New Insight into Correlation between Convergence Insufficiency/ Vestibular Abnormalities and Depression in Post-Concussion Syndrome

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Abstract

Post-concussion syndrome (PCS) causes a variety of cognitive/somatic symptoms. We previously showed that in PCS, convergence insufficiency (CI) was correlated with vestibular abnormality (VA). The cause of depression in PCS is not completely understood; however, neurotransmitter (e.g. serotonin) abnormalities play a significant role; the neurotransmitters like serotonin are mainly produced in brainstem. It is conceivable that damage to axons transporting neurotransmitters to the cortex, are responsible for cortical deficits. Previous studies suggest that (a) depression recovery in PCS is parallel to other PCS symptoms, and (b) depressed patients are less motivated and have a tendency to exaggerate their physical/cognitive deficiencies. Our results are in contrast with both of these suggestions.

Forty-eight PCS patients were tested with Electrovestibulography (EVestG) and the Montgomery-Asberg-Depression-Rating-Scale (MADRS). The last twenty patients were also tested with Rivermead-post-concussion-questionnaire (RPQ). Field Potential (FP) area was extracted and analyzed from EVestG data. CI was measured using prism-bars/cross-cover examination at near.

We previously reported that in PCS, FP-area and CI were significantly correlated. Here we report that based on MADRS score, CI is highest in the PCS without depression (CI = 7.5(PD) ± 1.2(SE)), moderate (CI = 5.2 ± 1.0) with mild-depression, and lowest with moderate/severe depression (CI = 1.6 ± 0.7).

We demonstrated a negative correlation between CI and depression in PCS, so lack of motivation in PCS did not play a significant role. Depression is likely localized to supra-tentorial brain areas although the source of the deficit might still be infratentorial, whereas CI/VA is associated with brainstem damage. We conclude that PCS generates mixed heterogeneous supra- and infra-tentorial neurological symptoms.

Keywords: *Mild Traumatic Brain Injury; mTBI; Concussion; Post-Concussion Syndrome; PCS; Electrovestibulography; EVestG; Vergence Eye Movement; Convergence Insufficiency; Depression*

Abbreviations

PCS: Post-Concussion Syndrome; EVestG: Electrovestibulography; CI: Convergence Insufficiency; RPQ: Rivermead Post-Concussion Questionnaire; RPQ3: Score of First Three Symptoms of RPQ; RPQ13: Score of Last Thirteen Symptoms of RPQ; mTBI: Mild Traumatic Brain Injury; VOR: Vestibule-Ocular Reflex; LGN: Lateral Geniculate Nucleus; FEF: Frontal Eye Field; NRTP: Nucleus Reticularis Tegmenti Pontis;

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SOA: Supraoculomotor Area; MLF: Medial Longitudinal Fasciculus; INO: Inter Nuclear Ophthalmoplegia; SPCS: Short-Term PCS; LPCS: Long-Term PCS; MADRS: Montgomery Asberg Depression Rating Scale; NEER: Neural Event Extraction Routine; AP: Action Potential; VOMS: Vestibular/Ocular Motor Screening; EVS: Efferent Vestibular System

Introduction

Biomechanical forces after rapid acceleration or deceleration of the head can cause concussion or mild Traumatic Brain Injury (mTBI), if the patient develops an alteration in consciousness or typical neurological and/or psychological symptoms (e.g. headache, nausea, vomiting, photophobia, imbalance, double/blurred vision, irritability, etc.) within a reasonable timeframe after the injury (2 - 4 weeks) [1-3]. Patients with rotational head movement injury seem to bear a high risk of concussion [4]. The advancement in technology and sport in the past few decades have increased the risk of involvement in accidents in sports, motor vehicles or any other high-speed activities. Concussion can also happen after falls which has become a health concern particularly in the older population. Forty two million people suffer from concussion worldwide every year [5] which makes it a serious personal and public health problem. Usually concussion symptoms recover within four weeks after the head injury; however, if they do not recover and last longer, the neurological condition is called post-concussion syndrome (PCS). PCS usually resolves within three months [6] but 5 - 15% of the PCS patients continue to have symptoms and functional impairments for many more months or even years [7,8], which is then called persistent PCS that disrupts patients' personal and social life significantly [9,10]. Surprisingly, a recent publication showed that 53% of patients with PCS report functional limitations at 12 months after head injury that was statistically significant compared to the control group [11].

Ocular and vestibular systems in PCS

We have recently discussed the ocular and vestibular system abnormalities in PCS in detail [12]. We also provided a detailed anatomy and pathophysiology description to explain how PCS could affect vestibular and ocular systems and particularly disturb convergence function and cause convergence insufficiency (CI) [12]. We reported that CI and afferent vestibular abnormalities (VA) are significantly correlated and the causes of both deficits were likely located in the infra-tentorial brain areas i.e. brainstem [12].

A significant number of PCS patients suffer from eye movement and vestibular abnormalities, many of whom go undiagnosed. Convergence is one of the four major eye movements i.e. saccade, smooth pursuit, vergence, and vestibule-ocular reflex [13]. Epidemiological studies have shown that convergence insufficiency is the most common eye movement abnormality in PCS [14-18], but the value of this deficit, that can be objectively measured, is underappreciated and controversial [19]. Eye movement abnormalities in PCS [13,17,20,21] might be an opportunity in developing paradigms and instruments for objective and early diagnosis of PCS [22,23].

There is less controversy about vestibular abnormalities compared to ocular abnormalities in PCS [24-26]. Dizziness and imbalance are two common presenting symptoms in PCS patients. The cause of dizziness is not yet well understood, but ocular and/or vestibular system abnormalities are possible candidates [27,28].

We studied the vestibular function with electrovestibulography (EVestG) technology that measured the spontaneous and activity driven vestibulo-acoustic, predominantly vestibular activities [29,30]. It has been hypothesized that EVestG can pick up and analyze efferent signals showing the status of central and peripheral vestibular systems. Recent studies have shown that EVestG can be used as a diagnostic tool for PCS [26,31-33] and its comorbidities, such as depression [34] as well as its recovery [35].

Depression in PCS

The physiopathology and cause of depression is unclear but it is well established that it is multifactorial i.e. includes genetic predisposition, environment, and psychological factors. Several hypotheses have been proposed such as abnormalities in monoaminergic system, immunological systems and functional-emotional circuit.

Monoamine neurotransmitters (MN) such as dopamine, serotonin and epinephrine, are involved in many brain functions including fight and flight, movement tuning, emotional regulation, etc. They exist in almost all vertebrates. These neurotransmitters are among the

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oldest in these species and help them to adapt to new environments [36,37]. MNs are produced in Monoamine nuclei in brainstem and are the major communication neurotransmitters in these nuclei (i.e. includes raphe nuclei, ventral tegmental area and locus coeruleus).

Abnormality in serotonergic system is one of the major candidates in explaining the pathophysiology of depression disorder. Although serotonergic system abnormality cannot capture all features of depression disorder, it can explain the majority of the clinical and physiological findings in depression; for instance, most of the major anti-depressive medications, either directly or indirectly, affect the serotonergic system. Serotonin is produced in Raphe Nuclei and transported to almost all cortical and subcortical areas of the brain through the vast projections of serotonergic system to the cortex [38,39]. The connections between Raphe Nucleus and some cortical areas such as orbital cortex, cingulate cortex, medial preoptic area, lateral preoptic area, and hypothalamus are mutual and therefore these areas modulate the serotonergic system. The connection between Raphe Nucleus and orbital cortex has been shown to be important in depression [40].

The Serotonergic system is involved in many cortical and subcortical brain functions and decreased serotonergic neurotransmission plays a significant role in depression [41]. Serotonin can affect different neurons in the cortex e.g. Pyramidal cells and Astroctyes [42-44]. The effect of Monoamine neurotransmitters on Astrocytes is particularly interesting as they play an important role in production of neurotrophin-3 by these cells [45]. Neurotrophins and Astrocytes play an important role in pathophysiology of PCS and its recovery. Neurotropins are involved in maintaining neuronal integrity and recovery after brain injury [46].

It has been shown that other Monoamine tramsmitters are affected in depression as well. There is evidence for decreased size of the locus coeruleus, decreased activity of tyrosine hydroxylase, and increased density of alpha-2 adrenergic receptor in depression which overal suggest decreased adrenergic neurotransmission [47,48].

It has also been found that biogenic amines play an improtant role in brain functional abnormalities in PCS as well [49]. It is concievable that the cause of depression in PCS is through the disturbance of production and/or transport of MNs to the cortex, which can help explain the infra- and supra- tentorial symptoms in PCS.

It is well-known that a number of cognitive functions including attention, visuospatial processing, working memory, speed processing and predictive behavior [50-53] are linked to ocular sensorymotor system which are found to be abnormal in PCS [54-56]. In our study, to our surprise we found a negative but significant correlation between depression and CI. To the best of our knowledge, this is the first report of such negative correlation. We provide some possible explanations for these findings in the discussion section.

Methodology

Participants and assessments

Concussed patients were recruited from neuro-ophthalmology clinic (author BM) (similar pool of participants to that reported previously [12,34]. Forty-eight individuals (16 males, 44.5 ± 14.9 years) with PCS (Table 1), ten patients (3 males, 43.2 ± 18.5 years) with short-term PCS (SPCS-concussion < 3 months prior to testing) and thirty-eight patients (13 males, 44.8 ± 13.7 years) with long-term PCS (LPCS- concussion > 3 months prior to testing) were tested.

Parameters	Drain (N = 76)	Non-drain (N = 92)	P value
Average age (in years)	53.45 ± 3.42	54.27 ± 2.35	0.378
Male/female	47 (61.8%)/29 (38.1%)	56(60.8%)/36(39.1%)	0.435
Diagnosis (OA: ONFH)	36:40	39:53	0.512
Body mass index (kg/m^2)	27.3 ± 1.7	28 ± 1.6	0.537
Duration of surgery (min)	112 ± 21	105 ± 18	0.230

Table 1: Baseline characteristics of patients.

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Majority of LPCS patients were tested between 3 months and 5 years after the head injury (only 2 patients were symptomatic for more than 10 years). EVestG recording, comprehensive neuropsychological assessments, and a screening hearing test were done at Neural Diagnostic Laboratory, Riverview Health Center, Winnipeg, Manitoba and RPQ Glasgow Coma Scale test and clinical examinations were done by a neurologist and neuro-ophthalmologist at Adult Medical Clinic, Victoria General Hospital, Winnipeg, Manitoba. University of Manitoba Biomedical Research Ethics Board approved this study and participants signed an informed consent form before they were tested. Screening hearing tests showed that all patients had normal hearing.

Convergence insufficiency

We discussed the CI measurement in detail previously [12].

EVestG recording

A typical EVestG recording procedure comprises placing active and reference electrodes. Active electrodes (Cotton Wool (Figure 1A)) were rested close to the tympanic membrane of each ear (Figure 1B). An identical reference electrodes were placed on the entrance of each ear canal. One common ground electrode (Biopac EL258S) was placed on the forehead. The EVestG was conducted with eyes closed and head supported to minimize the muscle artifacts on a hydraulic chair inside an electromagnetically shielded and sound attenuated (> 30 dB) chamber.
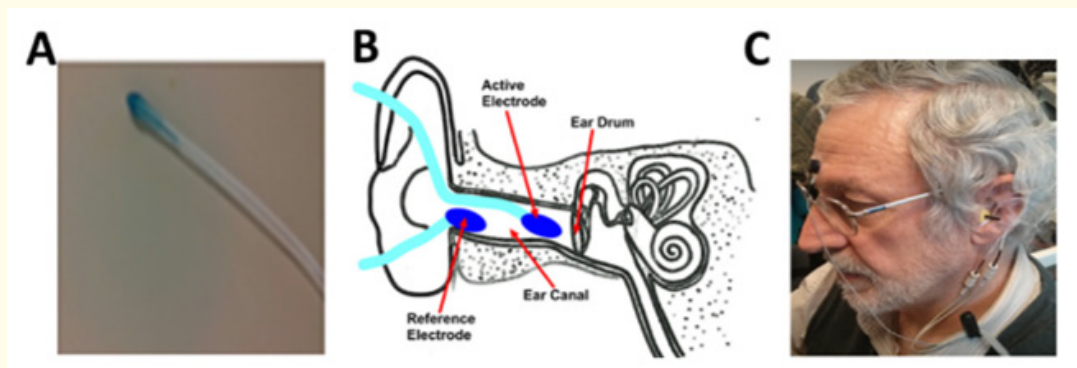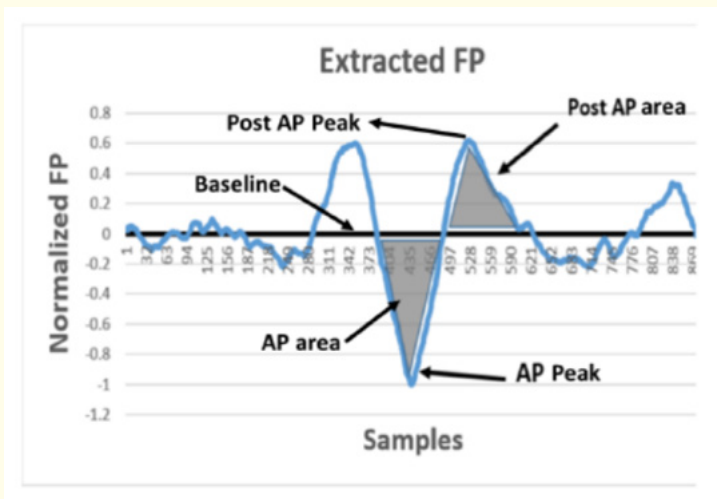

Figure 1: (A) Ear electrode; (B) electrodes placement; (C) participant connection.

The recording was performed whilst the chair was stationary and moving. However, we only analyzed the stationary segments to minimize the body movement artefacts resulted from the tilting. Previously, we showed that the analysis of stationary segment of the data of our results could separate PCS and healthy control populations [26].

To produce an average FP plot, shown in figure 2, the wavelet-based signal processing technique called Neural Event Extraction Routine (NEER) [29] averaged the detected spontaneous and driven FPs buried in the noise. AP area represents the area bounded between the baseline and the AP point as shown in figure 2.

An example of an averaged FP extracted from EVestG signal during the background phase was demonstrated in figure 2. The active electrode was placed proximal to the eardrum without touching it. Given that electrode contact impedance (read wax build up and dry skin) and placement variations could change the average extracted amplitude we normalized the FP to -1 to facilitate comparison between participants.

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Figure 2: A typical normalized FP extracted from EVestG signal during background phase. AP area: the bounded area between baseline and AP peak. Post AP area: area bounded between baseline and Post AP peak. The sum of the AP area and post AP area was used as a characteristic feature and called the FP-area. (Horizontal scale 44.1 samples = 1ms).

Neuropsychological assessments

Rivermead post-concussion questionnaire (RPQ) score was used to measure the severity of PCS [57,58] and contained questions about 16 post-concussion symptoms. The severity of each symptom was scored from 0 to 4. The RPQ score was divided into two sub-scores to achieve unidimensional constructs [57]: (1) RPQ-3 is the score of the first three symptoms, headaches, dizziness and nausea, which are categorized as most common symptoms in concussion [57], (2) RPQ-13 is the score of the thirteen symptoms, which are common symptoms in prolonged PCS [57]. RPQ-13 includes 4 questions regarding depression and mood as well.

Montgomery-Asberg depression rating scale (MADRS) MADRS is used to measure the severity of depression [59]. It contains a ten-item diagnostic questionnaire with a total score of 60. Score < 6 indicates no depression; score = 7 - 19 is considered as asymptomatic-mild depression and score > 19 indicates moderate/severe depression.

Analysis

Previous studies have shown association between abnormalities of eye movements and depression as well as other mood disorders [60]. In order to test different factors which might lead to CI development in PCS patients, we divided our PCS data into three subgroups: PCS with (a) no depression (n = 14), (b) mild depression (n = 19), and (c) moderate/severe depression (n = 15) (the depression level was determined based on their MADRS assessment); we considered each subgroup as an independent variable. Then, we used a univariate analysis to test the following measures in each of the sub-groups: (1) CI measured in prism diopters (PD), (2) EVestG AP areas, (3) MADRS score and (4) RPQ3 and RPQ13 scores, respectively.

We showed in our previous study [26] that PCS and healthy control average FP results were significantly different ($p < 0.05$) and the difference between PCS and control groups was in the action potential (AP) area (See figure 2). In the current study, in addition to the AP area as a characteristic feature for separating PCS and healthy controls, we also calculated the post-AP area (i.e. area bounded between the baseline and the post-AP peak) of the average FP (See figure 2). We then investigated the association between the combined areas and CI and depression in both pre- and post-AP areas.

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Results

For univariate tests, Mauchly's test indicated that the assumption of sphericity had not been violated for any of the dependent variables. Univariate analysis showed that there was no main effect for depression on the EVestG features. Post-hoc analysis showed a significant difference in the EVestG feature between PCS with no depression and PCS with moderate/severe depression ($p < 0.01$) and between PCS with mild depression and PCS with moderate/severe depression ($p < 0.01$).

No main effect was found for depression for the CI measure. However, post-hoc analysis showed a significant difference in the CI measure between PCS with no depression and PCS with mild depression ($p = 0.02$), PCS with no depression and PCS with moderate/severe depression ($p < 0.01$) and PCS with mild depression and PCS with moderate/severe depression ($p < 0.01$).

No significant correlation was found between RPQ13 and the CI or FP-area. However, when the PCS population was sub-grouped based on their MADRS score, RPQ13 showed a significant correlation with CI ($R = 0.8$, $p = 0.03$) and FP-area ($R = -0.8$, $p = 0.03$) in the PCS with no depression subgroup (Table 2).

Parameters		Drain (N = 76)	Non- drain (N = 92)	P value
Intra operative blood loss (ml)		282.3 ± 68.2	258.4 ± 71.1	0.339
Drainage volume after 48 hours (ml)		110 ± 123.14	00	0.000
Calculated blood loss (ml)		1008.8 ± 252.8	970.6 ± 199.1	< 0.05
Hemoglobin level (ml)	Pre-operative	11.70 ± 1.31	11.84 ± 1.42	> 0.05
	Post-operative after 48 hours	9.76 ± 1.12	10.72 ± 1.38	< 0.05
Hematocrit level		26 ± 6	29 ± 5	< 0.05
Blood transfusion patients		57 (75%)	48 (52.17%)	< 0.05
Total no. of Blood transfusion unit		55.5 ± 10.32	27 ± 11.37	< 0.05
Superficial wound infection		2 (patients)	2 (patients)	> 0.05
Hospital stay (day)		7.8 ± 1.23	5.2 ± 1.34	0.312

Table 2: Clinical outcomes between the two groups.

Figure 3 shows the correlation between CI and RPQ13 and CI and RPQ13 when only the 4 RPQ depression symptom questions are used. This figure demonstrates that the calculated correlation between RPQ13 and CI (or FP-area) increases when the PCS population is sub-grouped based on the depression score.
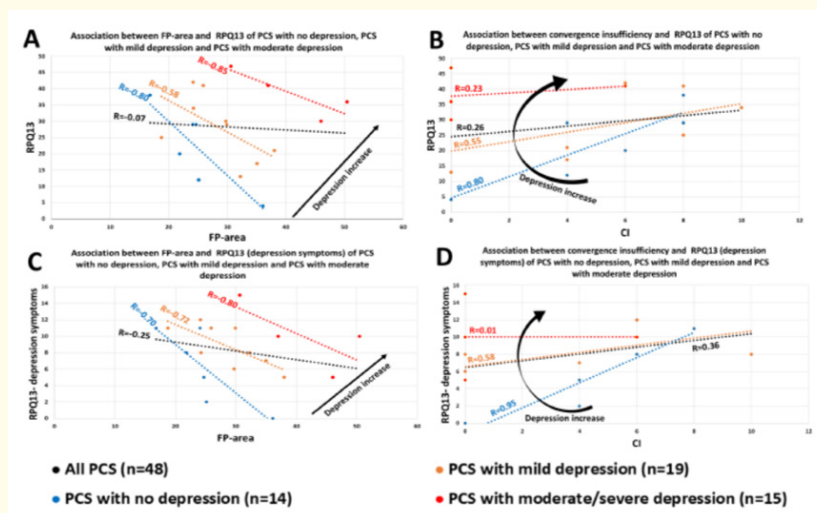

Figure 3: The calculated correlations between (A) FP-area and RPQ13, (B) CI and RPQ13, (C) FP-area and RPQ13 when only the depression symptoms were considered (D) CI and RPQ13 when only the depression symptoms were considered.

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Discussion

In our previous paper we describe possible pathophysiology of CI and its clinical significance [12,14-17]. We reported that CI was correlated with VA in PCS and it seemed that both abnormalities were caused by brainstem malfunction in concussion. In that study, no significant association was found between CI and the AP-area; however, a significant association was found when the AP-area and the post-AP area were combined (Figure 2). We hypothesized that by adding the post-AP area, we arguably included an increased representation of the brainstem activity. The significant association of CI and FP only when the post-AP was added to the AP-area suggested a more dominant role of brainstem vestibular abnormality in CI.

Unlike several previous studies which have shown depression and other mood disorders were positively associated with abnormalities in eye movements and visual information processing [60-62], here in our PCS group, the CI measure and depression were negatively correlated (Figure 3B). We found a significant difference between the PCS and comorbid depression subgroups, wherein PCS with no depression subgroup had the highest CI (CI = 7.5 PD ± 1.2(SE)), PCS with mild depression subgroup showed moderate CI (CI = 5.2 PD ± 1.0(SE)) and PCS with moderate/severe depression subgroup had the lowest CI (CI = 1.6 PD ± 0.7(SE)). Interestingly, the average FP-area increased with depression (See table 1). The cause of this negative correlation between CI or FP-area and depression is unclear.

Some studies have shown that depression after brain trauma may influence the patients' perception of PCS symptoms and those depressed PCS individuals usually report greater severity of symptoms in the RPQ score compared to non-depressed PCS individuals. However, this phenomenon cannot explain our results. In this study the PCS patients with moderate to severe depression showed the least CI. A possible explanation for our finding is that CI is a mainly infra-tentorial brain abnormality (i.e. brainstem dysfunction) whereas depression is a supra-tentorial dysfunction (i.e. cortical abnormality). Therefore, these two parameters can show different and opposite effects in different concussed patients which suggest that most likely PCS patients can be categorized into two population groups with dominantly supra- or infra-tentorial symptoms. Further evidence for this theory is that the significant correlation between RPQ13 and CI or FP-area was observed only in the PCS with no depression subgroup (Figure 3). This finding indicates that VA and CI which are 2 objective measures of infra-tentorial abnormalities in PCS were better correlated with the severity of PCS in patients without depression who hypothetically had less supratentorial abnormalities.

Further investigations should be conducted to explain why CI/VA and depression can behave in an opposite way in PCS. Our results show that EVestG can be useful in detecting comorbid depressive/mood symptoms and their potential confounding effects in PCS patients [34,63-65]. The main limitations of this study are: 1) The overall sample size was small, and 2) the EVestG signals, as well as the CI of healthy controls, were not included for comparison with the PCS population. We hope that our study as well as similar studies those have found objective evidence of eye movement abnormalities in PCS open the gate for further investigations in visual and vestibular abnormalities in PCS [15,28].

Conclusion

Previous studies have shown that depression and other mood disorders were associated with abnormalities in eye movements and visual information processing. Here in our post-concussion syndrome group, the convergence insufficiency measure and depression were negatively correlated. Our findings indicate that convergence insufficiency which is an objective measure of infra-tentorial brain abnormality in post-concussion syndrome (PCS) and can be measured by an ophthalmologist in clinic, was better correlated with the severity of PCS in patients without depression who hypothetically had less supra-tentorial abnormalities. This finding is novel and important because it provides the clinicians with an objective clinical measure in visual assessment of patients with concussion and compare that to their mood issues.

Disclosure of Interest

The author Brian Lithgow has less than 0.5% in the supporting company Neural Diagnostics Pty. Ltd.

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Volume 11 Issue 7 July 2020