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The Impact of Age on Post-Concussive Symptoms: A Comparative Study of Symptoms Related and Not Related to the Default Mode Network

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Summary

The Default Mode Network is a network of connected brain regions that are active when the brain is not focused on external tasks. Minor brain injuries, such as concussions, can affect this network and manifest symptoms. We measured the correlation between the symptoms people experienced after a concussion and their age at the time the concussion occurred. We hypothesized that some symptoms, including depression, anxiety, insomnia and other sleeping problems, have a higher correlation with age than other possible symptoms. Data were collected from 133 people who had experienced concussions, as well as data from 24 healthy controls. Investigation of healthy controls via regression analysis revealed no notable or significant patterns. In concussed individuals, the incidence of sleeping problems was not correlated with the maturity of the Default Mode Network; however, there was a higher percentage of people who had a concussion between the ages of 14–16 who experienced depression, anxiety, and insomnia, as compared to other age groups and symptoms. By comparing the regression analyses, we determined that the symptoms not related to the Default Mode Network were more linearly correlated with age than symptoms related to the Default Mode Network. This phenomenon is intriguing and deserving of further research.

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Introduction

Concussions have long-lasting effects that can make everyday activities, such as going to work, doing homework, or engaging in physical activities, difficult. Helping people recover from concussions mostly involves treating symptoms and ensuring the concussed person has adequate time to recover from their injury (i.e., time off of school, work, or physical activities). People who have experienced one or more concussions are at risk of developing Post-Concussive Syndrome (PCS), which is characterized by symptoms continuing for longer than expected based on the severity of their concussion (1). There is currently no known way of determining who is more likely to develop Post-Concussion Syndrome (2).

This study focused on the post-concussive symptoms of insomnia, sleeping problems, depression, and anxiety, and their correlation with age at the time of their concussion. This study does not focus on the grade or level of severity of a concussion.

The Default Mode Network (DMN) is active when a person is not focusing on something external, such as when engaging in a repetitive task, at rest, daydreaming, thinking about the future, or contemplating another person's mental/emotional state. It is also active during self-reflection, moral reasoning, and while internally replaying memories (3). Additionally, it plays a role in conscious awareness (3). Two hubs of the DMN include the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC) (4). Other areas include the angular gyri (AG), the bilateral inferior parietal cortices (IPl and IPr), the medial temporal lobe, and the ventral precuneus (5). Around the ages 10–13, the DMN undergoes enormous development and the connection between the mPFC and the PCC (the last brain connection within the Default Mode Network to fully develop, and is immature for a longer time than all the other connections within the Default Mode Network) becomes more integrated. Also during these ages, the DMN segregation increases, and therefore, becomes less interconnected with other networks (3). In the event of a mild traumatic brain injury (MTBI), the connectivity between the PCC and other regions, including the mPFC, is temporarily decreased (6). Therefore, one can infer that cognitive functions related to a well functioning connection between the areas of the DMN, specifically between the PCC and mPFC, would be affected after a concussion.

As brain maturity was not directly tested in this study, we were unable to investigate whether maturity of the DMN affects experienced symptoms; however, this study has implications regarding DMN maturity and does focus on DMN-related symptoms.

During sleep, the functional connectivity between the mPFC and PCC decreases. This connection becomes nearly insignificant the deeper a person falls into sleep (5). Given that DMN connectivity has been shown to be atypical after a concussion, it makes sense that

after a mild traumatic brain injury sleeping patterns are also atypical. In fact, 84% of people experience trouble sleeping after a concussion (7). It is for this reason we hypothesize that some of the post-concussive symptoms most related to age at the time of concussion are insomnia and other sleeping problems.

People suffering from anxiety disorders (including General Anxiety Disorder [GAD], Post Traumatic Stress Disorder [PTSD], and Obsessive Compulsive Disorder [OCD]) experience decreased activation in the mPFC and the PCC (8). As decreased activation between these two areas is known to occur in people after mild traumatic brain injuries, it seems natural that some people develop anxiety after concussions (6). It is possible that anxiety may be more likely to occur in people who have had concussions at an age when, based off of literature, their DMN is not fully developed.

Studies investigating depression and PCC connectivity have found different results. One such study found that people with depression exhibited increased functional connectivity of the PCC (9). Another study found that when at rest, people with Major Depressive Disorder have decreased functional activity between the mPFC and the PCC (10), suggesting that people diagnosed with depression demonstrate atypical functional connectivity of the PCC. Based on the information given, it is reasonable to hypothesize that depression as a post-concussive symptom is also uniquely linked to the age at the time of concussion. Due to the uncertain nature of the studies done on the topic, analyses of this symptom may need to be done separately.

Symptoms of PCS include anxiety and depression (1). Likewise, many symptoms of PCS are seen in people with anxiety and depression. Because of this, it has been hypothesized that people who already have psychiatric conditions may be more likely to develop PCS (11). It may also be possible that depression and anxiety, and their associated symptoms, are also symptoms of PCS because the cause of PCS and of those mood disorders is the same. Anxiety and depression are both related to atypical connectivity between the mPFC and the PCC – two central hubs of the DMN (8, 9). This connection's relationship with sleep and the relationship between insomnia and concussions suggestively support the hypothesis of this study.

Post-concussive symptoms include depression, anxiety, insomnia, memory loss, headaches, memory problems, trouble concentrating, sleeping problems, restlessness, apathy, sensitivity to noise or light, irritability, personality changes, dizziness, vertigo, and fatigue. We expected that symptoms related to the functional connectivity of the DMN would exhibit different age-related patterns. Specifically, if a concussion occurs before the age of thirteen (i.e., before the average person's DMN is developed, according to current literature), then the person would be more likely to experience insomnia, sleeping problems, anxiety, and depression.

Results

Data from 24 female participants and 19 male participants was analyzed. Participants experienced concussions at ages ranging from less than 1 years old to more than 50. These individuals were grouped into four populations: population 1 (concussion at age 13 or younger) included 14 people, 8 females and 6 males. Population 2 (concussion between ages 14–16) consisted of 11 people, 5 females and 6 males. Population 3 (concussion between ages 17–22) included 12 people, 5 females and 7 males. Population 4 (concussion at 23 years of age or older) was made up of 6 people, all of whom were female. Analysis by gender revealed no significant differences.

Interestingly, symptoms related to the connectivity between the mPFC and the PCC (depression, anxiety, insomnia), with the exception of sleeping problems, demonstrated a slightly different pattern than those that are not. In theory, the percentage of people that develop a given symptom after their concussion should increase the older they are. If someone were to have a concussion when they are 50 years old, they would be more likely to experience symptoms than if they had a concussion when they were 12 because their brain has less plasticity.

Symptoms not related to mPFC-PCC connectivity (i.e., trouble concentrating, memory problems, headaches, etc.) tended to follow the expected pattern (**Figure 1a**). However, for depression, anxiety, and insomnia, the highest percentage of people experiencing these symptoms was between the ages fourteen and sixteen (population 2). For sleeping problems, the highest percentage of people experiencing those symptoms was tied between population 3 and 4 (the oldest two age groups), which is more similar to the pattern displayed by other non-DMN symptoms (**Figures 1a and 1b**). If the different pattern seen in depression, anxiety, and insomnia was due to a high number of people in the ages 14–16 who experienced more severe concussions, we would expect a spike in the percentage of people in that age group that developed other symptoms; however, this unique pattern existed only in the symptoms of depression, anxiety, and insomnia.

In data collected from healthy controls, we found no strong age-related correlations, nor any consistently elevated percentage of individuals experiencing symptoms. There was also no notable difference between DMN and non-DMN-related symptoms when compared to age. These findings were confirmed by two

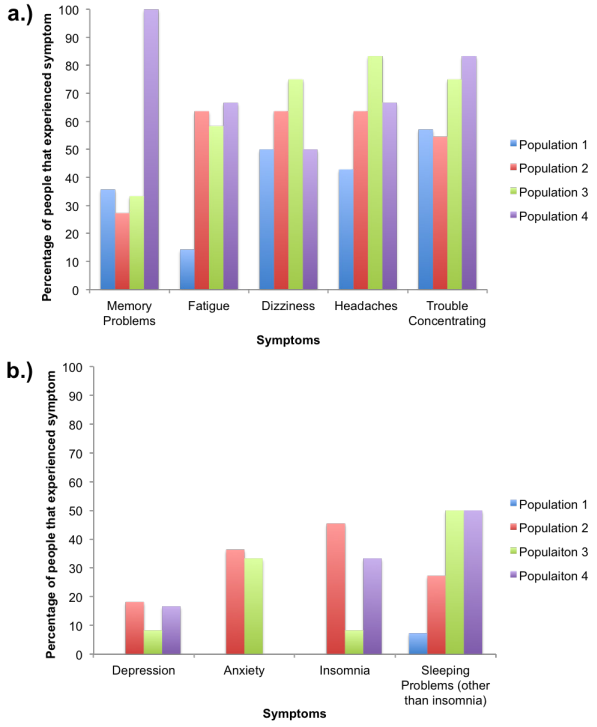

Figure 1: Percentage of people (who have had concussions) who experienced symptoms in each age group. Non-DMN-related symptoms are shown in **(a)** and DMN-related symptoms are shown in **(b)**.

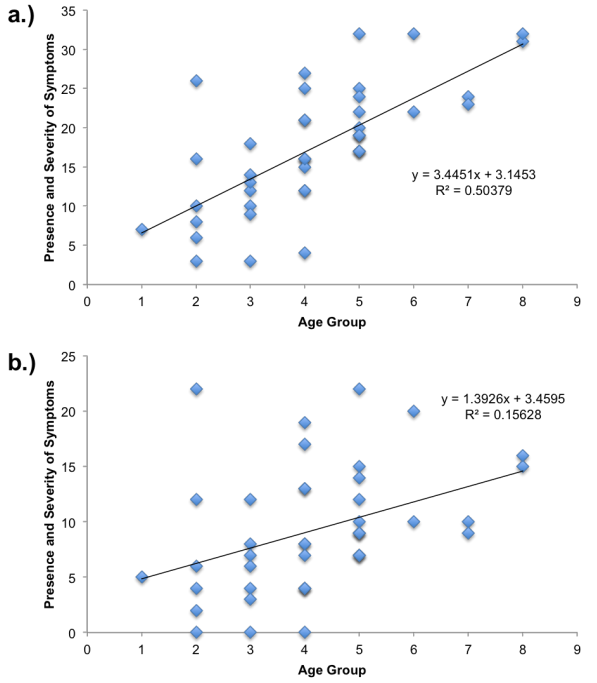

Figure 2: Age at time of concussions vs. symptoms. Non-DMN-related symptoms are shown in **(a)** and DMN-related symptoms are shown in **(b)**.

regression analyses on both DMN and non-DMN related symptoms, which revealed neither significant values nor noteworthy patterns.

To perform regression analyses on both healthy controls and concussed individuals, data on age was broken down into eight smaller age groups. Group 1 consisted of people who had a concussion when they were 5 or younger; group 2 between the ages of 6–9; group 3 between 10–13; group 4 between 14–16; group 5 between 17–22; group 6 between 23–39; group 7 between 40–50, and group 8 over 50.

Two regression analyses consisting of data from participants who had experienced one concussion were used to determine how well a symptom correlated with age in an increasing linear pattern (which it should if the presence and severity of symptoms was not affected by the maturity of the Default Mode Network). The presence and severity of non-DMN-related symptoms expressed as a function of age at the time of concussion explains a greater amount of variability than the presence and severity of depression, anxiety, insomnia, and sleeping problems in correlation with age. To further explore this pattern, another analysis was preformed to compare the correlation coefficients of the two graphs. It was found that non-DMN-related symptoms were significantly more linearly correlated with age at the time of concussion than were DMN-related symptoms ($p < 0.0005$). As people who experienced sleeping problems demonstrated an age distribution more consistent with non-DMN-related symptoms (**Figure 1b**), the comparison between the correlation coefficients derived from **Figures 2a and 2b** may have been even more significant had this particular symptom not been included.

In Figure 2b, the rankings of symptoms that are not related to the functioning of the DMN follow closely to the expected pattern: a steady increase of presence and severity of symptoms with age. The symptoms that are related to the DMN differ from their expected rankings much more, but they do not differ in such a way that they match the pattern that would be expected if brain maturity played no role at all (**Figure 1b**).

When compared to age group, no difference between the patterns of DMN and non-DMN-related symptoms was noticeable in the healthy control group. (**Figures 3a and 3b**).

Discussion

Post-Concussion Syndrome can be diagnosed if several of the symptoms of a concussion persist longer than typical for a traumatic brain injury of the given grade. These symptoms include depression, anxiety, insomnia, memory loss, headaches, dizziness, vertigo, fatigue, memory problems, trouble concentrating, sleeping problems, restlessness, apathy, sensitivity to noise or light, irritability, and personality changes (2). While there is no sure way of predicting PCS, it is

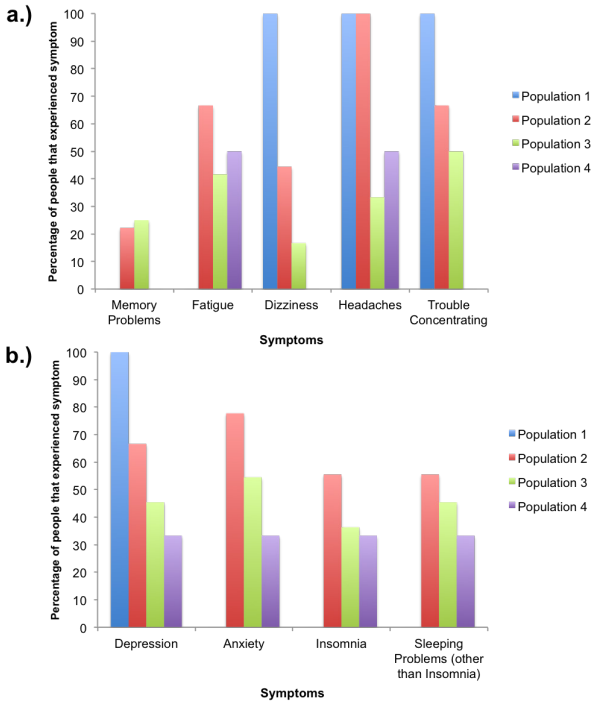

Figure 3: Percentage of healthy controls who experienced symptoms in each age group. Non-DMN-related symptoms are shown in **(a)** and DMN-related symptoms are shown in **(b)**.

theorized that because symptoms of PCS reflect and include the symptoms of anxiety and depression, that people with psychiatric conditions are predisposed to Post-Concussion Syndrome should they experience a traumatic brain injury (12). If the phenomenon that is studied in this research is indeed localized to people who develop PCS, it may be possible that this link between the symptoms of mood disorders and the symptoms of PCS is not due to a predisposition, but is in actuality due to a common cause shared by PCS and anxiety and depression. Further research into this idea could reveal if the development of PCS is related to abnormal connectivity between the mPFC and PCC.

As with any study where data is primarily collected through surveys, this study was dependent upon people providing accurate data. Some participants had concussions when they were very young, and in some cases, they did not remember if they had experienced particular symptoms after their concussion. If a person was unsure as to whether or not they had a symptom, it was assumed that they had not.

Numerous symptoms that a person may have experienced after a concussion could be affected by many other factors in their life that could not be controlled. It is possible that some of the people who developed symptoms, such as depression, after concussion were genetically pre-disposed to those symptoms, or there was something else that contributed to causing this symptom. These are all influences that could not be controlled.

In the healthy control group, there is a slight spike in the percentage of people who experienced a given symptom in Population 2 (ages 14–16). This may in part explain why this same spike is seen in DMN-related symptoms of individuals who experienced a concussion at that age. This does not explain why this same pattern did not occur in the group of participants with concussions in non-DMN-related symptoms. Thus, the difference in pattern between DMN-related symptoms and symptoms not related to the DMN remains an intriguing and unexplained phenomenon.

The hypothesis of this study was that age affects which symptoms individuals experience after a concussion. This study used age as an indirect means of measuring neural development. Age is an imperfect indicator of neural development, as every person's brain development is unique. Therefore, the relationship between actual neurological DMN development and concussion symptoms were not directly tested.

Data was collected to control for the presence of symptoms in people who had never had a concussion. However, the data for this group was collected nearly a year after the data from the people with concussions was gathered. As a result, one cannot state that this group perfectly operates as a control.

As with any study in which data is gathered mostly through surveys, data collection was difficult. More data would have made it easier to determine if there are any patterns that are small and difficult to spot or analyze. It is possible the difference in pattern between most DMN-related symptoms and other symptoms would have been even clearer if the presence of Post-Concussion Syndrome had been taken into account. If the brain takes a longer time to heal, as it does in people with Post-Concussion Syndrome, then there may be a higher correlation between age and specific symptoms. This may occur because depression, anxiety, insomnia and other sleeping problems are related to atypical functioning or connectivity of the brain, and therefore, their connection with age may become more apparent when the healing of the brain is also atypical. This is potentially very interesting and would require further study, as there is not enough data generated by this project to analyze this.

The brain has a unique ability to heal and learn in ways that can be surprising and even miraculous. This study has the potential to help people who have had concussions to better estimate what symptoms they may experience and what impact their concussion may have on the rest of their life. Ideally, a better idea of what someone may experience would help set out a clearer treatment plan and hopefully help our brains to recover.

Methods

Data gathered were mostly self-reported through surveys created by the researcher. Information about nine concussion patients was also gathered through de-identified data provided by physicians. The data collected included information about gender, the number of concussions the participant may have experienced, the severity of their concussion(s), and the age they were at the time of their concussion(s). Information was also collected about the symptoms experienced post-concussion(s), duration of symptoms, and diagnosis of Post-Concussion Syndrome (PCS). Questions were asked about the potential presence of depression, anxiety, insomnia, sleeping problems, diagnosed mood disorders including depression, GAD, PTSD, and Attention Deficit Hyperactivity Disorder (ADHD), the existence of other brain injuries such as a stroke, and any possible diagnosis of neurological illnesses including schizophrenia, autism, and Alzheimer's, and if these had existed before any concussions.

Data collected from healthy controls who had never experienced a concussion included information about age, gender, and whether or not they had within the past several years experienced symptoms associated with PCS, and the duration of those symptoms. No individuals within the healthy control group reported being diagnosed with any mood disorders, neurological illnesses, or any brain injuries including concussions and strokes.

Data were collected from people who had experienced any number of concussions, as well as from people who had never experienced one. We only analyzed data from the group of 43 people who had experienced only one concussion because age is the main variable focused on in this study, and we could not account for an individual having multiple concussions at different ages. The patterns seen when comparing concussion symptoms to age were compared to the presence of symptoms in controls of the same age group. No data from people who had other forms of Traumatic Brain Injuries (such as a stroke) were analyzed. Additionally, data from people who were diagnosed with anxiety, OCD, PTSD, depression, or insomnia, prior to their concussion were not analyzed.

This study indicates that age is very likely correlated with what symptoms manifest following a concussion. Symptoms not related to the functioning of the DMN closely follow the expected relationship between age and number and severity of symptoms. On the other hand, symptoms related to the DMN do not exhibit this relationship and instead demonstrate a spike in symptoms in ages 14-16. This is contrary to the hypothesis of this study, which predicted that DMN-related symptoms would show an inverse correlation with age. Further research may reveal the precise cause of the increase in DMN-related symptoms in ages 14-16, or investigate why sleeping problems do not appear to demonstrate the same age-related pattern as other symptoms related to the connectivity of the DMN.

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