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Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia ☆

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H I G H L I G H T S

- Reduced levels of consciousness due to delirium or anesthesia resulted in similarly reduced EEG connectivity.
- In hypoactive delirium there was a less integrated network in the alpha band.
- During recovery from anesthesia there was increased integration in the delta band.

A B S T R A C T

Objective: To gain insight in the underlying mechanism of reduced levels of consciousness due to hypoactive delirium versus recovery from anesthesia, we studied functional connectivity and network topology using electroencephalography (EEG).
Methods: EEG recordings were performed in age and sex-matched patients with hypoactive delirium ($n = 18$), patients recovering from anesthesia ($n = 20$), and non-delirious control patients ($n = 20$), all after cardiac surgery. Functional and directed connectivity were studied with phase lag index and directed phase transfer entropy. Network topology was characterized using the minimum spanning tree (MST). A random forest classifier was calculated based on all measures to obtain discriminative ability between the three groups.
Results: Non-delirious control subjects showed a back-to-front information flow, which was lost during hypoactive delirium ($p = 0.01$) and recovery from anesthesia ($p < 0.01$). The recovery from anesthesia group had more integrated network in the delta band compared to non-delirious controls. In contrast, hypoactive delirium showed a less integrated network in the alpha band. High accuracy for discrimination between hypoactive delirious patients and controls (86%) and recovery from anesthesia and controls (95%) were found. Accuracy for discrimination between hypoactive delirium and recovery from anesthesia was 73%.
Conclusion: Loss of functional and directed connectivity were observed in both hypoactive delirium and recovery from anesthesia, which might be related to the reduced level of consciousness in both states. These states could be distinguished in topology, which was a less integrated network during hypoactive delirium.
Significance: Functional and directed connectivity are similarly disturbed during a reduced level of consciousness due to hypoactive delirium and sedatives, however topology was differently affected.

1. Introduction

Although disturbed consciousness is common in intensive care unit (ICU) patients (Ely et al., 2001; Eijk et al., 2011; Barr et al., 2013), understanding of different mechanisms leading to reduced

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levels of consciousness is limited. Consciousness is a complex state of wakefulness and awareness. (Disturbance of) consciousness has been studied with various techniques, and there is compelling evidence that thalamocoritcal interactions and reduced (cortical) activity are signatures of reduced consciousness (Alkire et al., 2000; Schröter et al., 2012). Disturbance of consciousness may therefore be the result of disruption of interactions between brain areas (Moon et al., 2015). Several methods can be used to characterize these interactions: The (undirected) functional connectivity strength reflects the statistical interdependence of activity of remote brain areas. Directed connectivity could provide additional insight in patterns of the direction of information flow. Finally, the global organization of functional brain networks could be characterized using graph theory.

Two important causes for disturbed consciousness in the ICU are the use of sedatives and hypoactive delirium, which is an acute disturbance of awareness, attention, and cognition that fluctuates within hours due to acute brain dysfunction (American Psychiatric Association, 2013). Whereas the clinical expression of hypoactive delirium and sedation is similar (Zaal and Slooter, 2014), the underlying cause of the disturbance of consciousness is different. Therefore, connectivity patterns might be different as well. Reduced functional connectivity (Lee et al., 2013; van Dellen et al., 2014b), was found during both delirium and recovery from anesthesia in the alpha frequency band. The disturbance of directed connectivity band seemed similar between delirium and loss of consciousness, although in different frequency bands, being the delta and alpha frequency band, respectively. Moreover, during recovery of consciousness the directed connectivity in the alpha frequency band showed an intermediate state between feedforward and feedback patterns (Lee et al., 2013). This recovery of consciousness period is more similar to the level of consciousness in hypoactive delirious patients. However, connectivity alterations during delirium and recovery from anesthesia have not been compared directly. Delirium was studied in patients with advanced age after cardiac surgery (van Dellen et al., 2014b), while propofol-induced loss of consciousness was studied in healthy young subjects (Lee et al., 2013). Moreover, recent insights in methodology of EEG connectivity analysis suggest that the interpretation of these previous studies may be problematic. The directed phase lag index (dPLI) was used to characterize directed connectivity in these studies, which measures the consistency of the phase difference of two EEG time series. This phase difference is dependent on the EEG reference and cannot be interpreted unequivocally in terms of the direction of information flow (Hillebrand et al., 2016). The phase transfer entropy (PTE), an information theory-based measure of directed connectivity, has been introduced to solve these problems (Paluš and Vejmelka, 2007; Lobier et al., 2014; Hillebrand et al., 2016).

Both delirium and sedatives also appear to cause changes in functional brain network organization of alpha band (8–13 Hz) oscillations (Lee et al., 2013; Di Perri et al., 2014; van Dellen et al., 2014b). A more random network topology was found during these states of reduced level of consciousness, which might reflect an inability to properly integrate information (Bullmore and Sporns, 2009). However, the interpretation of these findings is problematic due to methodological issues (van Wijk et al., 2010), and altered network topology may merely reflect a general decrease in connectivity strength (Numan et al., 2015). The minimum spanning tree (MST) has been developed as an unbiased method to characterize network topology across conditions and groups. The MST can be seen as the backbone structure of the network, containing only the strongest connections without forming loops. Based on the MST, network measures can be calculated, which can be interpreted along the lines of conventional graph measures, while characteristics remain unaffected by differences in connectivity strength (Fig. 1) (Tewarie et al., 2015).

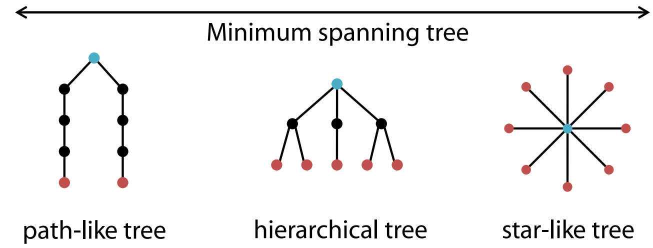

Fig. 1. Schematic presentation of the MST. MST structures can range between a path-like tree (i.e., less integrated network) to a star-like tree (i.e., more integrated network). A path-like tree has two leaf nodes (*red*), all other nodes are connected to their neighbors, which has the disadvantage of being inefficient. A path-like tree has a low leaf number and a high diameter. The other end of the spectrum is a star-like tree, which has one central node (*blue*) and all other nodes are leaf nodes. It thus has a high leaf number and a small diameter. Information can spread easily across the network, but the central node in the star-like tree might suffer from overloading of information. A hierarchical tree is a hypothesized optimal topology, combining a relatively low diameter (which indicates high efficiency) while the relatively low maximum number of connections per node or maximum degree prevents overload of central hub regions. Figure was made based on Fig. 2 in van Dellen et al. (2014a). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The aim of this study was to compare functional and directional connectivity as well as network topology between the episodes of hypoactive delirium and recovery from anesthesia, and non-delirious controls. Based on previous research we hypothesized that functional connectivity is reduced during reduced levels of consciousness, both hypoactive delirium and recovery from anesthesia (Lee et al., 2013; van Dellen et al., 2014b). However, we expected that the direction of information flow and the underlying brain network topology are different depending on the underlying cause of reduced levels of consciousness.

2. Methods

2.1. Study population and procedures

The study population consisted of three groups of cardiac surgery patients. Two groups were described before (van Dellen et al., 2014b). From this study, we included all patients with hypoactive delirium and age- and sex matched non-delirious control patients. In summary, patients were preoperatively included after obtaining informed consent for participation. During the first five consecutive days after cardiac surgery, patients were screened for delirium and examined by a geriatrician, neurologist or psychiatrist who made the classification delirious or non-delirious according to the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-R criteria (American Psychiatric Association, 2000). The Richmond Agitation and Sedation Scale (RASS) (Sessler et al., 2002) was used to determine the type of delirium, with negative RASS scores indicating hypoactive delirium. This study was approved by the local ethics committee (protocol number 11-073).

A third group of patients was included to study recovery from anesthesia, and EEG registrations were made at the ICU directly after cardiac surgery. These patients were age- and sex-matched with the hypoactive delirious and non-delirious control patients on group level. Exclusion criteria for the recovery from anesthesia group were cerebral damage prior to surgery based on chart review, postoperative signs of delirium, hallucinations without delirium, transient ischemic attack, stroke, or any other type of perioperative cerebral damage. The local medical research ethics committee waived the need for informed consent for EEG