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Review

# Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders

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ABSTRACT

*Background:* There is growing research interest in studying motivational deficits in different neuropsychiatric disorders because these symptoms appear to be more common than originally reported and negatively impact long-term functional outcomes. However, there is considerable ambiguity in the terminology used to describe motivational deficits in the scientific literature. For the purposes of this manuscript, the term “amotivation” will be utilised in the context of mood disorders, since this is considered a more inclusive/appropriate term for this patient population.

Other challenges impacting the study of amotivation in mood disorders, include: appropriate patient population selection; managing or controlling for potential confounding factors; the lack of gold-standard diagnostic criteria and assessment scales; and determination of the most appropriate study duration.

*Methods:* This paper summarises the search for a consensus by a group of experts in the optimal approach to studying amotivation in mood disorders.

*Results:* The consensus of this group is that amotivation in mood disorders is a legitimate therapeutic target, given the magnitude of the associated unmet needs, and that proof-of-concept studies should be conducted in order to facilitate subsequent larger investigations. The focus of this manuscript is to consider the study of amotivation, as a residual symptom of major depressive disorder (MDD) or bipolar depression (BD), following adequate treatment with a typical antidepressant or mood stabiliser/antipsychotic, respectively.

*Discussion:* There is a paucity of data studying amotivation in mood disorders. This manuscript provides general guidance on the most appropriate study design(s) and methodology to assess potential therapeutic options for the management of residual amotivation in mood disorders.

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## 1. Introduction and rationale

### 1.1. Terminology

Motivation is a term widely used by both clinicians and researchers, but is often used imprecisely and interchangeably with other descriptors such as volition, drive, desire and mental and physical energy. There is a growing research interest in studying motivational deficits because these symptoms appear to be more common than originally reported and negatively impact long-term functional outcomes (Spijker et al., 2001; Lavretsky et al., 2010; Rothschild et al., 2014; Sheehan et al., 2011; Uher et al., 2012). However, there is considerable ambiguity in the terminology used to describe motivational deficits in the scientific literature; for example the following descriptors have often been used for motivational deficits: apathy, amotivation, avolition, anhedonia, psychomotor retardation, fatigue and anergy (see Table 1). Adoption of these terms tends to depend on the context in which they are utilised, rather than the neurobiology. For example, the term "amotivation" appears to be employed more frequently in the psychiatric vs. neurological literature, where the term "apathy" is favoured.

Given the absence of a clear understanding of the neurobiology of these related constructs, this manuscript will use the terms "amotivation" and "apathy" synonymously within the context of mood disorders. Due to the rapidly evolving literature regarding

**Table 1**
Definitions of different terms used to describe motivational deficits.

| Term | Definition | References |
|---|---|---|
| Amotivation | Absence of motivation, frequently used to mean a diminution of motivation, ***without*** dysphoria | Cerejeira et al., 2012 |
| Apathy | Diminished motivation not attributable to emotional distress, cognitive impairment, or a diminished level of consciousness. If diminished motivation is attributable to these factors, then it is a symptom of disorders in these other domains, e.g. depression (emotional distress), dementia (cognitive impairment), or delirium (level of consciousness). Thus, apathy can present as both a symptom and a syndrome (Marin, 1991) | Marin, 1990; 1991 |
| | Symptoms must be present for at least 4 weeks and impairment must be present in at least **two** of three dimensions of apathy. (i) Reduced goal-directed behaviour (e.g. lack of/diminished initiative); (ii) Cognition (e.g. lack of/diminished interests) and emotions (e.g. flat affect). (iii) Impairments may reflect loss or diminution of self-initiated/spontaneous behaviours (e.g. starting a conversation, seeking social activities) **or** environmentally-stimulated behaviours (e.g. responding to a conversation, taking part in social activities). Identifiable functional impairments (e.g. personal, social, occupational) attributable to apathy. Symptoms should not be the result of physical or motor disabilities, diminished level of consciousness, or the direct physiological effects of a substance (e.g. drug of abuse, medication) | Robert et al., 2009 |
| Avolition | In individuals with schizophrenia, a reduced ability to initiate and maintain goal-directed behaviour is typically referred to as *avolition* | Foussias and Remmington, 2010 |
| Fatigue | Employed to label symptoms seen in several disorders, including depression, schizophrenia, multiple sclerosis and Parkinson's disease. Generally refers to a "central fatigue", which is used to describe the lack of mental or physical energy | Andreasen, 1981; Friedman et al., 2010; Waters et al., 2013 |
| Anergia | Lack of perceived energy. Often used to describe a reduced tendency to engage in physical activity. In depressed individuals, the term *psychomotor retardation* is commonly used to label the slowing of movement, or a generally reduced tendency to engage in motor activity | Markou et al., 2013 |
| Anhedonia | Originally defined as an inability to experience pleasure (Ribot, 1896). However, the experience of pleasure can be dissociated from anticipation of pleasurable outcomes | Berridge and Robinson, 1998; Gard et al., 2007; Markou et al., 2013; Salamone et al., 2007; Smith et al., 2011; Treadway and Zald, 2011 |

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