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COMMENTARY TO SPECIAL ARTICLE

What kind of thing is depression?

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Some 35 years of research on the aetiology of depression as it is defined in the Diagnostic and Statistical Manual (DSM) has not led to any conclusive theory that explains why some individuals become depressed and others not. Instead, depression nowadays is seen as a multifactorial disorder, which basically means it can occur as a function of many (combinations of) factors. There is no single theory that captures the majority of the variance of depression in the population, nor a single treatment that is helpful for all depressed individuals. In the scientific literature, a broad reorientation on the validity of the concepts used in psychiatry can be discerned, and it is in this light that Professor Patten articulates several of the *models or metaphors* of depression. In doing so, he effectively pushes the chain of reasoning about the nature and/or origins of depression to a more fundamental level (Patten, 2015). Of interest here is that instead of summarising the different theories on the etiology of depression, Patten describes the different *kinds of theories* describing the aetiology of depression and the potential influence that such theories may have on scientific developments. Such reflections are valuable as the theories that are associated with the concept of depression are highly influential – both in a positive and in a negative way – not only in guiding future directions of research but also as explanatory frameworks in the communication with patients. It is essential that psychiatry reflects on the models that are being used. As rightfully argued by Patten, these models can be productive and lead to testable hypotheses, but they can also be destructive and lead to inadequate representations and stigma.

Psychiatric disorders as practical kinds

The Special Article by Patten forms a nice extension to an earlier paper, entitled 'what kind of things are psychiatric disorders?' (Kendler *et al*. 2011). In that paper the authors argue that psychiatric disorders are often regarded as either *essentialist kinds* or as *socially constructed kinds*. When regarded as essentialist kinds, psychiatric disorders have an essence and exist independent of the fact that we recognise or classify them. When regarded as socially constructed kinds, psychiatric disorders are merely brought into being by cultures and societies and are no more than agreements we make regarding their classification. Kendler *et al.* argue that the associated question 'Do psychiatric disorders exist?' is not the most important to pose, and suggest to replace this question by 'What is the usefulness of classifying symptoms?'. When diagnoses are regarded in this light as *practical kinds*, the question is not whether psychiatric disorders really exist or not, but whether or not their conceptualisation is helpful in achieving goals: 'What is the most *useful* classification to organise the variety of symptoms that humans can suffer from?' Usefulness in this respect largely depends on the extent to which classification leads to a better understanding of a process and ideally results in effective treatment. Following this line of reasoning, Kendler *et al.* conclude that a specific form of practical kind, namely the mechanistic property cluster (MPC) kind represents the most useful view on psychiatric disorders. In MPC kinds, several features (e.g., symptoms) are inter-related and gradual prototypes of disorders (with fuzzy boundaries) are distinguished based on the inter-relations between the features. In this view, instead of being based on the presence of specific symptoms, disorders are based on the inter-relations between symptoms. Other than the mere presence of symptoms, these inter-relations may represent causal mechanisms that are useful for prediction and explanation. Members of MPC kinds may thus differ in appearance (symptomatology) but resemble each other (to a gradual extent) in terms of their patterns of interactions among symptoms.

Metaphors and subtyping of depression

Patten describes eight informal models or metaphors of depression. Six of these models or metaphors view

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depression either as the result of a chemical imbalance, an exposure to a toxic environment, an injury, a deficiency, a brain degeneration process, or as an evolutionary vestige, respectively. When these models or metaphors for depression are regarded as practical or MPC kinds, we need to focus on how well they can describe the process on how depression occurs (i.e., their usefulness rather than the question whether depression is an essence or social construct). Although the usefulness of these metaphors is beyond the scope of Patten's Special Article, it depends largely on how well they help to disentangle the heterogeneity that is often observed in the depression phenotype. Heterogeneity not only occurs at a symptom level, but also at a person level and time level (Wardenaar & de Jonge, 2013). The DSM does not fully account for this heterogeneity as it assumes a relative stability of symptoms and does not allow for interactions between different levels. Similarly, subtyping or reconceptualisation attempts of depression are mostly based on examining a single level at the time, for instance, by factor analysing symptoms (without taking time into account) or by distinguishing different courses (without taking symptom distribution and dimensionality into account). Examples of these subtyping efforts have been described earlier (Baumeister & Parker, 2012), where symptom-based subtypes include melancholia, psychotic depression, atypical depression and anxious depression, while time-based subtypes include early onset depression, late life depression and seasonal affective disorder.

These efforts have thus far not resulted in replicable subtypes with proven clinical use, i.e., in fine-tuning interventions (Van Loo *et al*. 2012). Elsewhere we have argued that reducing heterogeneity in psychiatry should encompass the patient- symptom and time level simultaneously and that we need to apply new statistical techniques suitable for analysing these three-dimensional (3D) data (symptoms × persons × time) to make this possible, such as three-mode principal components analysis or longitudinal network models (Wardenaar & de Jonge, 2013). Such techniques enable us to see how symptoms interact differently for different persons over time. As such, they are in principle capable of visualising the processes that are occurring in individuals when transferring from a healthy state to a state of disorder (Van de Leemput *et al*. 2014). The distinction between the depression metaphors described by Patten in our view serves the same purpose: depression as a consequence of a chemical imbalance is *aetiologically* different from depression resulting from a degenerative process in the brain. Even if these cases may look the same in terms of symptom presentation, they are likely to require quite different treatments. It is quite well possible, though, that a more fine-grained MPC approach is able to discriminate between such etiological subtypes. By monitoring how specific symptoms develop and interact over time within individuals, and by subtyping individuals on the basis of these individual-based models, it may become possible to develop more useful phenotypes in the near future. For instance, it is likely that a depressive episode resulting from an acute brain injury or exposure to a toxic environment differs from depression as a consequence of a brain degeneration process, in terms of time × symptom interactions.

Two more metaphors of depression were described by Patten: depression as an obsolete diagnostic term or as a diagnostic condition that yet has to be understood. These two metaphors are comparable in the sense that both are not coupled with an etiological theory, in the first because the term is outdated by recent knowledge and in the latter because the linkage to an etiological theory is yet to come. Current treatments for depression are remarkably similar in terms of effects and they are generally as effective for depression as for most other disorders in the internalising spectrum (e.g., generalised anxiety, social phobia, post-traumatic stress disorder and agoraphobia). Both indicate that the current phenotype of depression is not optimal in terms of its usefulness. As a result of this inherent limitation of the used phenotype, the chances are very small that a future discovery will suddenly reveal what is really going on in the aetiology of depression. Instead, there is a much higher chance that the current phenotype of depression will be replaced by one or more phenotypes with stronger usefulness, which in turn could accelerate the development of more specific and useful aetiological models. Interestingly, Patten links this to alternative approaches of classification, the RDoCs in particular (Insel, 2014). It seems evident that subtyping based on phenomenological data *alone* will be insufficient to arrive at optimal phenotypes. Perhaps such data, even when analysed with 3D data analytic techniques will be insufficient to account for all relevant heterogeneity among individuals, and should be supplemented with physiological data. It is time to review the possibilities of subtyping psychiatric disorders in the internalising spectrum in terms of the metaphors that explain them. In an era of limited scientific progress, it is a good thing to think in a more fundamental way about the kind of things we study and what we want to achieve in psychiatry. In the end this should be a better understanding of psychopathology and the development of more effective treatments.

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