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Delayed mood transitions in major depressive disorder

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ABSTRACT

The hypothesis defended here is that the process of mood-normalizing transitions fails in a significant proportion of patients suffering from major depressive disorder. Such a failure is largely unrelated to the psychological content. Evidence for the hypothesis is provided by the highly variable and unpredictable time-courses of the depressive episodes.

The main supporting observations are: (1) mood transitions within minutes or days have been reported during deep brain stimulation, naps after sleep deprivation and bipolar mood disorders; (2) sleep deprivation, electroconvulsive treatment and experimental drugs (e.g., ketamine) may facilitate mood transitions in major depressive disorder within hours or a few days; (3) epidemiological and clinical studies show that the time-to-recovery from major depressive disorder can be described with decay models implying very short depressive episodes; (4) lack of relationship between the length of depression and recovery episodes in recurrent depression; (5) mood fluctuations predict later therapeutic success in major depressive disorder. We discuss some recent models aimed to describe random mood transitions.

The observations together suggest that the mood transitions have a wide variety of apparently unrelated causes. We suggest that the mechanism of mood transition is compromised in major depressive disorder, which has to be recognized in diagnostic systems.

Introduction

The life-time prevalence of major depressive disorder (MDD) in the Western population is 10–20%. In approximately 50% of the cases MDD is diagnosed and treated by the general practitioner, while severe depressions with or without psychiatric co-morbidity are referred to psychiatrists. If not adequately treated, depression may become a life-threatening psychiatric condition. Indeed, suicide rate is high in depression. Antidepressant drugs, including serotonin reuptake inhibitors, are often the treatment of first choice, but their effectiveness is – at least in large cohorts – often little more than a placebo treatment [1–3]. In addition, the search for specific diagnostic markers for depression to enable better therapeutic results is rather unsuccessful [2,3]. Concerning psychotherapies there is little if any evidence of the best therapeutic efficacy among seven options including cognitive behavior therapy, interpersonal psychotherapy, behavioral activation, problem solving therapy, psychodynamic therapy, nondirective counseling, or social skills training [4 and references therein]. And, finally, authors have pointed to the scientific weaknesses of current classification systems, including the Diagnostic and Statistical Manual of Mental Disorders [DSM; 1,3]. Taken together, these notions illustrate the limited progress made of a scientific and clinical concept of MDD over the last six decades [1]. This lack of progress has often been attributed to the complexity of the brain and to the difficulties faced when trying to extract relevant information from the living brain. Another major problem is the presumed causal relationship between the nature of psychopathology and successful treatment. Does, for instance, the psychological content of depression, e.g., the depressive feelings, determine the timing of recovery, or do some underlying mechanisms govern the time course of depression? The therapeutic implications might than differ: the first mechanisms appeal primarily to psychotherapeutic approaches whereas the latter suggest interventions associated to some underlying, presumably neurobiological, mechanism or pathology. The latter idea implies that therapeutic efficacy is primarily limited by the probability of mood-normalizing transitions. The hypothesis forwarded here elaborates on this idea and in particular on the time structure of MDD and associated depressive episodes.

In the present report I use the Diagnostic and Statistical Manual of Mental Disorders version DSM IV-R and not the most recent DSM

Abbreviations: DSM, diagnostic and statistical manual of mental disorders; ECT, electroconvulsive therapy; MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors.

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V, because far most of the reviewed studies are based on earlier versions [3,5]. Generally speaking MDD is considered the collective impact of external challenges, cultural and social environment, personal experiences and biological disposition and is an amalgam of symptoms. A tacit assumption of the DSM is that MDD is an underlying pathology that manifests itself in a variety of symptoms, that might be personal with loose inter-symptom connections. The duration of the depressive condition is an essential characteristic: at least 2 weeks according to the DSM classification. Shorter periods of depression are considered as non-pathological and do not deserve psychiatric attention. We discuss some implications of our hypothesis for the scientific character of diagnostic systems.

Hypothesis

The hypothesis defended is that the core pathology in a significant proportion of patients suffering from MDD is the failure of mood-normalizing transitions which is not necessarily related to a presumed psychological content, i.e., sad thoughts.

I describe and discuss several examples on the timing of mood transition, which are summarized in Fig. 1. Fast mood transitions may occur following joyful or sad experiences in everyday life. Clinical and case reports of fast depressiogenic transitions have been observed following such interventions as deep brain stimulation, sleep deprivation and subsequent short naps. Other arguments are provided by clinical and experimental psychopharmacological interventions and epidemiological data surveys (depicted in Figs. 2 and 3). The transition-hypothesis's potential is therefore further underlined by analytical models (summarized in Fig. 4).

Fast mood switches in non-MDD subjects

A core assumption of our hypothesis is that transitions of the depressive mood in MDD might be fast, as is occasionally observed during deep deep-brain stimulation and in ultra-rapid mood-cycling patients. In normal life joyful or sad experiences may result in fast mood transitions within minutes or even seconds. Mood may become depressed after a message of the death of a beloved, or conversely, elated by a successful effort in one's career or in sports. These transitions may normalize in minutes or days, depending on the experienced impact. In clinical practice depression is often co-morbid with somatic conditions such as cancer, cardiovascular disease or diabetes. In these cases depression is commonly not diagnosed as MDD, but rather as depression associated to a general medical condition [5]. The associated depressive feelings may readily dissolve following successful treatment of the somatic syndrome.

Fast mood transitions have been observed in non-MDD patients. For instance, electrical stimulation of the subthalamic nucleus, aimed to alleviate tremor in Parkinson's disease, evokes a depressed mood within 5 s, which than disappeared within 30 s after cessation of the stimulation [6–9]. In some patients the depressive mood was induced repeatedly and was accompanied by suicidal ideation or attempt. Electrical stimulation does not imply that the neuronal pathway becomes more active: rather it impairs the integration of the stimulated pathway in a functional neuronal network. Hence, electrical stimulation might be seen as a reversible block of neuronal pathways, here perhaps dopamine neurons. Together these case reports demonstrate that a pathological or near-pathological depressive state of mood might precipitate and dissolve within minutes. The question remains open whether the very fast mood transitions during deep brain stimulation are characteristic for some subjects or whether they might be evoked in (almost) every individual.

Bipolar patients with manic or depressed episodes as short as a single day or a few days, were described more than 25 years ago [10]. About 25 cases of ultra-rapid cycling and 15 cases of ultradian cycling have been reported. Frequent short periods of depression (1–4 days) were noted in a systematic study of 203 bipolar patients

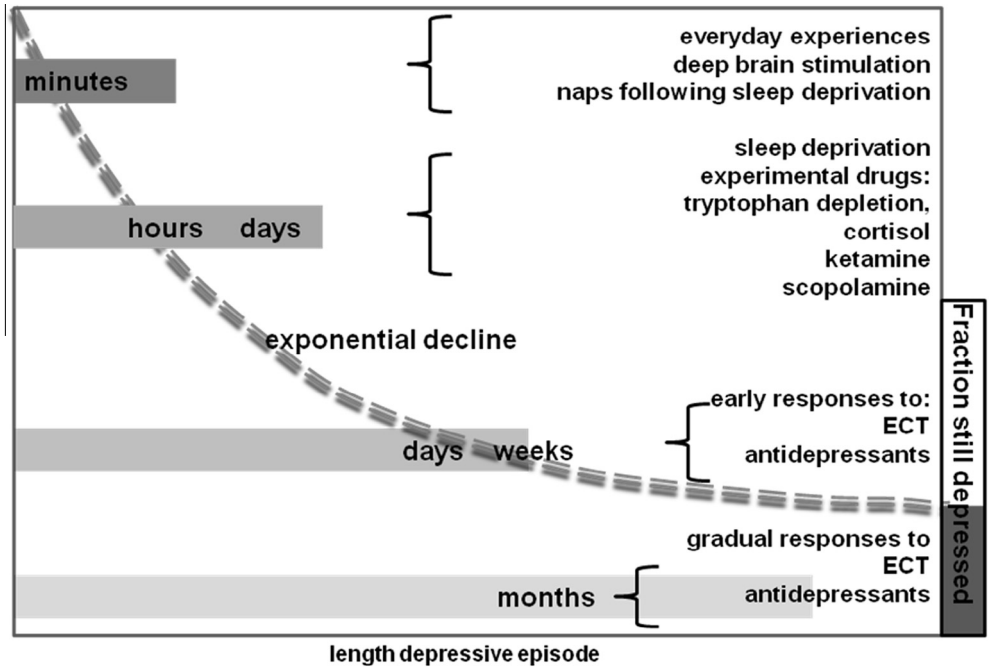

Fig. 1. Time frames of mood transitions. All time frames considered in the text are shown. Within-minute transitions include normal life experiences, deep brain stimulation and naps following sleep deprivation (SD). Antidepressive responses following various experimental drugs (ketamine, scopolamine, cortisol/hydrocortisone), the first two electroconvulsive treatment (ECT) sessions and the depressiogenic response to acute tryptophan depletion cause lasting or transient mood effects within hours or a few days. In the general population the time-to-recovery course is described with an exponential or a Weibull decay model: in these cases the is no average length. According to the Weibull model, placebo and antidepressant drugs may partially alleviate mood in some patients to about 50% (of depression scores) in one or two weeks, whereas the majority of patients follow a gradual antidepressant trajectory. Right panel signifies the fraction of depressive patients unresponsive to interventions. Details in the main text.