Attentional dysfunction and recovery in concussion: effects on the P300m and contingent magnetic variation

Lauren Petley, Tim Bardouille, Darrell Chiasson, Patrick Froese, Steve Patterson, Aaron Newman, Antonina Omisade & Steven Beyea

To cite this article: Lauren Petley, Tim Bardouille, Darrell Chiasson, Patrick Froese, Steve Patterson, Aaron Newman, Antonina Omisade & Steven Beyea (2018): Attentional dysfunction and recovery in concussion: effects on the P300m and contingent magnetic variation, Brain Injury, DOI: 10.1080/02699052.2018.1429022

To link to this article: https://doi.org/10.1080/02699052.2018.1429022

Published online: 22 Jan 2018.
Attentional dysfunction and recovery in concussion: effects on the P300m and contingent magnetic variation

Lauren Petley\textsuperscript{a,b,c}, Tim Bardouille\textsuperscript{a,b}, Darrell Chiasson\textsuperscript{c}, Patrick Froese\textsuperscript{c}, Steve Patterson\textsuperscript{b}, Aaron Newman\textsuperscript{b}, Antonina Omisade\textsuperscript{c}, and Steven Beyea\textsuperscript{a,b,c}

\textsuperscript{a}Biomedical Translational Imaging Centre (BIOTIC), IWK Health Centre, Halifax, Nova Scotia, Canada; \textsuperscript{b}Dalhousie University, Halifax, Nova Scotia, Canada; \textsuperscript{c}Nova Scotia Health Authority, QEII Health Sciences Centre, Halifax, Nova Scotia, Canada

\textbf{ABSTRACT}

Primary objective: To examine the effect of concussion on indices of attention using magnetoencephalography.

Methods and procedures: Thirteen patients were recruited from the emergency department and scanned within 3–6 days of injury. Five returned for follow-up scans one and three months post-injury. Thirteen healthy controls also completed testing. During MEG acquisition, participants performed the Attention Network Test (ANT). Cognitive evoked responses to this task include a cue-evoked P300m, a contingent magnetic variation (CMV) and a target-evoked P300m. The Rivermead Postconcussion Symptom Questionnaire and Sport Concussion Assessment Tool (SCAT3) were administered in all sessions.

Results: Patients suffering from concussion had slower response times and benefitted more from spatial cues than did controls. Global activation for all three evoked responses was lower for patients than controls. In a small sample of patients who returned for follow-up, the CMV and target P300m improved with recovery.

Conclusions: MEG-evoked responses to the ANT reveal neurophysiological evidence of attentional dysfunction within days of injury. A pattern of improvement was also observed over the course of three months for the P300m, while behavioural performance did not change significantly. Further development of this method may yield a useful adjunct to neurological examination for concussion diagnosis and monitoring.

Introduction

The general lack of abnormalities in conventional structural imaging of concussion has led many investigators to examine the potential of functional neuroimaging for the detection of neurological sequelae following injury; notably electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) (1). Efforts to identify an optimal task for evaluating concussion using these imaging modalities are complicated by the variability of symptoms between individuals. Despite this individual variability, evidence from meta-analyses suggests that processing speed, working memory and attention may be particularly susceptible to this type of injury (2,3). Indeed, deficits of attention are so commonly associated with concussion that targeted rehabilitation may be necessary to improve this functional domain following injury (4).

Attention is a complex construct that encompasses a variety of neural capacities that enable focused awareness. In their influential Attention Networks model, Posner and Petersen outlined three distinct attention networks: an alerting network, an orienting network, and an executive network (5). The Attention Network Test (ANT) is a task that interrogates all three of these networks in a relatively short amount of time (6). The behavioural properties of the ANT have been well-characterized in healthy individuals (6–8) and the test has been used both behaviourally and in combination with neuroimaging to study a number of clinical populations including patients with attention-deficit hyperactivity disorder, multiple sclerosis, mild cognitive impairment, and schizophrenia (9–15). Notably, one research group has demonstrated performance changes on the ANT as a consequence of concussion in young adults and adolescents (16–18). To date, the ANT has not been combined with any type of neuroimaging for the study of concussion.

Functional neuroimaging of concussion, particularly using event-related potentials (ERPs), has also provided substantial evidence to suggest that dysfunctions of attention are present in both the short- and long-term following injury. The majority of this evidence relates to an ERP known as the P300 (P300m in MEG), a cognitive response that reflects stimulus-driven activation of attention mechanisms and subsequent contextual updating in working memory (19). A variety of paradigms, both auditory and visual in nature, have repeatedly demonstrated reduced P300 amplitudes in individuals with concussion compared to healthy controls, which are suggestive of reduced attentional capacity (20–31). Some
studies have reported amplitude reduction months to years following injury, even in the absence of clinical symptoms, suggesting the presence of persistent neurophysiological changes (20,23,25,27,31). Very few studies have examined the P300 shortly following concussion (i.e. within a week of injury) and the vast majority of results have been reported only at the group level.

Trials in the ANT consist of a cue and a subsequent target, with variations of the cue providing participants with different amounts of information regarding the time and/or location at which the target can be expected (details and an illustration are provided in section 2.3 and Figure 1). When implemented with EEG acquisition, the ANT is associated with two P300 responses, one evoked by the cue at the beginning of the trial, and one following the target (12,13,32). Similarly to other ERP paradigms in which a target is preceded by a warning stimulus (33–36), the period leading up to the target in the ANT is additionally associated with a contingent negative variation (CNV, or CMV in MEG). The CNV is a slow evoked response that reflects the activation of a number of neural structures, including motor cortex (34), in preparation to produce a behavioural response to a target. There is some evidence that the CNV is diminished by concussion (37,38). This change may represent a deficit in the neural structures subserving anticipation (39). Thus, the ANT provides a convenient and well-characterized battery to examine the neurophysiological correlates of attention.

The present study examined the utility of using MEG, combined with the ANT, to detect changes in attentional function following concussion and during its recovery. MEG is similar to EEG in that it measures signals due to the summation of synchronous postsynaptic potentials, but measures the magnetic component of these fields and differs with respect to sensitivity across the cortex (40). MEG and EEG offer complementary views of neural activity and each modality has its own advantages and disadvantages. For the purpose of the present study, the patient-friendly capability of MEG to provide whole-head coverage with minimal setup time was considered preferable. The present paper employs a global sensor-level analysis to examine how attention-related MEG evoked responses are altered by concussion as an exploratory step towards developing a diagnostic and monitoring tool. In line with previous research, it was expected that the behavioural and neural indices of attention, including performance on the ANT and evoked response amplitudes for the P300m and CMV, would exhibit deficits immediately following injury which would resolve over the recovery period. It was additionally expected that the ANT would provide some specificity regarding the attention networks that are most affected by concussion.

Materials and Methods

Participants

Consecutive patients who presented to the QEII Health Sciences Centre Emergency Department with symptoms of mild closed head injuries were approached by their attending paramedic or physician for participation in the study. To encourage clinicians to use the same diagnostic criteria and personal judgment that would be used in their everyday practice, only three questions were asked to determine a patient’s eligibility: Did this patient sustain a mild closed head injury? Is the patient fit for discharge? Is the patient’s GCS greater than 13? An affirmative answer on all three questions was required to meet eligibility. Twenty-seven such patients agreed to participate. Of these, eight participants were removed due to a pre-existing psychiatric or neurological condition, learning disorder, or the use of psychoactive medication. Two participants were removed due to ambidextrous scores on the Edinburgh Handedness Inventory (41), and four participants were removed due to excessive head movement during MEG scanning (> 5 mm translation or > 3° rotation). Thirteen patients (4 males, mean age = 25.5 years, SD = 6.4) remained for the full analysis, six of whom had returned for follow-up scans at both one and three months post-injury. One of these six patients completed the ANT task incorrectly at the one month follow-up and was omitted from the longitudinal analysis. Seven of the thirteen patients recruited immediately following injury were invited for follow-up but did not return. A sample of thirteen healthy people also completed a single experimental session as a control group (5 males, mean age = 25.6 years, SD = 4.4). The healthy control and patient groups did not differ significantly in age [t(24) = 0.04, p = 0.97].

All participants for whom data was collected had normal or corrected-to-normal vision and reported no history of neurological or psychiatric conditions and no current use of psychoactive medications. Prior to MEG scanning, participants were instructed to remove any upper body clothing with metallic parts, and were screened for the presence of implanted or non-removable metal or electronic devices via a medical pre-screening questionnaire. The study received full
research ethics board approval and written informed consent was obtained prior to participation.

**Questionnaires and concussion tests**

In the first study session, participants completed the Edinburgh Handedness Inventory (41) to confirm right-handedness, a concussion self-report form to explain the cause of injury and describe symptoms at the time of injury, the Rivermead Postconcussion Symptom Questionnaire (RPQ (42)), and selected portions of the Sport Concussion Assessment Tool, version 3 (SCAT3 (43)), including the symptom evaluation scale (symptom severity score), the cognitive assessment (Standardized Assessment of Concussion, or SAC), balance examination (BESS), and coordination examination. The RPQ is a self-rated scale in which patients indicate the severity of their post-concussion symptoms in contrast to their recollection of premorbid function. The symptom evaluation scale of the SCAT3 is similar to the RPQ, but is not ranked by comparison to premorbid function. The RPQ and SCAT3 are both popular for research and clinical purposes, therefore both were used despite this similarity. There are no normative data or diagnostic thresholds for either of these tools. For this reason, the healthy control group also completed the SCAT3. These concussion metrics and symptom questionnaires were used to provide descriptive statistics on the study sample and were not used for participant screening or selection.

**The attention network test**

The ANT is illustrated in Figure 1. Trials consisted of a 200 ms cueing phase, followed by a 1300 ms delay, and then a target phase that terminated when the participant produced a response, to a maximum of 2000 ms. The inter-trial interval was randomly varied to prevent anticipation of upcoming trials (2000–4000 ms). Participants were seated in the upright position and stimuli were presented by a projector located outside the shielded room onto a screen one meter in front of the participant. All stimuli were black on a grey background.

The three cue conditions were randomized and equiprobable. The “no cue” condition entailed a continuation of the fixation cross from the inter-trial interval. The “neutral cue” condition provided a temporal warning for the upcoming targets via an asterisk in the centre of the screen. The “spatial cue” condition provided both a temporal and a spatial warning for the upcoming targets via a centrally-placed arrow pointing up or down. This cue always indicated the true location of the target. Fixation and arrow cue stimuli had a height of 0.9° visual angle, while asterisk stimuli had a height of 0.6°.

Target stimuli consisted of a row of five arrows 2.3° either above or below the centre of the screen. The arrow array had a width of 3.1° and individual arrows were separated by 0.3°. Participants were instructed to respond only to the middle arrow of the array, with their right thumb if the arrow was pointing right and their left thumb if it was pointing left. In the target phase of the ANT, response conflict was induced by the direction of the four flanker arrows, which could either reinforce (congruent) or contradict (incongruent) the direction of the target. These two flanker conditions were delivered equiprobably and targets were equiprobably distributed across the upper and lower positions of the screen. The combination of these three cue conditions and two flanker conditions result in a total of six trial types.

Participants were instructed to hold their heads as still as possible, to maintain their gaze at the position of the fixation cross and to use their peripheral vision to see the target. Participants completed a brief practice (4–10 trials) to ensure that task instructions were properly understood. During MEG scanning, participants completed two experimental blocks of 96 trials (32 trials per cue condition when collapsed across flanker conditions; 48 trials per flanker condition when collapsed across cue conditions). Each block lasted about 8 minutes and participants were offered a short break between blocks.

**Data acquisition**

In all sessions, participants completed concussion forms and tests prior to setup for MEG acquisition. Four head position indicator coils were placed on the participant’s head: two on the forehead, and two behind the ears, above the mastoid. The positions of these coils, as well as the nasion, left and right pre-auricular points, and a 150–250 point head shape were digitized using a Polhemus digitization device (Polhemus Incorporated, Vermont, USA). Four Ag/AgCl electrodes were attached to the participant’s face using electroconductive paste in standard bipolar EOG locations (above and below the left eye, and beside the outer canthus of each eye), and three electrodes were placed on the subject’s inner upper arms and left collarbone (ground) to record ECG.

MEG, ECG, EOG and head position were continuously acquired at 1000 Hz with a 330 Hz low-pass filter on a 306-channel Elekta Neuromag Triux system (Elekta Neuromag Oy, Helsinki, Finland) in a magnetically shielded room with active shielding coils. MEG data were thus recorded at 102 locations, each bearing one magnetometer and two orthogonal planar gradiometers.

**Analysis**

**Questionnaires and concussion tests**

All SCAT3 sub-tests (symptom severity, SAC, BESS, coordination) were compared between healthy controls and patients. Large differences in variance between the healthy controls and patients on the symptom severity score necessitated the use of a Welch t-test. The SAC and BESS were compared between groups by independent sample t-tests. The coordination score (0 or 1) was compared between groups by a Fisher Exact Test. Longitudinal changes in the RPQ, SCAT3 symptom severity, SAC, and BESS were all tested by repeated measures ANOVAs with Greenhouse-Geisser correction. Longitudinal changes in the SCAT3 coordination subtest were carried out by pairwise Fisher Exact Tests.

**Behavioural analysis**

Responses on the ANT were considered valid if they occurred 150 – 2000 ms following target onset. Earlier responses were considered to be false alarms and later responses were
considered to be invalid. No false alarms were observed and there were only six invalid responses across all participants and all three sessions.

As in the original ANT study (6), behavioural statistics were performed with two different dependent variables: response time (RT) for correct trials only and accuracy. Accuracy was very high for both healthy controls and patients, therefore for the purpose of statistical testing, accuracy was transformed to rationalized arc sine units (RAU) to help counteract ceiling effects (44). For each dependent variable, two ANOVAs were carried out. To examine early effects of concussion, a mixed ANOVA with the factors group (control, patient), cue (no cue, neutral cue, spatial cue), and flanker (congruent, incongruent) was carried out using all 13 patients and 13 controls. To examine longitudinal changes across the recovery period, a repeated measures ANOVA with the factors session (session 1, session 2, session 3), cue (no cue, neutral cue, spatial cue), and flanker (congruent, incongruent) was carried out using the five patients who attended and properly completed all three sessions.

**MEG data processing**

Sources of magnetic noise external to the participant were first removed via spatiotemporal signal space separation (45) using default parameters. The data was then low-pass filtered (40 Hz cutoff) and downsampled to 250 Hz using the MaxFilter software (Elekta Oy). A 0.1 Hz highpass filter was subsequently applied using MNE Suite (version 2.7.0 (46)).

Head movement compensation was not applied. MEG artifact correction was performed in Matlab (R2015b; Mathworks Inc.) using independent component analysis (FastICA v2.5, based on (47)). All components with a Pearson correlation ≥ 0.4 with one of the artefact reference channels (horizontal EOG, vertical EOG, and ECG), or with amplitudes that exceeded a manually-optimized threshold (1e−10 T for magnetometers, 1e−9 T/cm for gradiometers) were removed from the MEG signal. The corrected MEG signal was then segmented and averaged in 3500 ms epochs that were time-locked to cue onset, with a 500 ms pre-cue baseline separately for each combination of cue and flanker condition. Epoching and averaging were performed via command-line calls to the MNE Suite software package (version 2.7.0 (46)).

**Evoked response measurement**

Global Field Power (GFP) is typically calculated as a spatial standard deviation (48), although alternative computations also exist (e.g. (49)). Calculation of a spatial root mean square (RMS) is nearly identical to the classical standard deviation definition of GFP but avoids mean-centring (i.e. subtracting the mean activity across all sensors from each sensor). Mean-centring could conceivably mask inter-group or longitudinal differences therefore an RMS computation of field strength was considered preferable over classical GFP for the present study. RMS at a given time (t) was obtained using the following equation:

\[
RMS_t = \sqrt{\frac{2\sum_{i=1}^{n} a_i^2}{n}}
\]

Where \(a_i\) is the reading at magnetometer \(i\) and \(n\) is the total number of magnetometers. For the purpose of this paper, this shall be referred to as the Global Field Strength (GFS) to distinguish it from the classical GFP measure. Evoked responses were measured as mean amplitudes in the GFS waveform in the following latency windows: 200 – 600 ms post-cue for the cue-evoked P300m, 1000 – 1500 ms post-cue (the 500 ms leading up to presentation of the target) for the CMV, and 1700 – 2100 ms post-cue (200 – 600 ms post-target) for the target-evoked P300m. The cue-evoked P300m and CMV were only present in the neutral cue and spatial cue conditions and were measured in GFS waveforms that were averaged across flanker conditions. The target-evoked P300m was present in all conditions and was measured in GFS waveforms that were computed separately for each combination of cue and flanker.

**MEG statistical analysis**

Similarly to the behavioural data, amplitude measurements for each evoked response were subjected to two ANOVAs, one for early effects of concussion versus healthy controls, and one for longitudinal changes within the patient group. The cue-evoked P300m and CMV were only present in the neutral cue and spatial cue averages. Each was statistically evaluated using a mixed ANOVA with the factors group (control, patient) and cue (neutral, spatial) and a repeated measures ANOVA with the factors session (session 1, session 2, session 3) and cue (neutral, spatial). The target-evoked P300m was present in all conditions. Like the behavioural data, it was evaluated using a mixed ANOVA with the factors group (control, patient), cue (no cue, neutral cue, spatial cue), and flanker (congruent, incongruent), using all 13 patients and 13 controls, as well as a repeated measures ANOVA with the factors session (session 1, session 2, session 3), cue (no cue, neutral cue, spatial cue), and flanker (congruent, incongruent), using the five patients who attended and properly completed all three sessions. Greenhouse-Geisser epsilon and corrected \(p\) values were reported in cases where the assumption of sphericity was violated.

**Results**

**Concussion demographics**

Symptoms at the time of injury, as described on the concussion self-report form, were used to rate concussions according to the grading system of the American Academy of Neurology, AAN (50). Among the 13 patients, there were four Grade 3 concussions and nine Grade 2 concussions. The most common cause of injury was a fall (\(N = 7\)), followed by a motor vehicle accident (\(N = 3\)), recreational or organized sports (\(N = 2\)), and one accidental blunt trauma. This sample differs somewhat from the typical composition of this patient population in that it over-represents fall injuries, which have been reported to account for approximately 30% of concussions (51). While participants were not queried regarding involvement in litigation, patients experiencing a cause of injury that was likely to involve legal action (motor vehicle accidents) comprised the minority of the sample. The
majority of patients experienced injuries that were either self-inflicted or accidental (falls and sports injuries). Of the patients who returned for long term follow-up, one suffered a motor vehicle accident, one suffered a recreational sports injury, and four suffered fall injuries.

**Between-group results**

**Behavioural**

Healthy controls and patients differed significantly in symptom severity on the SCAT3 \[t(12.08) = -4.34, \beta = 0.00095\], but not the SAC \[t(24) = 0.63, \beta = 0.54\] or BESS \[t(24) = -0.83, \beta = 0.41\]. There was a near-significant trend for differences in coordination (one-tailed \beta = 0.080), in which patients were more likely to fail the test than healthy controls. Scores for all concussion test and questionnaire data are summarized in Table 1.

Performance is summarized in Table 2 for all main effects of the ANT and all sessions. The ANOVA for accuracy on the ANT revealed a significant effect of flanker type \[F(1,24) = 15.62, \beta = 0.00059\], in which responses were less accurate in the presence of incongruent flankers. No other effects reached significance. In particular, there were no group differences in accuracy on the ANT.

The RT ANOVA yielded significant main effects of group \[F(1,24) = 14.57, \beta = 0.00083\], cue \[F(2,48) = 71.15, \beta = 0.65\], adjusted \beta < 0.000001, and flanker \[F(1,24) = 259.00, \beta < 0.000001\] on the ANT. Healthy controls responded more quickly than patients and, across both groups, the typical pattern of ANT results was observed, including faster response times with more informative cues (neutral < no cue, spatial < neutral, and spatial < no cue; \beta < 0.0003 in all cases) and faster responses for congruent than incongruent trials. The RT ANOVA showed evidence of differential benefit from the cues by patients with concussion versus healthy controls, as indicated by a significant interaction between cue and group \[F(2,48) = 4.07, \beta = 0.65, \text{adjusted } \beta = 0.042\], which is illustrated in the top panel of Figure 2.

The nature of this interaction is clarified by examining the RT subtractions that are commonly employed with the ANT (Alerting network = no cue RT minus neutral cue RT, Orienting network = neutral cue RT minus spatial cue RT, Executive network = incongruent flanker RT minus congruent flanker RT). The results of these subtractions are shown in the bottom panel of Figure 2. A mixed ANOVA with the factors group and network yielded a significant group by network interaction \[F(2,48) = 3.31, \beta = 0.92, \text{adjusted } \beta = 0.050\]. Tukey post-hoc analysis demonstrated that, for healthy controls, the RT reduction associated with a spatial cue (Orienting network) was not significantly different from that associated with an alerting (neutral) cue (Alerting network, \beta = 1.0). However, for patients, this contrast was significant (Orienting network > Alerting network, \beta = 0.010). Tukey post-hoc analysis additionally indicated that the RT reduction associated with the Orienting network was larger for patients than controls (\beta = 0.057). Thus, patients sped up their responses more when provided with a spatial cue than did controls. This effect can be observed clearly in the bottom panel of Figure 2, which shows a larger response time reduction for the Orienting network in patients than in controls. This same effect is visible, but less obvious, in the top panel of Figure 2 as a sharper slope between the neutral cue and spatial cue conditions for patients than controls. No other networks demonstrated between-group differences.

**MEG evoked responses**

The grand-average GFS waveforms for healthy controls and patients with concussion at the earliest stage of injury (3–6 days post-concussion) are shown in Figure 3 for all cue conditions, as well as the two flanker conditions. Amplitude

---

**Table 1.** Means and standard deviations (in brackets) on concussion tests and questionnaires for all sessions. Frequency of successful test completion is reported for the SCAT3 coordination test.

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 13)</th>
<th>Patients (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RPQ</strong></td>
<td>n/a</td>
<td>7.8 (11.0)</td>
</tr>
<tr>
<td><strong>SCAT3 symptom severity</strong></td>
<td>1.3 (2.3)</td>
<td>46.9 (37.8)</td>
</tr>
<tr>
<td><strong>SCAT3 SAC</strong></td>
<td>27.7 (1.9)</td>
<td>26.8 (5.0)</td>
</tr>
<tr>
<td><strong>SCAT3 BESS</strong></td>
<td>3.8 (4.3)</td>
<td>5.5 (6.0)</td>
</tr>
<tr>
<td><strong>SCAT3 coordination</strong></td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 2.** Means and standard deviations (in brackets) of accuracy (in RAU) and response time (in ms) for all sessions and main effects of cue and flanker.

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 13)</th>
<th>Patients (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy (RAU)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Cue</td>
<td>109.41 (5.43)</td>
<td>110.16 (5.90)</td>
</tr>
<tr>
<td>Neutral</td>
<td>107.89 (6.53)</td>
<td>110.63 (4.53)</td>
</tr>
<tr>
<td>Spatial</td>
<td>110.52 (4.77)</td>
<td>109.71 (5.63)</td>
</tr>
<tr>
<td>Congruent</td>
<td>111.99 (3.04)</td>
<td>111.74 (4.29)</td>
</tr>
<tr>
<td>Incongruent</td>
<td>106.56 (7.51)</td>
<td>108.59 (6.18)</td>
</tr>
<tr>
<td><strong>RT (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Cue</td>
<td>612.3 (57.4)</td>
<td>110.29 (4.75)</td>
</tr>
<tr>
<td>Neutral</td>
<td>592.0 (55.0)</td>
<td>110.24 (6.33)</td>
</tr>
<tr>
<td>Spatial</td>
<td>570.7 (50.0)</td>
<td>111.93 (4.13)</td>
</tr>
<tr>
<td>Congruent</td>
<td>562.6 (59.6)</td>
<td>111.38 (3.99)</td>
</tr>
<tr>
<td>Incongruent</td>
<td>620.8 (47.8)</td>
<td>110.27 (4.18)</td>
</tr>
</tbody>
</table>
reductions are clearly evident for patients with concussion versus healthy controls in the temporal windows associated with the cue-evoked P300m, the CMV, and the target-evoked P300m. The repeated measures ANOVA for the effects of group and cue on the amplitude of the cue-evoked P300m revealed both of these effects to be statistically significant, with no interaction (cue [F(1,24) = 17.40, \( \epsilon = 0.0034 \), group [F(1,24) = 4.25, \( p = 0.050 \)]). For the CMV, there was only a significant effect of group [F(1,24) = 4.43, \( p = 0.046 \)]. The target-evoked P300m ANOVA demonstrated a significant effect of flanker type [F(1,24) = 4.01, \( p = 0.057 \)], a nonsignificant trend towards an effect of cue [F(2,48) = 2.44, \( p = 0.098 \)], and a significant effect of group [F(1,24) = 4.71, \( p = 0.040 \)], with no significant interactions. All evoked responses were larger for healthy controls than patients with concussion. Mean amplitudes for all evoked responses are summarized in Table 3.

Longitudinal results

Behavioral

Longitudinal scores on the RPQ and SCAT3 are summarized in Table 1 for the subset of patients who successfully completed all three experimental sessions. These patients demonstrated no significant longitudinal changes on any of these clinical tests: RPQ [F(2,8) = 1.42, \( \epsilon = 0.62 \), adjusted \( p = 0.30 \)], SCAT3 symptom severity [F(2,8) = 1.59, \( \epsilon = 0.62 \), adjusted \( p = 0.27 \)], SCAT3 SAC [F(2,8) = 1.25, \( \epsilon = 0.54 \), adjusted \( p = 0.33 \)], SCAT3 BESS [F(2,8) = 0.82, \( \epsilon = 0.54 \), adjusted \( p = 0.42 \)], or SCAT3 coordination (all pairwise Fisher Exact Tests one-way \( p \geq 0.50 \)).

An ANOVA on ANT accuracy could not be performed due to insufficient variance. The RT ANOVA revealed significant effects of cue [F(2,8) = 36.37, \( \epsilon = 0.83 \), adjusted \( p = 0.00032 \)] and flanker type [F(1,4) = 32.88, \( p = 0.0046 \)], but no main effect of session [F(2,8) = 0.92, \( \epsilon = 0.65 \), adjusted \( p = 0.41 \)]. The cue and flanker effects were identical to those typically observed on the ANT, with shorter RTs as the informational value of the cue increased and shorter RTs in the presence of congruent than incongruent flankers. There was a non-significant trend towards an interaction between study session and cue [F(4,16) = 2.23, \( \epsilon = 0.70 \), adjusted \( p = 0.14 \)].

MEG evoked responses

Longitudinal grand average GFS waveforms are shown in Figure 4 for the patients who successfully completed the entire study (N = 5) versus the healthy control group (N = 13). Increasing response amplitudes as a function of time from injury are particularly evident in the period associated with the CMV and the target-evoked P300m. The ANOVA for the cue-evoked P300m revealed no significant effect of session [F(2,8) = 0.045, \( \epsilon = 0.65 \), adjusted \( p = 0.89 \)] or cue [F(1,4) = 2.63, \( p = 0.18 \)]. The ANOVA for the CMV yielded near-significant trends for both session [F(2,8) = 3.40, \( \epsilon = 0.98 \), adjusted \( p = 0.087 \)] and cue [F(1,4) = 5.87, \( p = 0.072 \)]. Finally, the ANOVA for the target-evoked P300 yielded no significant effect of cue [F(1,4) = 1.63, \( p = 0.27 \)] or flanker [F(2,8) = 0.084, \( \epsilon = 0.73 \), adjusted \( p = 0.87 \)], but a significant effect of session [F(2,8) = 5.29, \( \epsilon = 0.84 \), adjusted \( p = 0.045 \)]. Tukey post-hoc analysis indicated that the amplitude of the target-evoked P300m was significantly larger in the third session, three months from injury, than the first session, 3–6 days from injury (\( p = 0.029 \)).

Individual amplitudes for all evoked responses, across the three longitudinal sessions, are shown in Figure 5 for all five patients who attended and properly completed the three scans. First and third session data are also shown for Patient 3, whose second session data were unusable. Patient 3 was not used for any statistical analysis of the longitudinal data. Patients 2–5 demonstrated clear enhancement of the target-evoked P300m in the third session versus the first session. Some enhancement of the CMV was also apparent. Patients 1 and 6 showed no improvement of the P300m.

Discussion

The goal of the present study was to examine the effect of concussion on attentional function, as revealed by the...
P300m and CMV, using the ANT to permit separate evaluation of the Alerting, Orienting, and Executive networks. By recruiting participants very early following injury (within one week) and following these patients, when possible, for several months, the study additionally permitted observation of the time course of these changes. Early following injury (3–6 days post-concussion), clear differences were evident at the group level between healthy controls and patients with respect to concussion symptoms as reported on the SCAT3. Consistent with previous studies of the ANT in concussion (16) as well as a variety of ERP studies (25,27,30), longer RTs were observed for patients versus controls. These results support the notion of reduced processing speed in concussion, for which there is ample neuropsychological evidence (2,3). Differential sensitivity of the attention networks to concussion was previously observed adolescent and young adult athletes using the ANT (16–18). Similarly to Halterman and colleagues (2006), who also examined patients within one week of injury, a larger Orienting effect (neutral cue RT minus spatial cue RT) was observed in patients than in healthy controls, suggesting that this may be an especially sensitive behavioural marker of concussion. This result might suggest that knowledge of the location of an upcoming target allows patients to offset, to some extent, the generalized slowing that is experienced following concussion. Unlike previous research, however, there were no longitudinal changes in performance over the recovery period and no sensitivity of the Executive network was observed to concussion. Given the small size of the present longitudinal sample, low statistical power may have played a role in the lack of statistically significant behavioural recovery.

The present study also demonstrated reduction of the P300m with concussion, which aligns with a rich literature implicating this evoked response as an index of concussion (20–31). This research has been performed using a wide range

---

**Table 3.** Means and standard deviations (in brackets) of global field strength evoked response amplitudes (in fT) for all sessions, cue conditions, and flanker conditions.

<table>
<thead>
<tr>
<th>Cue</th>
<th>P300m</th>
<th>Controls (N = 13)</th>
<th>Neutral</th>
<th>Spatial</th>
<th>Congruent</th>
<th>Incongruent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No Cue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>99.06</td>
<td>109.87</td>
<td>(24.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N = 13)</td>
<td>(19.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 1 (N = 13)</td>
<td></td>
<td>84.26</td>
<td>(15.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 2 (N = 5)</td>
<td></td>
<td>84.91</td>
<td>(16.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 3 (N = 5)</td>
<td></td>
<td>81.88</td>
<td>(12.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (N = 13)</td>
<td></td>
<td>84.67</td>
<td>(9.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 1 (N = 13)</td>
<td></td>
<td>68.44</td>
<td>(19.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 2 (N = 5)</td>
<td></td>
<td>80.59</td>
<td>(14.31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 3 (N = 5)</td>
<td></td>
<td>81.72</td>
<td>(11.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMV</td>
<td></td>
<td>84.26</td>
<td>(13.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 1 (N = 13)</td>
<td></td>
<td>68.44</td>
<td>(19.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 2 (N = 5)</td>
<td></td>
<td>80.59</td>
<td>(14.31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 3 (N = 5)</td>
<td></td>
<td>81.72</td>
<td>(11.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target</td>
<td></td>
<td>75.73</td>
<td>(22.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P300m</td>
<td></td>
<td>80.15</td>
<td>(16.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (N = 13)</td>
<td></td>
<td>89.05</td>
<td>(12.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 1 (N = 13)</td>
<td></td>
<td>107.42</td>
<td>(26.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 2 (N = 5)</td>
<td></td>
<td>114.60</td>
<td>(33.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Session 3 (N = 5)</td>
<td></td>
<td>131.62</td>
<td>(30.40)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Grand average GFS waveforms for all cue and flanker conditions, compared between healthy controls (gray) and patients 3–6 days following injury (black). The temporal windows used to compute mean evoked response amplitudes are indicated by gray boxes. Diminished amplitudes are visible with concussion for all three evoked responses. All waveforms have been smoothed for visualization with a 15 Hz lowpass filter.
of experimental paradigms and suggests reduced attentional capacity following injury. In line with the general slowing of RTs across all cue and flanker conditions of the ANT, reduction of the P300m was observed as a generalized deficit. Unlike our behavioural results, which additionally demonstrated an interaction in which patients derived greater benefit from spatial cues than healthy controls, there was no evidence of special sensitivity of any network of attention to concussion, with respect to P300m amplitude. Independence of the P300 from response strategies or compensation is a common, though not universal, finding (52). For this reason, the observed disparity between P300m and performance outcome measures in the present study is not unexpected, and indeed affirms that neurophysiological metrics are complementary to behavioural measures for the evaluation of concussion.

Very few studies of P300 in concussion have been carried out within a short time following injury (i.e. within one week). The majority of studies used participants whose concussions had occurred months or years prior (20–27,29–31). The present results therefore corroborate the findings of Pratap-Chand and colleagues, who studied patients approximately 4 days from injury, to confirm that P300 is reduced very early following concussion (28). This evoked response may be useful for diagnosing concussion in early stage recovery.

Much of the prior research has indicated that P300 amplitudes are chronically altered even despite the resolution of concussion symptoms (20,25,27,30). These findings are far from universal (24,31). A better understanding of P300 as a function of recovery from concussion requires a longitudinal design that follows patients after their injury, but there is a paucity of such research. In this respect, the present results again uniquely support those observed by Pratap-Chand and colleagues in 1988 (28), but with a smaller sample size, a more controlled follow-up schedule, and more time points along
the recovery period. Both studies indicate improvement of the P300 over time, with Pratap-Chand and colleagues indicating full recovery of the P300 at their long-term follow-up session (30 – 240 days later). The present results help to refine this observation to indicate that a follow-up at three months post-injury yields improvement of the P300 more consistently than follow-up at one month. While the lack of significant changes in performance (RT or accuracy) over time in the present study is likely attributable to the small size of its longitudinal sample, the observation of significant P300 effects despite low statistical power suggests that it might be more sensitive to the neurophysiological changes that follow concussion than behavioural measures are.

Not all patients in the small longitudinal sample of the present study demonstrated P300 recovery: two of the six patients showed no changes over time. Interestingly, these patients differed conspicuously in their initial SCAT3 symptom severity scores from the patients whose P300s improved over time. Patients 1 and 6 already had extremely low symptom severity scores in the first session (0 and 4, respectively), suggesting possible recovery from their injury at the time of intake to the study. By contrast, patients 2 – 5 had much higher scores (36, 27, 91, and 32, respectively). Concussion severity according to the AAN grading scheme did not differentiate patients with different patterns of P300 recovery. All of the patients in the longitudinal analysis experienced Grade 2 concussions, except for patient 3, who experienced a Grade 3 concussion. By the final session, symptoms had largely resolved for patients 1, 3, 5 and 6 (scores 0, 4, 1, 0, respectively), while patients 2 and 4 demonstrated improved but persisting symptomatology (scores 30 and 11, respectively). An ambitious but worthwhile goal for future research would be to examine whether improvement of the P300 is predictive of full recovery from concussion symptoms on a longer timescale.

In addition to P300m, the amplitude of the CMV decreased with concussion and tended to improve over time. Effects of concussion on the electrical CNV have been observed (37,38), but are not as common or robust as P300 effects. The CNV reflects preparation to respond to an upcoming target, and this capacity is often referred to as “orienting in time” (53). The present observation of an attenuated CMV as a consequence of concussion might be attributable to the complexity of the ANT versus conventional CNV paradigms. Measuring the CMV may provide a useful neurophysiological index of impaired anticipatory processes, which are thought to underlie a number of the cognitive deficits and persistent disabilities that are experienced in concussion (39). In the four patients who demonstrated improved P300s, these occurred in tandem with increased CMV amplitudes, but unlike the P300m, longitudinal changes in the CMV failed to reach statistical significance in the group-level analysis. Future research with a larger sample size would be helpful to replicate the P300 effects observed in the present study, determine whether the CMV adds value for detecting injury and monitoring recovery over and above P300, and examine how improvements in task performance might vary with these neurophysiological changes.

Conclusions

P300m amplitude reductions, indicating an impairment of attentional function, occurred within days of concussion and improved over the course of months following injury in a small longitudinal sample. Similar effects were observed for the CMV and both evoked responses demonstrated improvements that were consistent across all patients who were not already recovered at study onset. By using the ANT in MEG, several P300m and CMV responses can be measured within a relatively short time, but unlike RT measures, the neurophysiological changes resulting from concussion appear to be general to all of the attention networks that are probed by this test. Replication of these results with a larger sample and further development of this method might yield a clinically useful test for the diagnosis and monitoring of concussion.

Acknowledgements

The authors would like to convey their deep gratitude to the staff of the QEII Health Sciences Centre Emergency Department for their dedication to this project. Matthew MacLellan, Ronald Bishop, and Maggie Clarke are also thanked sincerely for their important supporting roles in this work. The authors also acknowledge the general support of BIOTIC’s facilities by a Brain Canada Platform Support Grant.

Funding

All work described herein was supported by an Atlantic Innovation Fund (AIF) grant from the Atlantic Canada Opportunities Agency (ACOA) for industry-partnered research. All or a portion of the reported results could contribute to the future development of a commercial product.

References


49. Gramfort A, Luessi F, Larson E, Engemann DA, Strohmeier D, Meier C, Ulbrich EJ, Johannes S. Altered cognitive pro-