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Research paper

Longitudinal monitoring of heartbeat dynamics predicts mood changes in bipolar patients: A pilot study

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ABSTRACT

Objectives: Recent research indicates that Heart Rate Variability (HRV) is affected in Bipolar Disorders (BD) patients. To determine whether such alterations are a mere expression of the current mood state or rather contain longitudinal information on BD course, we examined the potential influence of states adjacent in time upon HRV features measured in a target mood state.
Methods: Longitudinal evaluation of HRV was obtained in eight BD patients by using a wearable monitoring system developed within the PSYCHE project. We extracted time-domain, frequency-domain and non-linear HRV-features and trained a Support Vector Machine (SVM) to classify HRV-features according to mood state. To evaluate the influence of adjacent mood states, we trained SVM with different HRV-feature sets: 1) belonging to each mood state considered alone; 2) belonging to each mood state and normalized using information from the preceding mood state; 3) belonging to each mood state and normalized using information from the preceding and subsequent mood states; 4) belonging to each mood state and normalized using information from two randomly chosen states.
Results: SVM classification accuracy within a target state was significantly greater when HRV-features from the previous and subsequent mood states were considered.
Conclusions: Although preliminary and in need of replications our results suggest for the first time that psychophysiological states in BD contain information related to the subsequent ones. Such characteristic may be used to improve clinical management and to develop algorithms to predict clinical course and mood switches in individual patients.

1. Introduction

In contrast to all the other branches of medicine, psychiatry has suffered since birth from a lack of external indices to validate the diagnosis and to monitor the clinical course of disorders. With the exception of psychiatric conditions caused by a primary somatic disorder (e.g., Major Depression due to hypothyroidism), no biological marker to date has proven to be reliable, consistent and accurate enough to be used in practice for clinical (Antonijevic, 2008; Ozerdema et al., 2013; Teixeira et al., 2013) as well as forensic purposes (Sartori et al., 2011). Specifically, while sleep alterations (e.g., REM latency) (Antonijevic, 2008), hormonal changes (e.g., cortisol rhythm alterations) (Antonijevic, 2008; Teixeira et al., 2013), and brain metabolic (e.g. metabolism reductions in the prefrontal cortex) (Ozerdema et al., 2013) or structural alterations (e.g., reductions in hippocampal volume) (Arnone et al., 2012; McKinnon et al., 2009) have been found to be altered in mood disorders, none of these changes has shown enough sensitivity or specificity to make any of them feasible for a clinical use.

Recently, the study of the Autonomic Nervous System (ANS) has provoked a growing interest in the assessment of both psychiatric as well as somatic disorders. Significant alterations in heartbeat dynamics, including alterations in the Heart Rate Variability (HRV) – which is the complex modification of the heart rate over time - have been detected in several somatic and mental disorders (Alvares et al.,

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2016; Henry et al., 2010; Rajendra Acharya et al., 2006). A recent meta-analysis, for instance, has shown a consistent reduction of different HRV measures in patients with psychiatric disorders as compared to controls (Alvares et al., 2016). Such decrease in HRV was smaller for anxiety disorders and maximal in psychotic patients. It is important to note that this meta-analysis found such a consistent reduction by grouping different measures of HRV. As a matter of fact, HRV analysis does not provide a single index, but a series of features that describe different and independent information. HRV can be characterized using distinct methods, which assess it either in time or in frequency domains (Henry et al., 2010; Rajendra Acharya et al., 2006). In particular, frequency domain methods consider two components of the variability, the low (Low Frequency -LF, 0.04–0.15 Hz) and the high (High Frequency - HF, 0.15–0.4 Hz) frequencies. The HF component of the HRV is basically determined by parasympathetic activity (Rajendra Acharya et al., 2006), while LF is affected by both parasympathetic and sympathetic modulation. In fact, components above 0.15 Hz (i.e., HF band) seem to be exclusively mediated by vagal activity (Henry et al., 2010; Rajendra Acharya et al., 2006), where the strongest contribution to HF power modulation is due to respiration (the so-called Respiratory Sinus Arrhythmia). On the other hand, changes below 0.15 Hz (i.e., LF band) are mediated by both cardiac vagal and sympathetic nerves with the contribution of other hemodynamic- and vascular-mediated modulations (Saul et al., 1991), including baroreflex activity (Goldstein et al., 2011; Rahman et al., 2011). For this reason, it has been proposed that the LF/HF ratio may be a valid index of the sympatho-vagal balance (Montano et al., 2009). However, given the fact that LF is mediated both by vagal and sympathetic innervations, and by the previously mentioned other hemodynamic- and vascular-mediated modulations, both the exact physiological meaning of LF component and the reliability of the LF/HF ratio as a measure of sympatho-vagal balance are controversial (Goldstein et al., 2011; Heathers, 2012; Rahman et al., 2011). In fact, recent reports suggested that the main SNA component of LF is parasympathetic as well (McCraty and Shaffer, 2015; Reyes del Paso et al., 2013). Studies on both physiological (e.g., physical exercise (Warren et al., 1997)) and pharmacological (e.g. adrenergic agonists (Ahmed et al., 1994)) sympathetic stimulation failed to show the expected LF power increases and, more in general, the published findings are far less consistent than one can glance at a first sight (Reyes del Paso et al., 2013).

Another way to assess HRV is by measuring its nonlinear domains, including complexity and fractal features (Rajendra Acharya et al., 2006). Analysis methods derived from nonlinear system dynamics have started a novel approach for studying the characteristics of HRV. These methods differ from the conventional ones because they are designed to assess the quality, scaling and correlation properties of the signals (Aubert et al., 2009). Although nonlinear analyses are more difficult to interpret in terms of physiological meaning, it has been suggested that "*Nonlinear control of HRV poses potential physiological advantages in the possibility of adapting quickly and more subtly to changes in physiological needs*" (Aubert et al., 2009). Although some authors highlighted some shortcomings in the use of this type of features, including some reproducibility matters (Tan et al., 2009), they have been suggested to have some valid prognostic and diagnostic uses (e.g., (Leistedt et al., 2011; Yang et al., 2013; Yang and Tsai, 2013)).

HRV alterations have been found in cardiac disorders, including coronary disease and heart failure (Feng et al., 2014; Harris et al., 2014; Peterson et al., 2014; Radaelli et al., 2014; Sandercock and Brodie, 2006; Wendt et al., 2014). Particularly, HRV alterations may predict prognosis and can be used as a marker of the *health* of the heart (Sandercock and Brodie, 2006). The most frequent findings are reduced variability, changes in the HRV spectral distribution and a reduction in HRV complexity. Thus, in general, a loss of variability or a prevalence of the LF component of the spectrum are associated with a more compromised heart function and a poorer prognosis (Sandercock and Brodie, 2006). On the contrary, an increased HRV is associated with a better health not only in patients but also in healthy volunteers, so as to be considered a valuable indicator of general well-being (Gonçalves et al., 2014). Given this data, it is not surprising that other studies have shown that HRV can be used as a marker to assess the severity of distinct clinical conditions, including stroke (Tang et al., 2015), epilepsy (Lotufo et al., 2012), multi-organ failures (Liu et al., 2013; Zhang et al., 2015), cancer fatigue (Crosswell et al., 2014) and autoimmune diseases (Adlan et al., 2014; Holman and Ng, 2008).

Regarding mood disorders, several indications support a link between heart function and mood: a) There is a frequent occurrence of comorbidity between mood disorders (particularly, but not only, Major Depression) and cardiovascular conditions (particularly, but not only, coronary artery diseases) (Jiang, 2008; Lichtman et al., 2014; Rovai et al., 2015); b) occurrence of mood disorders in patients with heart diseases is associated with a worse clinical prognosis (Lichtman et al., 2014); c) presence of cardiovascular disorders significantly increases the risk of developing a Mood Disorder (Jiang, 2008); d) a common biological *milieu* has been proposed for such a frequent comorbidity and HRV alterations can be part of it (Rovai et al., 2015).

Thus, it is not surprising to find research on autonomic nervous system and its alterations in relation to psychopathology. HRV alterations have been found in acute and chronic stressful conditions (Jones et al., 2014; Parker et al., 2014; Tanev et al., 2014), shift-workers (Lo et al., 2010), insomnia (Jiang et al., 2015; Maes et al., 2014), psychosomatic disorders (Salvioli et al., 2015) and major mental disorders such as schizophrenia, anxiety and mood disorders (Akar et al., 2014; Clamor et al., 2014; Kemp et al., 2014; Moon et al., 2013; Sanchez-Gonzalez et al., 2014; Valenza et al., 2013). Particularly, as far as mood disorders are concerned, changes in the features derived from HRV analysis were found in Major Depression (Stapelberg et al., 2012; Wang et al., 2013) and, recently, in Bipolar Disorder patients, who, as a group, showed a significantly decreased HRV and parasympathetic activity as compared to healthy individuals (Cohen et al., 2003; Henry et al., 2010). Finally, a recent study highlighted that the steeper the reduction of HRV, the more severe was the clinical symptomatology both in bipolar and schizophrenic patients (Quintana et al., 2015).

On the other hand, modulation of the autonomic nervous system seems to have relevant effects on the central nervous system both under physiological, and even more so, pathological conditions. For instance, vagal nerve stimulation (VNS) has been widely applied in patients with Major Depression so to become approved by FDA for the treatment of drug-resistant depression (Berry et al., 2013; Martin and Martín-Sánchez, 2012). However, results on VNS efficacy remain inconsistent and largely based on open-labeled studies (Daban et al., 2008). Another indication of the potential link between autonomic nervous system and mood is provided by the use of relaxation techniques based on autonomic nervous system modulation, including cardio-feedback. These techniques are widely used for managing stress and negative emotions (Karavidas et al., 2007; Lehrer and Gevirtz, 2014). Nonetheless, the pathophysiological relationship between ANS and mood is still debated (Thayer and Lane, 2009). Recently, it has been suggested that the relationship between HRV and mood may be based on the role of parasympathetic activity, which affects the cardiac dynamics and plays a role in emotional regulation and flexibility, as well as in social cognition (Chang et al., 2013; Cristea et al., 2014). For instance, recent studies have shown an association between HRV and cerebral blood flow in the middle prefrontal cortex, which is actively engaged during emotional modulation tasks (Chang et al., 2013; Thayer et al., 2012). On the basis of these results, the authors claimed that HRV may be an index of the activity of a central autonomic network that directly influences both the heart and the control over behavior (Thayer et al., 2012). Moreover, HRV alterations were thought to be in a strict relationship with cholinergic mediated inflammatory modulation and with changes in endocrine and allostatic systems (Alamili et al., 2015; Kenney and Ganta, 2014). It is interesting