeletal injury in collegiate athletes. *Sports Med*. 2017;47(5):1003-1010. doi:10.1007/s40279-016-0607-9

22. Dubose DF, Herman DC, Jones DL, et al. Lower extremity stiffness changes after concussion in collegiate football players. *Med Sci Sports Exerc*. 2017;49(1):167-172. doi:10.1249/mss.0000000000001067

23. Howell DR, Lynall RC, Buckley TA, Herman DC. Neuromuscular control deficits and the risk of subsequent injury after a concussion: a scoping review. *Sports Med*. 2018;48(5):1097-1115. doi:10.1007/s40279-018-0871-y

24. Dessy AM, Yuk FJ, Maniya AY, et al. Review of assessment scales for diagnosing and monitoring sports-related concussion. *Cureus*. 2017;9(12):1922. doi:10.7759/cureus.1922

25. Tjarks BJ, Dorman JC, Valentine VD, et al. Comparison and utility of King-Devick and ImPACT® composite scores in adolescent concussion patients. *J Neurol Sci*. 2013;334(1-2):148-153. doi:10.1016/j.jns.2013.08.015

26. Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics sports medicine battery. *Arch Clin Neuropsychol*. 2007;22(1):101-114. doi:10.1016/j.acn.2006.10.008

27. Eckner JT, Kutcher JS, Richardson JK. Pilot evaluation of a novel clinical test of reaction time in national collegiate athletic association division I football players. *J Athl Train*. 2010;45(4):327-332. doi:10.4085/1062-6050-45.4.327

28. Hugenholtz H, Stuss DT, Stethem LL, Richard MT. How long does it take to recover from a mild concussion? *Neurosurgery*. 1988;22(5):853-858. doi:10.1227/00006123-198805000-00006

29. Lempke LB, Johnson RS, Schmidt JD, Lynall RC. Clinical versus functional reaction time: Implications for post-concussion management. *Med Sci Sports Exerc*. 2020;52(8):1650-1657. doi:10.1249/mss.0000000000002300

30. Galetta KM, Barrett J, Allen M, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. *Neurology*. 2011;76(17):1456-1462. doi:10.1212/wnl.0b013e31821184c9