**Brede context:**

Aisa:

* there is an increasing evidence implicating stress in brain disturbances thought to underlie certain forms of depression or particular components of the depressive syndrome (Kessler, 1997; Kendler et al., 1999; Van Praag, 2004).
* There are important memory disturbances in stress-related psychiatric disorders (Bremner and Narayan, 1998; Bremner et al., 2003)
* There is compelling evidence that exposure to early stressful adverse life events may increase vulnerability to psychopathology in adult life. In fact, individuals who experience early trauma, such as parental loss, sexual abuse or physical assault in childhood, present an increased risk for suffering depression later in life (Heim and Nemeroff, 2001).

Kalinichev:

* A large body of evidence indicates that exposure to early adverse life events in the form of childhood neglect and abuse can increase vulnerability to psychopathology in adult life (Heim et al., 1997, 2000; Ladd et al., 2000; Caldji et al., 2001).

**HPA-as:**

Aisa:

* The hypothalamic–pituitary–adrenal (HPA) axis is an essential component of an individual’s capacity to cope with stress and in fact, a hyperactivity of the HPA axis is observed in the majority of patients with depression (review by Arborelius et al., 1999; De Kloet et al., 2005).
* Stress stimulation of the axis starts when corticotropin releasing factor (CRF) released by the paraventricular nucleus of the hypothalamus (PVN) stimulates the release of corticotropin (ACTH) from the anterior pituitary, which in turn, stimulates secretion from the adrenal cortex.
* Many of the behavioural consequences of stress are thought to be mediated by the activation of the glucocorticoid receptor by stress-induced high levels of glucocorticoid hormones (De Kloet et al., 1998; Oitzl et al., 2001; Roozendaal et al., 2006a) and subsequent alteration in gene expression (see review by Berton and Nestler, 2006).

**Maternale separatie:**

Aisa:

* Based on these arguments, it has been shown that prolonged periods (41 h) of maternal separation (MS) during the first weeks of life result in animals with behavioural and neuroendocrine signs of elevated stress reactivity as adults (Anisman et al., 1998; Ladd et al., 2000; Lehman and Feldon, 2000; Ploj et al., 2003).
In addition to an increase in immobility time in the Porsolt forced swimming test, anhedonia, and an enhanced anxiety-like behaviour, MS animals exhibit a dysfunction of the HPA axis reactivity to stress and therefore, the MS model in rat is considered nowadays as a robust model of enhanced stress responsiveness and depressive-like behaviour (Ladd et al., 2000; Van den Hove et al., 2005).

Kalinichev:

* Periodic neonatal maternal separation in the rat has been used by several investigators as a rodent model of the effects of early adverse life events on adult physiology and behavior. In this procedure, neonatal rats are removed from the mother for several hours daily during the first 2 weeks of life (Plotsky and Meaney, 1993; Wigger and Neumann, 1999; Kalinichev et al., 2000; Huot et al., 2001; Boccia and Pedersen, 2001).
* When tested as adults, maternally separated (MS) adult offspring exhibit a cluster of behavioral and neuroendocrine signs similar to those observed in patients with depression and anxiety disorders (Amsterdam et al., 1987; Heit et al., 1997; Ladd et al., 2000).

**Eerdere bevindingen**

Aisa:

* MS rats show in adulthood
* depressive-like behaviour in the forced swimming test (Willner, 1990; Plotsky et al., 1998; Hall, 1998; Ladd et al., 2000),
* anhedonic behaviour (Willner et al., 1987; Zurita and Molina, 1999; Huot et al., 2001) and
* anxiety behaviour (Wigger and Neumann, 1999; Huot et al., 2000),
* increased HPA axis responsiveness to stressors (Rosenfeld et al., 1992; Plotsky and Meany, 1993; Ladd et al., 1996; Wigger and Neumann, 1999) and
* elevated CRF mRNA in the PVN (Plotsky and Meany, 1993; Ladd et al., 1996).

Kalinichev:

* A primary feature of the MS phenotype has been an enduring dysregulation of hypothalamic–pituitary–adrenal (HPA) axis reactivity to stress (Ladd et al., 2000; Caldji et al., 2001).
* MS males have elevated basal CRF levels in the median eminence and elevated levels of the CRF mRNA levels in the hypothalamus (Plotsky and Meaney, 1993).
* In response to stress, such as restraint or air-puff startle, MS males display a potentiation in ACTH and corticosterone (CORT) secretion compared to either H (restraint) or H and animals that received typical animal husbandry (animal-facility reared, AFR; air-puff; Plotsky and Meaney, 1993; Huot et al., 2001).
* In accord with the neuroendocrine changes, there is some evidence of behavioral alterations in MS animals that resemble those observed in patients with affective disorders. MS rats appear to exhibit increased anxiety-like behavior, anhedonia, increased preference for ethanol and impairment in male sexual behavior (Wigger and Neumann, 1999; Caldji et al., 2000; Ladd et at., 2000; Huot et al., 2001; Rhees et al., 2001).

**Wetenschappelijke relevantie**

Kalinichev:

* The increased interest in the paradigm of maternal separation by several laboratories also has resulted in discrepancies among findings, especially concerning behavioral signs of anxiety in MS animals (Lehmann and Feldon, 2000).
* According to some authors, MS males exhibit increased anxiety compared to NH males, as indicated by decreased open-field activity and increased likelihood of approaching food in a novel arena when food deprived (Ogawa et al., 1994; Caldji et al., 2000). However, in other measures of novelty-induced suppression of feeding and in the plus-maze test, MS and NH males are similar (McIntosh et al., 1999; Caldji et al., 2000).
* Furthermore, plasma levels of CORT and ACTH following stress are also similar in MS and NH males (Plotsky and Meaney, 1993; Liu et al., 2000). According to others, plasma CORT levels during (Ogawa et al., 1994) or following (Pryce et al., 2001) restraint stress are even higher in NH than in MS males.