USING GRANGER CAUSALITY TO CHARACTERISE BIDIRECTIONAL INTERACTIONS IN THE HUMAN BRAIN DURING INDUCTION OF ANAESTHESIA

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Abstract: General anaesthesia is a reversible state whereby conscious experience is disrupted and reflexes to afferent stimuli are depressed. The precise method of action of anaesthetic agents is still largely unknown. However, the administration of anaesthetics causes observable changes in the electrical brain activity (EEG), the study of which can provide an insight into the mechanism of action of general anaesthesia. This paper investigates the patterns of bidirectional interactions that are manifest in brain activity during anaesthetic induction with propofol. Granger Causality is applied to the EEG of patients scheduled for surgery under general anaesthesia as a means of characterising the interactions between different brain areas prior and after the administration of the anaesthetic agents. Strong unidirectional information flow between frontal and posterior areas was found to occur shortly after anaesthetic induction.

1 INTRODUCTION

General anaesthesia (GA) is a reversible state of unconsciousness and depression of reflexes to afferent stimuli, induced by the administration of chemical agents (Hammeroff, 2006). Desirable supplements of it include immobility (analgesia), loss of conscious awareness and amnesia. Since the mechanism by which consciousness emerges is still not fully understood, the mechanism by which general anaesthetics prevent consciousness is also largely unexplained. One approach to understanding this critical mechanism is to look for invariant changes that manifest themselves in observables of the human brain, such as the electroencephalogram (EEG), as patients lose and regain consciousness under the effect of various anaesthetic agents. The appearance of spindle-like waves and background slow δ (1.5-3.5Hz) activity is probably the most prominent EEG sign of GA (Bennett et al., 2009). In general, the EEG shows signs of decreased fast activity (α and β rhythms) and increase of the slow and large-amplitude δ and θ components as the depth of anaesthesia increases. In very deep anaesthesia the EEG may develop a peculiar pattern of activity known as burst suppression, during which alternating periods of normal to high activity and low voltage (or even isoelectricity) are observed (Rampil, 1998).

The changes in the EEG observed under GA are also important for monitoring the depth of anaesthesia. Lately devices that monitor the depth of anaesthesia are utilised during surgery to provide additional information concerning the general state of hypnosis of the patient, including anaesthetic overdose or even potential regaining of consciousness during surgery. The latter is a serious concern as the incidence of awareness ranges from as low as 0.11% for general surgery (Ranta, 2002), up to an astonishing 20% for trauma surgery (Myles et al., 2003). The rates of awareness are affected by a number of factors, such as the patient gender, the type of surgery, the anaesthetic agent administered, faults in the anaesthetic apparatus, and individual

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differences in pharmacokinetics (Ranta, 2002, Myles et al., 2003). This is one of the most distressing aspects of surgery as in the majority of times the patients are unable to alert the anaesthetist that they have regained consciousness during surgery, and are in pain, due to the routine co-administration of neuromuscular blocking agents with the anaesthetic agents.

The most widespread commercial monitors of hypnosis currently in use are the BIS monitor (Aspect Medical Systems, Natick, MA) (Sigl and Chamoun, 1994) and Datex-Ohmeda S/5^{TM} Entropy Module (originally by Datex-Ohmeda Division, Instrumentation Corp., Helsinki; now with GE Healthcare) (Viertiö-Oja et al., 2004). Such devices operate by extracting a number of features from the EEG in order to deduce the relative depth of hypnosis, which is then easily visualised as a number from 0-100 (100: fully awake, 0: no activity). Even though these devices offer additional support to the work of the anaesthetist, they still suffer from some important reliability issues (Russell, 2006, Barr et al., 1999, Dahaba, 2005, Messner et al., 2003).

The main reason behind some of the problems faced by existing monitors can be pinpointed to the fact that they utilise a number of empirical measures from the EEG, which are then combined in a proprietory way into a single number denoting the depth of anaesthesia. The information utilized is, thus, representative of the characteristics of the observed activity and not of the physiological process that occurs during anaesthesia. Strong evidence for this provide reported incidences of awareness despite monitors displaying adequate depth of anaesthesia (Rampersad and Mulroy, 2005, Mychaskiw et al., 2001), and the inability of some monitors to distinguish between the EEG of an anaesthetized patient and the EEG of somebody who is asleep (Russell, 2006, Sleigh et al., 1999). The latter is not surprising considering that sleep and anaesthesia share some common mechanisms (Voss and Sleigh, 2007). However, despite the large similarities, there are fundamental differences in the particular physiological mechanisms of the two processes which a true monitor of anaesthetic depth should be able to identify. Thus, a successful monitor should extract information from the observed activity that is representative of the deeper interactions and which reflects the physiological changes that occur from administration of the anaesthetic agents as these are manifest in the observed activity. In other words, the measures utilised must be based on 'neurobiologic phenomena that represent the *necessary* and *sufficient* conditions for consciousness in a specific individual' (Hudetz, 2008).

In recent years it has been shown that measures which characterise the interactions between different brain areas can provide an insight into how integration of information is achieved in the brain during various cognitive tasks. One such measure is Granger causality, a linear measure quantifying the bidirectional interaction between two time series. Even though Granger causality has provided useful information from EEG activity in a number of applications (see (Pereda et al., 2005) and references within), it has yet to be applied in the study of general anaesthesia. In this work, the interactions between different brain areas during induction of anaesthesia are investigated using Granger causality. Anaesthetic induction is important as one can readily study the point of loss of consciousness that occurs from the administration of a bolus of anaesthetic agent. Such information is important in subsequent monitoring of anaesthetic depth and identification of potential regaining of consciousness during surgery.

2 METHODOLOGY

2.1 Dataset

The data has been collected from 10 male patients (mean age 34.6±18) undergoing general and urological surgery at Nicosia General Hospital, Cyprus. The study has been approved by the Cyprus National Bioethics Committee and patients gave written informed consent for their participation. Participants were not taking any medication acting on the central nervous system and were of normal weight. EEG data was collected using the 24-channel configuration of the TruScan32 system (Deymed Diagnostic) at a sampling rate of 256Hz. Electrodes were placed at positions Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2, according to the International 10/20 system. Data was recorded with an FCz, and ground was located on the head. No filtering was performed during data collection. Data recording commenced while patients were still awake prior to administration of the anaesthetic agents, continued through loss of consciousness, during the entire surgery, and until patients regained consciousness at surgery end. During the recording event markers were manually inserted to indicate important events, such as administration of anaesthetic agents.

GA was administered by the anaesthetist in charge following standard procedures. All patients were preoxygenated prior to anaesthesia induction with a propofol bolus. During induction boluses of fentanyl (for analgesia) and varying quantities of neuromuscular blocking agent (cisatracurium) were also administered. Maintenance of GA was achieved with a constant intravenous administration of propofol at concentrations ranging between 20-40ml/h, except in 1 patient were sevoflurane was used for maintenance. Given that data collection was performed during actual surgery, propofol concentrations for induction varied based on specific patient characteristics and the type of subsequent surgery.

In these investigations we are only interested in studying induction of anaesthesia, and subsequently the point at which patients lose consciousness. Loss of consciousness was defined as the point at which the patient stopped responding verbally to commands by the anaesthetist and occurred some seconds after administration of the anaesthetic bolus.

2.2 Granger Causality

The investigation of causal relationships is of great interest, particularly when dealing with neurophysiological data. Granger Causality (GC) has been developed explicitly tailored to allow inferences about causality between two time series to be made (Granger, 1969). Wiener defined causality as: "for two simultaneously measured signals, if one can predict the first signal better by incorporating the past information from the second signal than using only information from the first one, then the second signal can be called causal to the first one" (Wiener, 1956). This was later given a mathematical formulation by Granger through the use of univariate and bivariate autoregressive models (AR). According to Granger: for two signals, *A*, and *B*, if *A* is influenced by *B*, then the addition of past values of *B* in the regression of *A* will improve its prediction. This can be assessed from the variances of the prediction errors of the fitted univariate and bivariate AR models.
For the univariate case,

$$a(t) = \sum_{i=1}^{P} c_{ai} a(t-i) + e_a(t) \quad (1)$$

$$b(t) = \sum_{i=1}^{P} c_{bi} b(t-i) + e_b(t) \quad (2)$$

where $c_{ai}(c_{bi})$ are the estimated univariate AR coefficients for the AR model of order P, and $\mathbf{e}_a(\mathbf{e}_b)$ are the residuals (prediction errors) of the AR process. For the bivariate AR case,

$$a(t) = \sum_{i=1}^{P} c_{abi} a(t-i) + \sum_{i=1}^{P} d_{abi} b(t-i) + e_{ab}(t) \quad (3)$$

$$b(t) = \sum_{i=1}^{P} c_{bai} b(t-i) + \sum_{i=1}^{P} d_{bai} a(t-i) + e_{ba}(t) \quad (4)$$

where $c_{abi}(d_{abi})$ and $\mathbf{e}_{ab}(\mathbf{e}_{ba})$ are as for the univariate AR case. Granger Causality can then be defined as:

$$GC_{B\to A} = \ln \frac{\sigma^2_{A/A\_}}{\sigma^2_{A/AB}} \quad (5)$$

If by using past values of *B* the prediction of *A* is improved, then the variance of the prediction errors of the bivariate AR model, $\sigma^2_{A/AB} = \mathrm{var}(\mathbf{e}_{ab})$, will be smaller than the variance of the univariate AR model, $\sigma^2_{A/A\_} = \mathrm{var}(\mathbf{e}_a)$. Thus, $GC_{B\to A}$ will increase. If, however, the past of *B* does not improve the prediction of *A*, then $\sigma^2_{A/A\_} \approx \sigma^2_{A/AB}$, and $GC_{B\to A}$ will be close to zero. Similarly, $GC_{A\to B}$ is defined accordingly. If both $GC_{B\to A}$ and $GC_{A\to B}$ are high, then this indicates a bidirectional coupling or feedback relationship between *A* and *B*.

In order to characterise the direction and strength of coupling between *A* and *B* one can look at the difference between the GC values:

$$D = GC_{B\to A} - GC_{A\to B} \quad (6)$$

$$D \begin{cases} > 0, \text{strength of coupling } B \to A \text{ is stronger} \\ < 0, \text{strength of coupling } A \to B \text{ is stronger} \end{cases}$$

In this way, changes in the direction of coupling can be readily identified by following the changes in the sign of *D*. However, if *D* is close to zero, then one can deduce that there either exists bidirectional coupling of similar strength or no coupling at all. In this case, one must look at the individual GC values to identify which of the two scenarios holds.

In the following investigations AR models of order 6 were utilised. This choice was guided both by the literature (Tseng et al., 1995, Vaz et al., 1987) and by preliminary investigations which showed that the use of higher order models did not have an effect on the results.

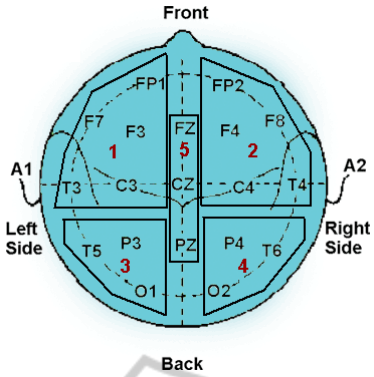

Figure 1: The five brain areas defined and the electrodes contained in each grid. The brain areas were left (grid 1) and right (grid 2) frontal area, left (grid 3) and right (grid 4) posterior area, and midline area (grid 5).

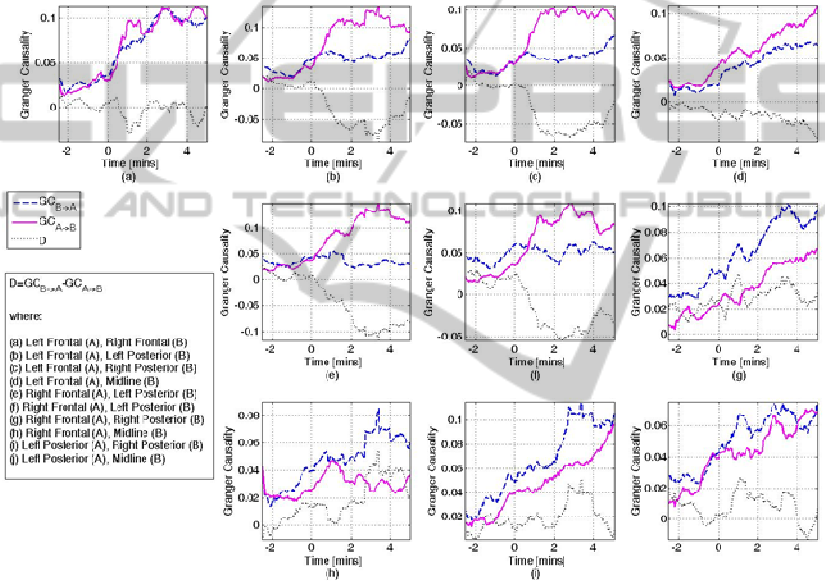

Figure 2: This figure shows the changes in the direction of coupling, estimated as the difference between $GC_{B\to A}$ and $GC_{A\to B}$. The legend indicates which area is considered as *B* and which as *A* in each of the individual plots. The x-axis shows time in minutes, where t=0 denotes the point at which the anaesthetic agent was administered. Patient was awake for t<0, and asleep for t>0. For example, plot (c) denotes the GC between Left Frontal (A) and Right Posterior (B). Thus, the solid line corresponds to $GC_{LeftFrontal\to RightPosterior}$, the dashed line to $GC_{RightPosterior\to LeftFrontal}$ and the dotted line to $D = GC_{RightPosterior\to LeftFrontal} - GC_{LeftFrontal\to RightPosterior}$. In this case, a strong unidirectional coupling from the left frontal area to the right posterior area is observed after anaesthetic induction. Note the different y-axis scales.

3 RESULTS AND DISCUSSION

To assess the interactions between different brain areas, five electrode grids were first defined (see figure 1). Each electrode grid represents the gross activity from each of the following brain areas: left and right frontal, left and right posterior, and midline area. The activity of each of these areas is estimated as the average activity from the electrodes contained within the specified electrode grid. For some subjects not all electrodes were available. Specifically, the following electrodes were unavailable: (1) S1: P4, T6, Pz; (2) S2: C3, O1; (3) S3: P3, P4, T6, O2, Cz; (4) S4: T5; and (5) S5: Cz. The EEG segments extracted were of 8-minute duration, where 3mins are prior to and 5mins are after induction, based on the event markers

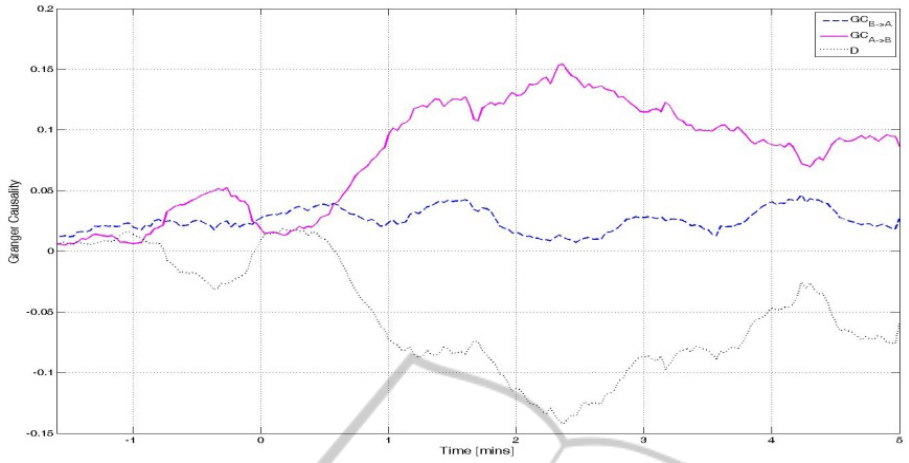

Figure 3: Granger causality between left frontal (*A*) and right posterior (*B*) for a single subject, and their difference, *D*, prior and after induction of anaesthesia (at time t=0). Prior to anaesthetic induction GC indicates weak interactions between the two areas. However, administration of anaesthesia induces strong unidirectional interaction from the left frontal to the right posterior area. This is reflected as a change in the sign of *D*.

indicating administration of anaesthesia in each patient record. Each 8-minute segment is then split into 2-second non-overlapping windows and Granger causality is estimated for each window. No artefact removal has been performed as averaging removes the effect of some artefacts present in the data. In addition, after anaesthetic induction there is minimal presence of artefacts as the patient is not moving and surgery has not yet commenced.

Figure 2 shows the interactions between the different brain areas as characterised by Granger causality and the difference, *D* (equation 6). The results shown are averaged over all subjects and a moving average of order 20 has been applied for better visualisation. Changes in the sign of *D* indicate a change in the direction of interaction. Whether *D* is positive or negative depends on which brain area is taken as *B* and which area as *A*. Thus, the actual sign of *D* is not important, but the change in the sign is: negative values indicate a stronger interaction from *A* to *B*, and vice versa for positive values.

A clear change in the direction of interactions before and after induction of anaesthesia is observed. All changes in the GC values at pre- and post-induction are statistically significant (ANOVA F-test, α=0.05, p=0; except for GC from LP to RP, where p=0.03). While the patients are awake, weak interactions between all brain areas can be observed, resulting into values of *D* around zero. The administration of the anaesthetic agent increases the strength of interactions in all directions, except of interactions from posterior to all other areas, which remain at the same level as prior to anaesthetic induction. The most striking change related to anaesthetic induction is the strong unidirectional inter- and intra-hemispheric interactions from frontal to posterior areas (fig.2 (b), (c), (e), (f)). These interactions start occurring approximately 20-30 seconds after induction, thus there is strong reason to hypothesize that they indicate the point of loss of consciousness. The strongest interactions are observed from the left and right frontal areas to the left posterior area. Figure 3 shows the interaction between left frontal and right posterior area for a single subject, whereby this switch of the direction of interaction induced by administration of the anaesthetic agent is clear. An increase in the strength of interaction from midline to all other areas is also observed, indicated by the positive D values (fig.2 (d), (g), (i), (j)). Anaesthetic induction also induces strong bidirectional intra-hemispheric frontal interactions (fig.2 (a)), which are not mirrored in the posterior areas (fig.2 (h)). In general, administration of anaesthesia appears to increase information flow from frontal to posterior areas and from midline to all other areas.

The lack of strong unidirectional interactions while the patient is awake is a direct reflection of the lack of generalised ‘synchrony’, as each brain area is involved in performing individual tasks. However, induction of anaesthesia induces strong unidirectional interactions. This indicates that the brain has now entered a ‘synchronised’ state, with frontal and midline areas in the focus. This is in agreement with observations that anaesthetic drug administration causes frontal predominance by

increasing frontal cortical activity (Jameson and Sloan, 2006).

Cortical sensory integration is considered as a common mechanism of anaesthetic suppression of conscious experience. It now seems more and more likely that unconsciousness during anaesthesia is a result of the brain's inability to integrate information (Hudetz, 2008, John and Prichep, 2005). One possibility is that anaesthesia induces unconsciousness through degradation of information integration by disconnecting communication between cortical networks. Another possibility is that anaesthesia disrupts consciousness by putting cortical networks in a synchronised state such that they are no longer able to integrate incoming information. Indeed, anaesthesia and other consciousness-depressing mechanisms are associated with increased cortical synchrony (Rampil, 1998). Our observations here suggest that Granger causality has indeed managed to capture this shift of the brain activity to a more synchronised state, and with decreased communication from posterior to all other areas. Thus, Granger causality can capture the physiological changes in the EEG activity, which are associated with administration of anaesthetic agents.

This work raises some additional considerations. Firstly, an interesting observation is that the strength of interaction appears to decrease towards baseline some minutes after induction of anaesthesia for interactions between the left frontal areas and other areas, whereas the strength of interaction remains at the same level for interactions between the right frontal and other areas. It would be interesting to observe longer periods after induction of anaesthesia in order to investigate the role of each frontal hemisphere in synchronisation during maintenance of anaesthesia, whether this is disrupted by strong stimuli, such as tracheal intubation, and whether the same patterns of interactions are observed again at the end point of anaesthesia, but in the reverse direction. Secondly, the effect of neuromuscular blocking agents on the EEG is still not fully understood. Thus, it would be useful to investigate whether the observed patterns of interaction are similar when neuromuscular blocking agents are not administered. Thirdly, analysis with increased spatial resolution would allow us to identify a more exact location of the areas that are acting as synchronisation pacemakers. For this, Granger causality should be estimated for smaller electrode grids, and even for individual electrodes. However, these are beyond the scope of this work and remain the subject for future investigations.

Taking these additional considerations in mind, if changes in the bidirectional interactions identified by Granger causality could be expressed in the form of a single number from 0-100, then it might be possible in the future to utilise this measure to alert the anaesthetist in cases of impending awareness during surgery.

4 CONCLUSIONS

We have shown that Granger causality can be used to extract information reflecting the physiological interactions between different brain areas during induction of general anaesthesia. A measure that can extract the deeper interactions within the brain through the observed EEG activity would be useful not only for studying the physiological mechanisms of anaesthesia, but also in a monitor of anaesthetic depth to provide objective assessment of the state of hypnosis of the patient.

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