Timing in psychiatry: exploring resonance in biological systems for treatment of mental disorders.

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Abstract

In mood disorders, the duration of symptoms is key, since observed behavior might be considered as physiological responses to environmental stress. Studies have connected biological features to clinical observations, however full profiling is difficult to obtain and rare in literature, generally targeting one domain in restricted settings. The acquisition of technologies such as mobile phones and wearables enabled intensive data collection in ecologically valid scenarios (Ecological Momentary Assessment, EMA). We explore an intervention strategy making use of resonance in biological systems. Specifically, spectral decomposition of behavioral data may leverage the search for ‘sweet spots’ when planning schedules for intervention. One could then target moments when patients are more susceptible to beneficial changes in treatment. Successful cases in endocrinology and cardiology illustrate how this rationale is used by other medical specialties. We describe two experiments deploying mobile data capture of affective states and investigate how it relates to biological phenotypes. The Brazilian High Risk Cohort is a 9-year long ongoing cohort investigating neurodevelopment. It includes genotyping, genetic expression and repeated measures neuroimaging. ARKETP is a small-scale double-blind clinical trial comparing isomers of ketamine for treatment resistant depression, including a set of biological measures (e.g. BDNF, Interleukins, TNF- α , IFN- γ and microRNA).

Keywords: Affective disorders, Ecological Momentary Assessment, Depression, Bipolar Disorder, Resonance, Oberth effect

1. Introduction

Mood disorders are defined after several instances of behavior considering severity, functional impairment and chronology. The duration of such states is key, otherwise the symptoms might be considered as physiological responses to environmental stress [1].

In fact, the diagnostic criteria for affective disorders include a minimal duration of symptoms (e.g. 4 weeks in major depression) to be considered clinically significant. Other time related phenomena in affective disorders are its seasonal manifestation and circadian rhythm disruption [2].

Studies have connected biological features to clinical observations, however full profiling is difficult to obtain and rare in literature, generally targeting one domain in restricted settings [3].

Performing full-time assessment of humans in natural conditions requires tackling several obstacles. One generally has to infer states from brief pictures (e.g. clinical interviewing and self-report). Real-time data gathering in ecologically valid scenarios (Ecological Momentary Assessment, EMA) has been made possible by the acquisition of technologies such as mobile phones and wearables. We explore an intervention strategy allowed by the information obtained from analyzing time series data from the perspective of dynamical systems and spectral theory.

1.1. Behavioral rhythms and affective states: biological clocks, neurotransmitters and inflammatory markers

Evolving from simple processing organs wired to rudimentary motor responses, mammals' brain possesses structures with marked distinct connections, functioning and developmental pathways [2, 4].

We outline regular chronological patterns in systems putatively considered to play a major role in affect regulation and mood disorders. Namely, monoamine neurotransmitters, inflammatory mediators, biological clocks and the HPA axis (Hypothalamus, Pituitary and Adrenal glands)[3, 5, 6]. Through gene expression and molecular cues, they intertwine: sleeping; feeding and growth; reproduction; responses to environmental (e.g. sunlight exposure) or psychological stress; metabolic activity; immune system activation [7, 8, 9, 10].

Biological clocks compose the complex signaling system in human organisms, which synchronizes functions to regulate homeostasis [11, 12].

Some key signaling pathways and genetic encodings underlying this machinery are evolutionarily conserved elements and have been described to some extent. The CLOCK (Clk) and BMAL1 (Bmal1) gene proteins dimerize to positively influence the expression of E-Box gene families (Cryptochrome, Cry, and Period, Per), which negatively influence Clk/Bmal1, forming a closed loop [13].

This set is also related to affect regulation and the reward circuitry. For instance, interfering with monoamine synthesis (dopamine) through Tyrosine Hydroxylase [14].

Other key genes taking part are Dbp; Nfil3; RORA, RORB and RORC; Nr1d and Nr1d2 (interaction with Clk/Bmal1 through REV-ERB and ROR elements)[15, 16]. Numerous results systematically gathered [17] identify maniac like behavior in mice carrying $\Delta 19$ mutations of the CLOCK gene. These include disruption of the circadian cycle, reward seeking and drug seeking behavior, along with induction of cycles after dopaminergic daytime spikes [14]. In humans, population studies targeting mental disorders have identified alleles of CLOCK, Bmal1 and its related pathways [6, 18, 19].

Depression is also characterized by abnormal responses to stress, which heavily depends on the HPA axis. Evaluation of the axis's reaction to exogenous corticosteroid injection (dexamethasone response test) was one of the first procedures using biological markers tested to diagnose depression, although results were not consistent [20]. Several other related occurrences have been observed in patients, including hypersecretion of CRF, impaired negative feedback of the axis, enlarged adrenal glands and hypercortisolemia [21].

Regular circadian rhythms in the immune system were first detected decades ago. Findings include IL-1 cyclic patterns in healthy subjects [22] and pro-inflammatory cytokines (e.g. TNF, IL-1 β) peaking during active phases [23, 24].

Inflammatory markers abnormal variations also seem to be related to depressive states in patients (e.g. IL-1b, IL-2, IL-6, TNF- α , CRP and PGE2) [25].

Major hypotheses consider monoamines to play a main role in the mechanisms underlying affective disorders. Serotonin (5-HT), norepinephrine (NE) and dopamine (DA) are often addressed when describing the pathophysiology of depression [5]. They are either directly implied through consequences of concentration alteration or indirectly, through more comprehensive theories regarding malfunctioning in related neurocircuitry [26, 27, 28]. In terms of

chronological fluctuations, 5-HT and its transporter (SERT) levels seem to be influenced by regular rhythms [29, 30, 31], as it is the case for NE and DA [32, 33, 34].

We describe two experiments deploying intensive mobile data capture of affective states and investigate how it relates to phenotypes (reward circuits, biological clocks and related mechanisms). The Brazilian High Risk Cohort (HRC) is a 9-year long cohort investigating neurodevelopment. It includes genome sequencing and repeated measures neuroimaging in conditions free of intervention. Data capturing treatment response is from ARKETP, a small-scale double-blind clinical trial comparing isomers of ketamine for affective disorders, also including serum markers (e.g. BDNF, Interleukins, TNF- α , IFN-G and microRNA).

1.2. Perspectives

Here, we outline the usage of resonance phenomena in biological systems to explore novel possibilities in treatment. Information obtained from spectral analysis of time series dynamics can leverage chronological planning for interventions, exploiting cyclic features in human behavior (Figure 2, Bottom). For instance, the schedule to deploy behavioral therapy combined with pharmacotherapy may benefit from individual detailed profiles by targeting ‘sweet spots’ when one is more susceptible to changes. Successful cases in endocrinology and cardiology illustrate how this rationale is used in other medical specialties.

2. Ecological Momentary Assessment Software

Assessment is performed through mobile phone (4 weeks intensive, 1 year sparse). Participants are asked to install and interact with an in-house Electronic Momentary Assessment (EMA) software. The application gathers input through screen prompted self-report items. Users consent to every step of data collection. The protocol measures human behavior using multiple targets, such as: sleep patterns and quality, self-reported behavior, subjective emotional perception, composition of environmental surroundings, average dislocation by step count and social media activity. Questions were taken from previously validated instruments (Urban Minds, mMARCH, SDQ). Each individual profile is measured as a multidimensional time series of self-reported scores (Well-being, Calmness, Relaxation, Activity, Happiness, Energy, Sleep Duration, Sleep quality). This application conforms to ethical

109 norms and its used was approved by national and regional ethical research
110 committees. It also obeys privacy and user right policies enforced by major
111 online distribution stores for mobile applications. *Supplementary informa-*
112 *tion* provides a detailed reference list of items, including sources, description
113 of prompted stimuli, measurement data types and referred code section.

114 2.1. *Brazilian High Risk Cohort*

115 The Brazilian High Risk Cohort (HRC) is a large ($n = 2,512$) commu-
116 nity sample of youths (inclusion age range: 6-14y) stratified for high risk
117 for mental disorders from 9,937 candidates. Three data collection phases
118 occurred: 2010-2011 (Baseline/Wave 0, w0); 2013-2014 (Wave 1, w1); 2018-
119 Current (Wave-3, w3). Further details can be found in the previous reports
120 [35]. Extensive phenotype profiling was performed, including full sample
121 ($n=5,864$, including children and their parents) microarray genotypes pro-
122 cessed with Global Screening Array; gene expression arrays ($n=120$ at w0
123 and at w1) and 450k methylation arrays ($n=24$ at w0 and at w1). Collected
124 material includes blood and serum DNA samples ($n=600$ at w0, $n=500$ at
125 w1, $n=1257$ at w2); blood RNA ($n=600$ at w0; $n=500$ at w1). Measures
126 also include repeated measures fMRI, clinical and neuropsychological scales.
127 750 participants possess at least one brain scan available. A relationship be-
128 tween major depression symptoms and brain networks assumed as relevant
129 has been previously verified in this data [36].

130 2.2. *ARKETP trial*

131 Ketamine is an anesthetic drug, an N-methyl D-aspartate receptor an-
132 tagonist which when used in sub-anesthetic doses provides rapid antidepressant
133 action. It has recently been highlighted as one of the most effective
134 therapeutic options in refractory depressions. Most studies related to the
135 antidepressant action of ketamine, however, involve its racemic mixture and
136 its isolated S (+) enantiomer (esketamine). Nevertheless, studies involving
137 the R (-) enantiomer, also called arketamine, are not identified in the liter-
138 ature in depressed subjects. This molecule has demonstrated in preclinical
139 studies the potential of an antidepressant effect that is longer lasting than
140 the other ketamine presentations. In addition, a possible lack of dissociative
141 effects may be extremely beneficial in clinical practice because of the ease of
142 administering the drug and reducing the risk of abusive use.

143 ARKETP studies the mechanism of action and efficacy of arketamine
144 in human volunteers with treatment-resistant major depressive disorder or

145 bipolar depression. It is designed to be 14 days trial. At first, 20 participants
146 will randomized to either placebo or arketamine conditions. Patients not re-
147 sponding after 7 days will receive an additional esketamine infusion session.
148 Blood samples will provide levels of BDNF, IL-1, IL-6, TNF- α , IFN-G, mi-
149 croRNA 206 and 1202. Dosages are to be performed before infusion sessions
150 and later at 5, 20, 40, 120, 240 minutes, 24 hours and after 7 days. Depressive
151 symptoms are measured using Montgomery-Asberg Depression Rating Scale
152 (MADRS).

153 Participants will be instructed to install EMA software during registering.

154 This trial was approved by the Brazilian national council, CONEP. Cer-
155 tificate of presentation for ethical appreciation, CAAE, 04096018.8,1001.0049;
156 Decision number: 3.425.064.

157 *2.3. Preliminary data concerning EMA adhesion in the HRC study*

158 As the current phase of data collection is still ongoing, some participants
159 did not went through full evaluation (6 measures x 28 days) by the time of
160 this report (February of 2020). A subset of 139 participants engaged for at
161 least 2 weeks, out of which 134 were engaged in responded to mood items, 94
162 only to sleep items and 89 to both classes. The total sample of self-reported
163 states include 43716 measures (Sleep duration and quality: 4560 each; Mood
164 states: 5766 each).

165 Participants were progressively less engaged during follow-up, resulting
166 in increasing mean proportion of missing values (Figure 1) for mood (Weeks:
167 1, 43.4%, 2, 58.2%, 3, 67.3%, 4 78.5%) and sleep (Weeks: 1, 33.8%, 2, 53.3%,
168 3, 63.6%, 4, 76.1%) items through time.

169 **3. Time tuning of interventions**

170 Circadian rhythms have been addressed by direct interventions. Chronother-
171 apies [3, 37] for mental disorders aim at normalizing natural cycles through
172 assets such as light therapy (light exposition at early morning), sleep depriva-
173 tion (wake therapy) [38], social rhythm therapy [39] and standard behavioral
174 interventions for insomnia [40, 41]. Several systems in the human body ex-
175 hibit measurable indicators whose dynamics have been reverse engineered
176 with remarkable precision, such as the hypothalamo-pituitary-thyroid axis
177 [42, 43], kidney blood flow [44], and Blood Glucose-Hemoglobin A1c [45].

178 Whereas the concept of benefiting from dynamical properties of systems
179 is new to psychiatry [3], it is a common asset to other medical specialties.

Figure 1: Visualization of adhesion through time (28 days) considering morning prompts with sleep items (bottom half) and random prompts (upper half). Participants show less engagement progressively.

180 On the face of rhythms insusceptible to cardioversion, specialists induce fa-
 181 vorable patterns using drugs (e.g. amiodarone). Also, the electrical shock is
 182 synchronized with a sweet-spot in ECG's (R wave), preventing ventricular
 183 fibrillation [46]. Gynecologists monitor menstrual cycle in order to deliver
 184 precise care, from basic birth-planning to varying-dose contraceptive drugs
 185 [47].

186 Psychiatrists are generally interested in understanding patterns, triggers
 187 and potential assets associated with onset, remission and re-incidence (a com-
 188 mon feature of the disease) or mental disorders. Aside from the precise pro-
 189 filing previously discussed to target diagnostics and follow-up, one may think
 190 of tuning intervention strategies based on time states. Indeed, researchers
 191 are already looking for the optimal schedules in multiple session interventions
 192 (e.g. infused ketamine or electroconvulsive therapy). Such information may
 193 also be useful to decide the best moment for actions.

194 *3.1. Exploring resonance in treatment of mental disorders*

195 An intuitive example of resonance usage can be observed in a children's
 196 toy, the playground swing. In order to optimize efforts, adults push the
 197 seat synchronizing it with the pendulum natural motion, when going down-
 198 and-forward. This maneuver uses information about the cyclic motion in
 199 order to maximize kinetic energy and make transitions to orbits of larger
 200 amplitudes. We can make use of a similar time-wise rationale to fine tune
 201 treatment. For instance, the synergistic effect of cognitive behavioral therapy
 202 (CBT) and antidepressants may be optimized by starting and delivering CBT
 203 when susceptibility to changes is at maximum. We are currently ignorant
 204 of whether an optimal schedule exists to for CBT in order to achieve higher
 205 remission rates. Similarly, oscillatory availability of antidepressant concen-
 206 trations may also boost efficacy. Although remission is generally achieved
 207 after 4 weeks, early effects of antidepressants on behavior are noticed since
 208 the first week[48, 49]

209 Aside from resonant cyclic interventions, single time interventions (e.g.
 210 ketamine infusion) may also benefit from optimal scheduling. The identifi-
 211 cation of underlying dynamics allow for the introduction of perturbations on
 212 'sweet spots'. In orbital mechanics, the Oberth effect poses that an aircraft
 213 gains more kinetic energy when accelerating at the nearest point to a cen-
 214 tral body, where potential is lowest and speed is highest. Hence, one can
 215 shift between orbits with minimal effort, revolving around a different attrac-
 216 tor. European Swedish-designed satellite SMART-1 (2003) and India's recent

(2019) lunar mission, Chandrayaan-2, used this family of trajectories to spiral out of Earth. The abnormal dynamics of brain networks in depression have been described in terms of their natural attractors [2, 50] Intensive data capture of behavior and environment in natural settings (a.k.a. experience sampling, ecological momentary assessment) may help to reliably measure affective states and environmental factors. *Supplementary information* contains an in-depth framework of analysis based on results from previous EMA literature [51].

3.2. Perspectives for clinical applications

Models for co-expression of genes are reasonably straightforward, since one can make precise measures directly from blood samples. Basic intrinsic periods and interactions have been described for several biological systems. For instance, the feedback loop with 12h phase shift between expression of Clock/BMAL1 and PER/CRY complexes [13, 16]. On the other hand, physical states related to mood must be inferred from indirect measures, amounting to significant noise. Previous methods yielded too sparse data for reliable estimates. Fine grained measures obtained using Ecological Momentary Assessment (EMA) is proving itself to be a valuable asset to tackle this problem. The identification of attributes in basis cycles underlying behavior might also suggest relationships to relevant biological markers presenting compatible rhythms. Examining the dynamics of affective states with tailored models may enable new ways to help people with mental disorders. Interventions from other medical specialties may inspire psychiatrist on how to look for optimal time-windows in interventions when treating affective disorders.

Vignette 1

Vignette 1: Ketamine infusion – Mr. Joseph Fourier is a patient referred to a specialized Psychiatry Unit center. He tells a long history of struggling with depression. He also shows physician reports confirming Treatment Resistant Depression: symptoms have not responded to previous treatment with 3 different anti-depressant drugs. The multidisciplinary team rules out contraindications for ketamine infusions. Mr. Joseph installs a mobile application which measures his affective states for one week. Later on, a clinical-assistant contacts him to schedule the first session. The suggested dates conciliates professional availability at the specialized center and optimal time windows for response based on patient’s individual patterns.

Vignette 2

SSRI and CBT – Upon medical examination, Ms. Krieger is diagnosed with first episode Major Depression. Her physician decides to start treatment using a combination of SSRI and psychotherapy. Ms. Krieger asks whether she should wait for medication to take effect before starting psychotherapy sessions. She is instructed to use a wearable device which tracks her activity levels. Further analysis identifies time related patterns in her mood and suggests possible schedules for psychotherapy adjunct treatment in adequate time.

Figure 2: **(Bottom)** Spectral decomposition of simulated data for 28 days (4 measures per day) generated with three spectral basis components. **(Top)** MADRS 10 (suicide ideation rating) score through time in 63 patients with treatment resistant depression (4 measures). Shaded gray areas mark approximate phase subspaces for high and low levels of suicide ideation.[52]

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