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Executive attention deficits after traumatic brain injury reflect impaired recruitment of resources

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ABSTRACT

Deficits in attention are a common and devastating consequence of traumatic brain injury (TBI), leading to functional impairments, rehabilitation barriers, and long-term disability. While such deficits are well documented, little is known about their underlying pathophysiology hindering development of effective and targeted interventions. Here we evaluate the integrity of brain systems specific to attentional functions using quantitative assessments of electroencephalography recorded during performance of the Attention Network Test (ANT), a behavioral paradigm that separates alerting, orienting, and executive components of attention. We studied 13 patients, at least 6 months post-TBI with cognitive impairments, and 24 control subjects. Based on performance on the ANT, TBI subjects showed selective impairment in executive attention. In TBI subjects, principal component analysis combined with spectral analysis of the EEG after target appearance extracted a pattern of increased frontal midline theta power (2.5–7.5 Hz) and suppression of frontal beta power (12.5–22.5 Hz). Individual expression of this pattern correlated ($r = -0.67$, $p < 0.001$) with executive attention impairment. The grading of this pattern of spatiotemporal dynamics with executive attention deficits reflects impaired recruitment of anterior forebrain resources following TBI; specifically, deafferentation and variable disfacilitation of medial frontal neuronal populations is proposed as the basis of our findings.

1. Introduction

Impaired attention is the most common and debilitating cognitive deficit following traumatic brain injury (TBI), leading to rehabilitation barriers and long-term disability (Stierwalt and Murray, 2002; Ashman et al., 2006; Brenner, 2011). Chronic deficiencies selective to executive attention, such as the capacity to monitor and resolve conflict (Fan et al., 2002), have been demonstrated in both mild and severe TBI (Halterman et al., 2006; Rodríguez-Bailón et al., 2012). Lesion and neuroimaging studies have linked these impairments, measured using tests of conflict processing, to focal cortical and white matter damage in the medial frontal (Niogi et al., 2008), fronto-parietal (Hu et al., 2013), fronto-striatal (Hartikainen et al., 2010) and thalamic regions (Kubat-Silman et al., 2002; Van der Werf et al., 2002; Little et al., 2010; Baker et al., 2016). However, these correlations with structural injuries alone do not provide insight into the underlying pathophysiological mechanisms associated with executive attention deficits after TBI.

In severe TBI and related structural brain injuries, the selective functional vulnerability of anterior forebrain systems has been accounted for by a mesocircuit hypothesis that links the graded deafferentation of central thalamic neurons (Maxwell et al., 2006) to behavioral outcomes as a result of their specializations for activation of frontal and striatal neuronal populations (Schiff, 2010; Fridman et al., 2014; Liu et al., 2015). Neurons within the central thalamus have extensive afferent connections to the anterior cingulate (ACC) (Barbas et al., 1991) and provide important complementary support to frontal cortical contributions during sustained attention (Kinomura et al., 1996; Paus et al., 1997). This is supported by evidence of joint increases in theta power and decreases in beta power in the local field potentials of central thalamic neurons that project to medial frontal populations during the short-term allocation of sustained attention in non-human primate studies (Schiff et al., 2013). Human subject studies of short-term attention also demonstrate increased blood flow in the central thalamus during attentional shifts in visual attention reaction time tasks (Kinomura

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et al., 1996), comparable BOLD activity increases in both ACC and central thalamus during forewarned reaction time tasks (Nagai et al., 2004), and indexing of performance by co-variation of decreasing blood flow within the ACC and central thalamus during auditory attention tasks performed over long vigils (Paus et al., 1997). The continuity of this account of the role of the anterior forebrain mesocircuit network in cognitive impairment after TBI is more specifically supported by recent studies that correlate focal neuronal damage within medial frontal cortices, anterior cingulate, and the thalamus with executive function measures using ^{11}C Flumazenil-PET and ^{18}FDG-PET measurements (Kato et al., 2007; Kawai et al., 2010).

The goal of the present study is to obtain a direct and quantifiable measure of attention specific neuronal activity that reflects the pathophysiology at the individual level in TBI subjects. We hypothesize that executive attention performance reflects the integrity of anterior forebrain resources known to be vulnerable to TBI and that EEG dynamics can provide a direct measure of their functional engagement. Here, we combine the well-vetted Attention Network Test (ANT) paradigm (Fan et al., 2002, 2005), which measures three attention networks - alerting, orienting, and executive, with simultaneously measured EEG. Executive attention, also known as conflict attention, is supported by specific brain regions including the anterior cingulate, medial frontal, lateral prefrontal cortices and striatum (Petersen and Posner, 2012). The EEG dynamics during the ANT have been reported before in healthy subjects (Fan et al., 2007) and in a comparison of young and elderly subjects (Deiber et al., 2013), but not to our knowledge in subjects with brain injury.

Here we develop a novel methodology of EEG analysis to reveal the pathophysiology at the individual subject level; because the TBI subjects in our study have heterogeneous structural damage, we do not source model the scalp signal to predefined regions of interest (Fan et al., 2007) or average across the subjects (Deiber et al., 1996). Instead, we employ principal component analysis (PCA) to reduce data dimensionality and as a way to filter and identify unique dynamical elements that grade with measured behavior. Taking this approach, we find evidence for a physiological measure that indexes performance at the individual subject level and has a direct mechanistic interpretation in the context of traumatic brain injuries.

2. Materials & methods

2.1. Subjects

Thirteen participants who had sustained a TBI were recruited at the JFK-Johnson Rehabilitation Institute in Edison, NJ. All TBI subjects had sustained a TBI (mild, moderate or severe) as a result of a blow to the head followed by a loss of consciousness or period of being dazed and confused, a period of post-traumatic amnesia, or clinical signs of altered neurological function. Based on prior neuropsychological evaluation or self-report with medical documentation of TBI, at the time of the experiment, all 13 participants had persistent cognitive difficulties of varying severity. We only included subjects who were at least 6 months post-TBI. We excluded subjects who had a history of drug or alcohol abuse, and visual, auditory, and/or motor impairments that would interfere with cognitive testing. Clinical profiles of the TBI subjects are shown in Table 1. Injury severity was calculated using the American Congress of Rehabilitation Medicines guideline (Ruff et al., 2009), which uses the duration of alteration of consciousness. All participants were oriented to time, place, and person, spoke English, and were able both to provide informed consent and to complete questionnaires and cognitive testing. Twenty-four control subjects with no history of neurological disease (mean age 43 years, range 23–65 years; 20 males) also participated in the study. The control subjects were age-matched to the TBI subjects as follows. For each of 11 TBI subjects, 2 age-matched control subjects ($\pm$5 years) were included ($n = 22$). For 2 TBI subjects, 1 age-matched control subject each ($\pm$5 years) was included ($n = 2$). Both the Weill Cornell Medical College Institutional Review Board and the JFK-Johnson Rehabilitation Institutional Review Board approved the studies described herein. Written consent was obtained from all study participants.

2.2. Attention network test

Subjects performed the ANT paradigm (Fan et al., 2002), shown in Fig. 1, which is designed to examine three attention networks: 1) alerting, 2) orienting, and 3) executive. The ANT was presented using Eprime (Psychology Software Tools) on a standard flat screen monitor. The total duration of the experimental session was approximately 25 min. The ANT began with a training block of 24 trials with feedback on performance, followed by three blocks of 96 trials, each, with no feedback. Each trial began with a variable fixation period during which the subject fixated on a cross on the center of the screen. There were three cue conditions that preceded the target – no cue, center cue and spatial cue (96 trials each). Both center and spatial cues preceded the target by a fixed time (400 ms). Center cue gave subjects information about timing of the upcoming target, while spatial cues additionally alerted subjects to location of the subsequent target (i.e. above or below fixation). Following this, a set of 5 arrows was presented above or below center fixation. There were two target conditions – congruent (all arrows point in the same direction) and incongruent (center arrow in opposite direction to flanker arrows) (144 trials each). Subjects were asked to push the left or right mouse button indicating the direction of the target (center) arrow. The trials were randomized to present all possible combinations of the three cue and two target conditions. All trials were self-paced, and subjects took brief breaks between the blocks if needed.

Reaction time (RT) was calculated as the time interval between target onset and response button press. Accuracy was defined as the

Table 1
Patient demographics.

ID	Gender	Education (yrs)	Age at time of injury	Injuries	Loss of consciousness	Altered consciousness	Post-traumatic amnesia	Injury severity score	Post-injury (months)
1	M	12	20	1	20 min	24 h	2 months	1	24
2	F	13	47	1	3–4 days	Minimal	1.5 months	3	9
3	M	14	21	1	22 days	2 days	2 weeks	3	6
4	M	16	50	2	30 min	>7 days	60 min	2	8
5	M	18	62	3	2 min	1 h	Seconds	1	16
6	F	15	61	1	<30 min	3 days	0	1	89
7	M	14	61	3	<30 min	30–60 min	0	1	8
8	M	16	48	25	<20 min	6 months	30 min	1	31
9	M	12	49	3	2 months	Unknown	Unknown	3	8
10	F	17	51	3	Few min	>30 min	>30 min	2	46
11	M	19	29	3	1 month	Few months	Unknown	3	25
12	M	12	19	3	>30 min	>30 min	>30 min	2	25
13	F	12	43	1	10 days	2 months	2 months	3	28