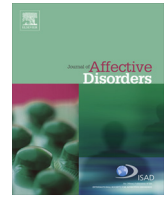




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Research report

The use of symptom dimensions to investigate the longitudinal effects of life events on depressive and anxiety symptomatology

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ABSTRACT

Background: Findings on the association between life events and depression have been quite inconsistent. This could be due to the heterogeneity of traditionally used depression outcomes. The aim of this study was to investigate whether specific symptom dimensions can be used as an alternative to detect more specific life event effects.

Methods: Participants with/without psychiatric diagnoses were included ($n=2252$). Dimensions of the tripartite model (General Distress [GD], Anhedonic Depression [AD] and Anxious Arousal [AA]) were assessed at baseline, 1-year and 2-year follow-up. Life events occurring between measurements were assessed retrospectively. Longitudinal associations between life events and dimensional scores were analysed with Linear Mixed Models.

Results: Occurrence of negative life events was associated with increasing GD and AA, and less with AD. Positive life events were associated with decreasing GD and AD, but not with AA. The association between negative life events and AD was larger in the absence of previous psychiatric problems, lending support to a dimension-specific 'kindling' effect. Also, the negative association between negative life events and GD was stronger in those with high neuroticism. Multivariable analyses with individual life events showed that a few strong independent effects remained for each dimension.

Limitations: Life event reports were retrospective; only three outcome dimensions were used.

Conclusions: These results show that the effects of life events and modifying factors depend, to an extent, on the symptom domain that is considered as outcome, illustrating the need to account for symptom heterogeneity in etiological life event research.

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1. Introduction

There is evidence for a relationship between the occurrence of life events and the onset, recurrence and persistence of depression (e.g. Kessler, 1997; Mazure, 1998; Hammen, 2005). Early case-control studies showed that adverse life events were more common in depressed patients than in controls (e.g. Paykel et al., 1969; Brown and Harris, 1978). Later, life events were also shown to be associated with first onset of depression and with recurrence in lifetime depressed patients (e.g. Mazure 1998; Ormel et al., 2001). In addition, adverse life events have been shown to be associated with more comorbidity (Paykel, 2003) and longer time to remission (Spinhoven et al., 2011). Also, some depression

subtypes have been found to be more sensitive to the effects of life events: for instance, severe melancholic depression was found to be more sensitive to minor life events than non-melancholic depression (e.g. Harkness and Monroe, 2006). Interestingly, the effects of stressful life events have been found to diminish with increasing numbers of prior episodes (Kendler et al., 2000; Monroe and Harkness, 2005). This is in line with the broadly held 'kindling' hypothesis (Post, 1992), which states that the relative contribution of exogenous factors to depression becomes smaller with each depression recurrence. Often replicated, this phenomenon has clarified the dynamic association between life stress/negative life events and depression recurrence over time (Monroe and Harkness, 2005).

Although there is quite some support for the abovementioned associations and phenomena there also is inconsistency in the literature as a whole. There are, for instance, studies that report no or very small associations between life events and depression (e.g.

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Spinhoven et al., 2010), no or little support for kindling (e.g. Roca et al., 2013), and no associations between life events and depression subtypes (Sun et al., 2012). This could be due to design variations across studies (e.g. in samples, measures and definitions; Mazure, 1998; Hammen, 2005) or methodological issues that affect all life event assessments to some extent (e.g. reporting bias/‘stress generation’, Hammen, 2005; mediating factors, e.g. Kessler, 1997; Michl et al., 2013). Interestingly, much less is known about the role of positive life events. Although these events are hypothesized to decrease depressive severity (e.g. Brown et al., 1988), this effect is under investigated and in little available studies have been found to be modified by other factors. For instance, Oldehinkel et al. (2000) found that positive life events led to more improvement of depression in those with high neuroticism, suggesting a role of person-specific vulnerability and/or reactivity to external stimuli. Apart from the literature's quite narrow focus on negative events, an issue that has received relatively little attention in life event research, but is very important for the replicability and interpretability in any strain of depression research, is the definition of the used outcomes.

The traditional depression construct is very heterogeneous (Widiger and Clark, 2000). Two patients that meet DSM-criteria for a depressive episode or have similar scores on a depression severity scale can be very different in terms of their symptom profiles, leading to a situation where traditional psychopathology outcomes show a lot of internal variation. Although more homogeneous subtypes of depression (e.g. melancholic/atypical) have been proposed as a possible solution, these subtypes have limited validity and are quite heterogeneous themselves (Stewart et al., 2007). As a result, most previous research has only been able to detect general effects of life events. This is unfortunate since studies that have employed more specific definitions of life event types and symptom outcomes, have shown relatively consistent patterns of specific associations. On the one hand, life events that involved social loss (e.g. ‘death of a loved one’ and ‘romantic loss’) were found to be associated with increased crying and arousal. On the other hand, life events that were characterized by failure and prolonged stress (e.g. winter) were associated with increased feelings of fatigue and pessimism (Keller and Nesse, 2005). These results were corroborated by a second study (Keller and Nesse, 2006) and further extended in a third (Keller et al., 2007). In this large study, social loss was found to be associated with higher levels of sadness, anhedonia, appetite loss and guilt. Failure and chronic stressors were associated with increased fatigue and insomnia, but less with sadness and anhedonia. This work suggest that the effects of life events vary across different depressive symptoms instead of being syndrome-broad.

The abovementioned studies used individual depressive symptoms as outcomes. *Symptom dimensions* could help to further investigate the specific effects of life events. Dimensions cover distinct symptom domains and follow a severity-continuum from healthy to severely pathological (Goldberg, 2000). As such, dimensions have the advantage that they can be measured reliably with psychometric scales (in contrast to assessment of individual symptoms) and can be used to assess continuous change. Compared to DSM-categories, dimensions also have advantages: they are more homogeneous, circumvent comorbidity (Widiger and Clark, 2000), better represent continuous variations observed in real life (Goldberg, 2000) and provide more statistical power/sensitivity to change (MacCallum et al., 2002).

The *tripartite model* is a well-known dimensional model of depressive and anxiety symptomatology and assumes three underlying dimensions (Clark and Watson, 1991). *General Distress* (GD) covers symptoms of psychological distress (e.g. feeling guilty and worry), common to depression and anxiety. *Anhedonic Depression* (AD) covers symptoms of decreased positive affect and energy,

specific to depression. *Anxious Arousal* (AA) covers symptoms of somatic hyperarousal, specific to anxiety. The model has been well-validated psychometrically (Watson et al., 1995; Keogh and Reidy, 2000) and its external validity has been confirmed by associations with biological mechanisms, such as the Hypothalamo–Pituitary–Adrenal-axis (Wardenaar et al., 2011), metabolic factors (Luppino et al., 2011) and gene sets (van Veen et al., 2012), and with clinical prognosis (Wardenaar et al., 2012).

Only few studies have looked at the associations between life events and the tripartite dimensions or comparable constructs/scales. Several cross-sectional studies have shown that negative life events are associated with increased negative affect/GD and positive life events with increased positive affect/decreased AD (Reich and Zautra, 1981; Zautra and Reich, 1983; Suh et al., 1996). One adolescent study found that negative life events combined with high GD was combined with depression and anxiety; whereas negative life event occurrence and high AD (low positive affect) was specifically associated with depression, in line with the tripartite model (Fox et al., 2010). Another cross-sectional study found several general and specific associations between retrospectively assessed life events and the tripartite dimensions (van Veen et al., 2013). Prospective studies have employed experience sampling methods to measure affective responses to daily hassles, and have also found effects of negatively experienced events on negative affect (e.g. Suls, 1998; Gable et al., 2000; Moberly and Watkins, 2008; Peeters et al., 2003). The latter studies looked at day-to-day effects of events, rated as stressful by respondents, and provide insight in daily life emotional responsivity.

The prospective design of the above work could be extended to investigate the more extreme effects of *major* life events on an epidemiological scale of months/years. In addition, a broader range of dimensions could be included (GD, AD and AA) and both healthy subjects and patients could be included. Importantly, such a design would enable the investigation of the actual added value of dimensions in life event research. This could be done by comparing the effects that are captured by the dimensions with the effects that are captured by traditional DSM-based course-trajectory classifications.

The current study was aimed to investigate the associations between, on the one hand, negative and positive life events, and on the other hand, longitudinal change on the tripartite model dimensions. To this end, symptom-dimension scores and life event reports were collected in a large group of subjects with and without psychiatric diagnoses ($n=2252$) at three consecutive measurements (baseline, 1-year and 2-year follow-up). Associations between life events and change on the dimensions were analysed with Linear Mixed Models (LMM). These analyses were adjusted for DSM-based course trajectories to evaluate the actual added value of the dimensions to capture unique life event effects. Also, analyses were performed to investigate the modifying effect of the presence/absence of a lifetime diagnosis on the effect of negative life events on the dimensions, in line with the kindling-hypothesis. In addition, analyses were done to investigate the potential modifying effect of baseline neuroticism on the association between positive life events and the dimensions.

2. Methods

2.1. Participants

Participants came from the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal study to investigate the course of depressive and anxiety disorders ($N=2981$), who were recruited from community, primary care and specialized mental health care organizations. At baseline, the mean age was 41.9

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