



## Neural evidence that conscious awareness of errors is reduced in depression following a traumatic brain injury



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### ARTICLE INFO

#### Article history:

Received 19 September 2014

Accepted 20 January 2015

Available online 28 January 2015

#### Keywords:

Electroencephalography (EEG)  
Error related negativity (ERN)  
Major depressive disorder (MDD)  
Error positivity (Pe)  
Traumatic brain injury (TBI)

### ABSTRACT

Impaired error awareness is related to poorer outcome following traumatic brain injury (TBI). Error awareness deficits are also found in major depressive disorder (MDD), but have not been examined in the MDD that follows a TBI (TBI–MDD). This study assessed neural activity related to error awareness in TBI–MDD. Four groups completed a response inhibition task while EEG was recorded – healthy controls ( $N = 15$ ), MDD-only ( $N = 15$ ), TBI-only ( $N = 16$ ), and TBI–MDD ( $N = 12$ ). Error related EEG activity was compared using powerful randomisation statistics that included all electrodes and time points. Participants with TBI–MDD displayed less frontally distributed neural activity, suggesting reduced contribution from frontal generating sources. Neural activity during this time window is thought to reflect conscious awareness of errors. The TBI-only and MDD-only groups did not differ from controls, and early error processing was unaffected, suggesting early error detection is intact.

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### 1. Introduction

Individuals who have suffered a traumatic brain injury (TBI) are significantly more likely to develop major depressive disorder (MDD) than the general population (Jorge et al., 1993; Kaponen et al., 2002; Satz et al., 1998). While research has examined the psychosocial factors contributing to the development of TBI–MDD, little research has examined changes in brain activity. Advancing our understanding of brain activity alterations in this group is likely to be valuable to efforts to predict the development of TBI–MDD and the identification of treatment methods. Impairment in conscious

recognition of mistakes (or error awareness) is associated with poorer rehabilitation and quality of life outcomes following TBI, and may also be a feature of MDD (Pizzagalli, Peccoralo, Davidson, & Cohen, 2006; Sherer et al., 1998; Trudel, Tyrone, & Purdum, 1998). Therefore, impaired error awareness following TBI may be related to the development of MDD following TBI (TBI–MDD). If this is the case, it would suggest that treatments that focus on error awareness may help prevent MDD following a TBI. Electroencephalography (EEG) can measure neural activity related to erroneous responses, so is a good method with which to examine error processing in TBI–MDD.<sup>1</sup>

Two EEG recorded event related potentials (ERPs) reliably index error processing – the error related negativity (ERN) (Gehring, Goss, Coles, Meyer, & Donchin, 1993) and the error positivity

*Abbreviations:* TBI, traumatic brain injury; MDD, major depressive disorder; TBI–MDD, depression following traumatic brain injury; Pe, error positivity; ERN, error related negativity; GCS, Glasgow coma scale; LOC, loss of consciousness; PTA, post-traumatic amnesia; BDI-II, Beck depression inventory II; MADRS, Montgomery–Asberg depression rating scale; WTAR, Weschler test of adult reading; TANOVA, topographic analysis of variance; TANCOPA, topographic analysis of co-variance; GFP, global field potential; TCT, topographical consistency test; RAGU, randomisation graphical user interface; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

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<sup>1</sup> TBI, traumatic brain injury; MDD, major depressive disorder; TBI–MDD, depression following traumatic brain injury; Pe, error positivity; ERN, error related negativity; GCS, Glasgow coma scale; LOC, loss of consciousness; PTA, post-traumatic amnesia; BDI-II, Beck depression inventory II; MADRS, Montgomery–Asberg depression rating scale; WTAR, Weschler test of adult reading; TANOVA, topographic analysis of variance; TANCOPA, topographic analysis of co-variance; GFP, global field potential; TCT, topographical consistency test; RAGU, randomisation graphical user interface; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

(Pe) (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). The ERN is a frontal deflection occurring within 150 ms of an error. There are a number of different theories of the functional significance of the ERN. Research has suggested that it is related to error detection (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), or response evaluation (Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). A review of the literature has also suggested that the ERN reflects the conflict detection process between the correct response and the error response being performed (Larson, Clayson, & Clawson, 2014). The ERN is generated even when participants are unaware of having made an error (Nieuwenhuis et al., 2001). As such, it is considered an indicator of whether reduced error awareness is related to impairments in early automatic processes.

Increased ERN amplitude has been reported in MDD (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2010), although not consistently (Olvet, Klein, & Hajcak, 2010; Schrijvers et al., 2008, 2009). Variability in findings may be due to differences in depression severity across studies (Olvet et al., 2010). A number of studies have examined the ERN in TBI, most focusing on severe TBI. Of the two studies focusing on mild TBI, one showed no changes to the ERN (Larson, Clayson, & Farrer, 2012), while the other showed a reduced ERN amplitude (Pontifex, O'Connor, Broglio, & Hillman, 2009). Of the research examining severe TBI, one study showed no changes (Larson & Perlstein, 2009), while other research has shown reduced ERN amplitude in severe TBI (Larson, Kaufman, Schmalfuss, & Perlstein, 2007), in TBI involving orbitofrontal cortex lesions (Solbakk et al., 2014). Multiple TBIs have also been shown to reduce ERN amplitudes (De Beaumont, Beachemin, Beaulieu, & Jolicœur, 2013). Smaller ERN amplitudes have also been found in individuals exhibiting negative affect following severe TBI, suggesting depression modulates error processing following a TBI (Larson, Kaufman, Kellison, Schmalfuss, & Perlstein, 2009). Results from this group of researchers have indicated that negative affect following severe TBI is even more predictive of reduced ERN than cognitive impairment (Larson, Fair, Farrer, & Perlstein, 2011).

In contrast to the ERN, the Pe (a central–parietal deflection occurring 150–450 ms after an error) is thought to represent processes related to *conscious awareness* of the error, as it is only generated when participants are aware of the error, and is modulated by error salience or significance (Nieuwenhuis et al., 2001; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). Other research has suggested the Pe may relate to affective processing of an error, or behaviour adaptation processes to improve performance (Falkenstein, 2004). However, there is less evidence for these possibilities (Overbeek et al., 2005). Similar to the ERN literature, altered Pe activity is not consistently found in MDD. Some studies have shown reductions in Pe amplitude (Olvet et al., 2010; Schrijvers et al., 2008, 2009), while others have shown no change (Holmes & Pizzagalli, 2008, 2010). This inconsistency may also be an artefact of differences in depression severity across studies. Reductions in Pe amplitude have been consistently found in groups with severe MDD (Olvet et al., 2010; Schrijvers et al., 2008, 2009), while no differences are reported in groups with mild to moderate severity (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008). Only two studies have explored the Pe amplitude in mild TBI. These studies indicated no difference between mild TBI and controls (Larson et al., 2012; Pontifex et al., 2009). Research examining severe TBI has shown mixed results, with some showing no changes to the Pe (Larson et al., 2007), some research showing an increased Pe in patients with orbitofrontal cortex lesions, and other research showing smaller Pe amplitude related to lower self-reported awareness of deficits following severe TBI (Larson & Perlstein, 2009), and that cognitive impairment predicts reduced Pe amplitude, while negative affect does not (Larson et al., 2011).

While previous research does suggest that error processing is altered in both MDD and TBI, nearly all the studies examining the ERN and Pe in these groups have used single electrode analyses and focused on specific time periods of interest. Analyses of this type are vulnerable to false positives (Kilner, 2013), and require a number of assumptions which can differ between studies and lead to inconsistencies in results (Overbeek et al., 2005). These types of analyses are also unable to differentiate between altered neural response strength and altered topographical distributions of activity in the group of interest. More recently, new analysis methodologies have become available that use powerful randomisation statistics to examine all electrodes and time points, resolving these issues while minimising assumptions (Koenig, Kottlow, Stein, & Melie-Garcia, 2011). Additionally, despite the fact that impairments in error awareness are seen following a TBI, and neurophysiological markers of error awareness are altered in MDD, research has not yet examined the effect of TBI–MDD on error awareness. Answering this question may highlight the importance of error awareness as a treatment target for behavioural therapies following TBI, and provide a potential neurophysiological indicator for the development of psychiatric co-morbidity following neurological insult.

As such, the aim of this study was to determine whether neural activity related to error awareness is altered in TBI–MDD. The study compared this neural activity to control, TBI-only, and MDD-only groups to determine whether impairment is consistent with the presence of the TBI, MDD, or unique to the occurrence of TBI–MDD. We compared erroneous response locked EEG epochs across these groups using powerful randomisation statistics that include all electrodes and time points while controlling for multiple comparisons. These methods also differentiated alterations in topographic distribution of activity and neural response strength, and retain good statistical power even with a small sample, enabling strong conclusions to be drawn from a very difficult to recruit population. Given that previous research in MDD has shown inconsistent increases in ERN amplitude, while one of two studies examining the ERN in mild TBI indicated decreased ERN amplitude, we tentatively hypothesised that individuals with TBI–MDD would show unchanged ERN amplitudes and reduced Pe amplitudes, reflecting reduced conscious awareness of errors. It was also hypothesised that the same pattern would be found in the MDD group, but the changes would be of a smaller magnitude than the TBI–MDD group (the changes were expected to be larger in the TBI–MDD group due to the ‘double impact’ of TBI and MDD). Previous research has suggested error processing impairments in MDD are related to altered dorso-lateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) function (Holmes & Pizzagalli, 2008; Pizzagalli et al., 2006), so it was tentatively hypothesised that the MDD groups would show alterations in the frontal regions of activity topographies. Previous research examining mild to moderate TBI-only has shown mixed results for the ERN, and no changes in the Pe. As such, it was hypothesised the TBI-only group in the current study would show no change in the ERN or Pe.

## 2. Methods

### 2.1. Participants

Seventy-one adult participants were recruited across four groups: healthy controls ( $N=18$ ), MDD ( $N=19$ ), TBI ( $N=20$ ), and TBI–MDD ( $N=14$ ). Participants were recruited from a combination of community advertising and the emergency department of the Alfred Hospital in Melbourne. All participants had normal or corrected-to-normal vision. Participants were assessed with the MINI International Neuropsychiatric Interview for the DSM-IV (Sheehan et al., 1998) and excluded if they met criteria for any axis 1 psychiatric disorder (with the exception of depression and generalised anxiety disorder in the MDD groups). Participants in the MDD or TBI–MDD groups were excluded if they did not meet the MINI criteria for current

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