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Title: Deciphering the links between psychological stress, depression, and neurocognitive decline in patients with Down syndrome

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1 Introduction

Down syndrome (DS) is a genetic disease caused by an extra copy of chromosome 21 or part of it. This extra copy is known to cause several types of dysfunction, such as language and cognitive deficiencies, an average IQ that is significantly lower than that of the general population, an elevated prevalence of epileptic seizures, and a three- to five-fold higher prevalence of Alzheimer's disease (AD) than in the non-DS population (Snyder et al., 2020). This review was sparked by the observation that we made in our clinical practice that patients with DS quite often enter an early cognitive decline soon after a traumatic psychological event, such as an aggression (verbal, physical, sexual), the loss of a beloved parent, or the leaving of a caregiver. Thus, the issue of the vulnerability of patients with DS to stress appears to be increasingly important and yet still difficult to clearly demonstrate. We therefore explored the molecular and cellular events that may, to some extent, explain or support these clinical observations.

It is well known that patients with DS are prone to develop early AD by the age of 60 and that all already have senile plaques by the age of 40 (Lott and Head, 2019). Indeed, the pathophysiology of DS and AD share common pathways and the patients may use the same medications (Hartley et al., 2015). However, several studies have reported the additional impact of stress on the incidence and susceptibility to develop this disease. Traumatic psychological stress has been found to lower the age of initiation of AD in the general

population but this has not been specifically shown for people with DS (Xie et al., 2016). Patients with DS are more susceptible to depression because of their socio-cognitive disabilities and morphological differences. We wished to know whether stress can influence the progression of patients with DS towards AD, given the relationships between higher exposure to stress, a higher risk of depression (Walker et al., 2011; Walton and Kerr, 2015), and the known higher prevalence of AD in the DS population.

Here, we review the events involved in psychological stress (acute and chronic), depression, and AD in the general population and attempt to decipher how DS-related molecular and cellular abnormalities may potentiate such events into triggering a rapid cognitive decline in people with DS when subjected to psychological stress. Finally, we propose means to explore these hypotheses.

2 Pathophysiology of psychological stress

2.1 Short definitions of stress and resilience

Since its description by Hans Selye in 1952, stress has been extensively studied in various ways. Indeed, stress has many facets, including physical, chemical, biological, and psychological as recalled in a recent review (Szabo et al., 2017). Various types of stressors have been described for psychological stress, including those of Sharpe and Lewis, such as performance, social threat, boredom, lack of control of a situation, bereavement, and physical threat (Sharpe and Lewis, 1995).

Assessing the intensity of such stressors is not easy, as stress may be felt very differently from one individual to another (Sele et al., 2020).

Thus, several automated methods have been suggested to monitor the level of psychological stress (Brown et al., 2020; Hong et al., 2018; Liu et al., 2020). However, these methods still need to be validated for people with cognitive impairment.

Resilience can be defined as the complex process that leads an individual's capacity to adapt to various sources of stress and help him/her return to a normal state, or at least to a less harmful state (Windle et al., 2011). Of course, each individual responds to stress using his/her own resilience mechanisms, which include genetic, educational, environmental, and familial factors. As for the intensity of stress, assessing or measuring resilience is not an easy task and several scales have been proposed, with questionable results (Windle et al., 2011).

2.2 Impact of psychological stress on brain structures

Acute psychological stress increases cortisol secretion, which acts as a transcriptional factor on mineralocorticoid (MRs) and glucocorticoid receptors (GRs), both present in the hippocampus. Moreover, cortisol activates the hippocampus and amygdala, which is involved in anxiety, the regulation of fear, and remanent memory of traumatic events.

Chronic psychological stress is not entirely different from acute stress, for which it is more a matter of intensity and/or repetition. In the long term, repeated cortisol exposure induces desensitization of MRs and

GRs in the hippocampus, alters brain neuroplasticity, and induces emotional-cognitive deficiencies and hippocampal atrophy (Chen et al., 2010; Maras and Baram, 2012; Schoenfeld et al., 2017). Once exposure to chronic psychological stress ends, irreversible amygdala hypertrophy remains, which may be an element of vulnerability to ulterior stress, as the amygdala is involved in the systemic reaction to acute stress. Finally, situations of chronic psychological stress (humiliation, exclusion, loneliness, or social rejection) dysregulate the cortico-limbic system, resulting in hyposensitivity of the GRs and an increased likelihood of inflammation (Algava et al., 2010). This may explain why child abuse and household dysfunction may induce early death in adulthood (Felitti et al., 1998).

Moreover, based on the fact that lymphocytes, macrophages, and granulocytes bear receptors for certain neurotransmitters, such as norepinephrine, the neuro-inflammation induced by psychological stress can be explained by psychoneuroimmunology, a cross-road field of research between psychiatry, immunology, and endocrinology (Ader et al., 1995). Finally, stressful events, such as grief or divorce, can be associated with alterations of the immune system caused by the release of glucocorticoids and the activation of the HPA axis (Ader et al., 1995; Haroon et al., 2012). A systematic review recently proved that chronic psychological stress causes microglia hypertrophy and increased pro-inflammatory cytokine release (Calcia et al., 2016).

2.3 Sleep disorders in patients with DS: a confounding comorbidity

Studying the impact of psychological stress on the onset of AD in patients with DS requires the consideration of specific confounding comorbidities, such as sleep disorders. It is of particular concern to track down such comorbidities, as they are frequent, underdiagnosed, and treatable conditions that can increase the incidence of anxiety, depression, and dementia in patients with DS.

Obstructive sleep apnea syndrome (OSAS) affects 23% to 78% of patients with DS because of their upper airway anatomical malformations, with severe forms accounting for 30% according to a recent publication (Giménez et al., 2018). This is of particular concern, as it can impair working memory and cause atrophy of the hippocampus, independently of the development of AD (Lott, 2012). Behavioral sleep disturbances, another group of sleep disorders, affect 15% of patients with DS and significantly increase the incidence of anxiety, depression, and dementia (Esbensen, 2016), as does fragmented or fractured sleep, a 40% prevalent comorbidity in patients with DS (Esbensen and Schwichtenberg, 2016). Patients with fragmented sleep spend very little time in slow-wave sleep (SWS) (Varga et al., 2016), a period of sleep associated with increased clearance of cerebral amyloid beta and decreased amyloid production (Cordone et al., 2019). Finally, as stated in a recent review, sleep disorders increase susceptibility to psychological stress, depression, neuroinflammation, tau aggregation, and cerebral oxidative stress, which are key elements in the initiation of AD pathophysiology (see section 3.1) (Sadeghmousavi et al., 2020).

Thus, evidence is mounting that underscores the importance of psychological stress in the incidence of psycho-neurological decline through epigenetic and molecular mechanisms. Herein, we will focus on the dynamics of progression between stress, depression and, AD as part of a hypothetical stress-depression-AD continuum.

3 Stress, depression, and Alzheimer's disease: a bio-continuum?

A cause and effect relationship has been established between psychological stress (acute and/or chronic) and major depressive disorder in the general population (Slavich and Irwin, 2014). The same relationship has been recently envisioned between depressive disorders and dementia, including AD (Dafsari and Jessen, 2020; Liew, 2019). Psychological stress promotes depression, which in turn promotes dementia and AD. In addition, they all share common pathophysiological elements and pathways. Thus, there appears to be a psychobiological continuum between psychological stress, depressive disorders, and neurocognitive degenerative processes (Rodrigues et al., 2014; Sotiropoulos et al., 2019).

In the following, we present pathophysiological elements involved in depression and AD that are triggered or augmented by stress.

3.1 Pathophysiological elements of Alzheimer's disease

The pathophysiology of AD has been extensively studied. The most important bio-cellular actors in AD onset and progression are briefly summarized below. Historically, abnormal accumulation of fibrillar amyloid plaques in the extra-neuronal compartment – amyloidosis – has been the key lesion described in AD. Such amyloid plaques dysregulate neuronal connections, increase cerebral oxidative stress, enhance cerebral inflammation and cerebral amyloid angiopathy, and ultimately lead to neuronal apoptosis (Tarawneh, 2020).

Hyperphosphorylation of intracellular Tau proteins was later recognized to be a major step in AD, as it leads to dysregulation of the neural cytoskeleton, cytologically characterized by neurofibrillary tangles (NFTs) (Silva and Haggarty, 2020). In AD, such NFTs are first observed in the hippocampus and entorhinal cortex, causing local cerebral atrophy, before wider cerebral extension (Congdon and Sigurdsson, 2018).

As for certain other neuro-degenerative diseases, AD is characterized by cortical atrophy, of which the most characteristic feature is hippocampal atrophy, leading to severe memory impairment. However, patients with AD also suffer from cortical atrophy in the inferior temporal, precuneus, and parietal regions (Wang and Initiative, 2020).

Neuroinflammation is both a cause and consequence in the initiation and progression of AD pathophysiology. Indeed, increased amyloid aggregates lead to microglial inflammation (Griffin and Mrazek, 2002), which in turn increases beta-amyloid protein synthesis (Sivandzade et

al., 2018), inducing a vicious pro-inflammatory circle. Such neuronal inflammation leads to increased autophagy, with subsequent apoptosis and cerebral atrophy and increased oxidative stress (Bostancıoğlu, 2019; Forloni and Balducci, 2018; Newcombe et al., 2018; Nizami et al., 2019).

Because of structural misfolding, beta-amyloid aggregates catalyze the production of reactive oxygen species, increasing cerebral oxidative stress and the level of free radicals (Cheignon et al., 2018). Similarly to neuroinflammation, increased free radical levels and oxidative stress disturb beta-amyloid clearance, which in turn induces cerebral amyloidosis (Tönnies and Trushina, 2017). Neuronal oxidative stress also alters mitochondrial metabolism, enhances neuroinflammation, and increases apoptosis, causing neuronal loss and hyperphosphorylation of Tau proteins (Butterfield and Boyd-Kimball, 2018; Perluigi et al., 2020).

Patients with AD also exhibit low neuronal GABA levels (Solas et al., 2015), which is thought to be caused by the overexpression of APP, ApoE4, and altered tau proteins (Huang and Mucke, 2012). Moreover, the dysregulation of the balance between the GABA and glutaminergic systems in AD is believed to be associated with increased excitotoxicity (Hynd et al., 2004).

3.2 Towards a Stress-Depression-Alzheimer continuum hypothesis?

Predementia states of AD have recently been extensively studied, with the hope of implementing potential preventive actions. A clinical continuum between subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD is commonly recognized (Apostolova, 2016; Ávila-Villanueva et al., 2020; Dubois et al., 2016). In 2018, the National Institute of Aging-Alzheimer's Association (NIA-AA) proposed an amyloid and tau-based definition of the AD spectrum, emphasizing the hypothesis of a biological continuum between SCD, MCI, and AD (Jack et al., 2018). Based on common biological patterns, it was later hypothesized that there may be another bio-continuum between stress, depression and AD (Sotiropoulos et al., 2008). Indeed, it is now well-established that psychological stress increases cerebral amyloid plaque formation (through the upregulation of APP gene expression) (Catania et al., 2009), as it does NFT formation (Vyas et al., 2016), hippocampal atrophy (Ansell et al., 2012; Schoenfeld et al., 2017), neuro-inflammation (Vyas et al., 2016), oxidative stress, (Schiavone et al., 2012), and a GABA/Glutamate imbalance (Martisova et al., 2012). Interestingly, all these key stress-induced elements in AD progression are also elevated in depressive disorders (Katon et al., 2012; Khan et al., 2020; Kitzlerová et al., 2018; Moraros et al., 2017; Wu et al., 2018). In this hypothesis, supported by recent well-referenced studies, it has been suggested that stress may be the spark for a decompensation cascade, starting with depression before evolving towards AD (Dafsari

and Jessen, 2020; Justice, 2018; Kurakin and Bredesen, 2020; Sotiropoulos et al., 2019).

4 The impact of psychological stress on patients with Down syndrome: a triggering element towards Alzheimer's disease?

To make the following part of this article understandable, we propose a putative scale called the 'global psycho-cognitive state', which globally encompasses the cognitive and psychological performance of a person. Of course, this index needs to be clearly defined, but could resemble the Clinical Global Impression (CGI) scale, both for severity and improvement (CGI-S, CGI-I) (Busner and Targum, 2007). We use this putative scale in Figure 2.

Improvement and resilience depend on many parameters, such as the type of stress, intensity, and number of repetitions, as well as genetic background and social environment. Furthermore, resilience may be complete, in the best cases, or incomplete. Thus, the evolution of resilience must be carefully scrutinized.

As explained earlier, stress may be seen as a trigger event in the progression towards AD in the general population. Patients with DS are exposed to both increased stress (psycho-morphological specificities, cognitive impairment) and endogenous susceptibility to AD (see section

4.1). Thus they are likely to be at extremely high risk of developing AD when exposed to stress.

4.1 Down Syndrome: a predisposition for Alzheimer's disease

A close relationship in terms of mechanisms has been described between AD and DS by Hartley et al. (Hartley et al., 2015). Indeed, DS is the leading cause of early onset Alzheimer's disease (EOAD) (Gomez et al., 2020). This can be partially explained by the location of several genes that are involved in AD pathophysiology on chromosome 21, thus increasing the risk due to a gene dose effect. For example, the triplication of APP, ETS2, BACE2, and DYRK1A expose individuals to increased amyloidosis (Gomez et al., 2020; Wilcock and Griffin, 2013). Moreover, triplication of the S100B and APP genes upregulates the expression of IL-1B protein, which increases neuroinflammation (Wilcock and Griffin, 2013). In terms of oxidative stress, patients with DS show higher oxidative stress levels because of alterations of the kynurenine metabolic pathway, decreased production of antioxidants, and triplication of the SOD1, RCAN1 and APP genes (Gomez et al., 2020; Perluigi et al., 2020). Finally, patients with DS also show (i) increased tau hyperphosphorylation because of the triplication of the ETS2 and DYRK1A genes (Gomez et al., 2020; Hartley et al., 2015), (ii) increased neuronal apoptosis caused by the coordinated action of SOD1, DYRK1A, and ETS2 (Martínez-Cué and Rueda, 2020), (iii) increased mitochondrial dysfunction linked to the triplication of the S100B and SOD1 genes (Dierssen et al., 2020), and (iv) altered endocytosis and synaptic trafficking because of triplication of the

RCAN1 and SYNJ1 genes (Gomez et al., 2020). All of the elements mentioned above (summarized in Figure 1) potentially increase the probability of high vulnerability of patients with DS to AD.

However, not all patients with DS develop AD as early as others and neuroimaging can be informative to assess whether or not a patient with DS will develop AD early in life. Individually, metabolic imaging using (C-11) Pittsburg Compound-b (PiB) or Amyloid PET have failed to predict the onset of AD in patients with DS, with contradictory results or a lack of power (Abrahamson et al., 2019). Patients with DS who develop AD show a thinner cortex and hypometabolism in the temporoparietal, precuneus-posterior cingular, and frontal regions relative to those without AD (Fortea et al., 2020), consistent with previous results suggesting that the association of various types of imaging (in this case, MRI and PET) are required to predict the onset of AD in patients with DS (Matthews et al., 2016). Finally, it appears that a reduction in default mode network (DMN, by functional imaging) connectivity in posterior brain areas could be predictive of the onset of AD in C-PiB positive patients with DS (Wilson et al., 2019). This all underscores the difficulty of diagnosing or predicting AD in patients with DS.

4.2 Specificity of depression in patients with Down syndrome

Patients with DS exhibit suboptimal attachment behaviors, classifiable as Type D by the Ainsworth classification (Ganiban et al., 2000), suffer from intellectual disability (Irons and Gilbert, 2005), have a smaller

hippocampus, and show altered neurotransmission (Walker et al., 2011). They are thus at a high risk of developing depressive and anxiety disorders or major depression (Bond et al., 2019). However, communication disabilities make the diagnosis of depression or depressive-like disorders of DS patients more difficult, with an underestimation of their true psychological state. Several clinical research studies have assessed cognitive regression in patients with DS after having to cope with harsh life events, such as the loss of a caregiver, bereavement, or aggression (Fonseca et al., 2014). For example, a teenager with DS exhibited cognitive and developmental regression following a modification of lifestyle (onset of menses and a change of school). This happened to be a case of reactive depression, for which antidepressant medication and psychotherapy completely reversed the neurocognitive alterations (Stein et al., 2017). It echoed a previous retrospective cohort study of DS patients which reported that for every case of acute regression, they had also experienced severe emotional stress before early cognitive regression (Mircher et al., 2017). This highlights that acute cognitive decline in the DS population can be associated with either depression or pre-dementia states, requiring caution in differentiating and properly treating it in the clinic.

4.3 Down Syndrome: a risk factor for stress and poor resilience

Resilience, which is the process of adapting to significant sources of stress and the capacity to bounce back (Windle et al., 2011), can vary quite noticeably from one person to another. The HPA axis appears to

play a major role in resilience, through CRH, GRs, and MRs (Faye et al., 2018) and exhibits sex-related differences (Bangasser et al., 2017). Gaffey *et al.* proposed an interactive model for stress and resilience in aging people: the Aging, Stress, and Resilience Model (ASRM) (Gaffey et al., 2016). This model, based on a meta-analysis of the current literature, suggests that resilience to psychological stress is related to modulation of the HPA axis in older adults, based on the fact that resilience to psychological stress in older adults is associated with modulation of the diurnal cortisol blood concentration, which is considered to be a marker of HPA axis activity.

Patients suffering from cognitive disabilities often suffer from low resilience to psychological stress (Deng et al., 2018; Panicker and Chelliah, 2016). Because they have an average IQ significantly below that of the general population, patients with DS are more likely to show low resilience. Although not yet proven, such low resilience to stress has been clinically observed by some of us (unpublished data) in a national center for patients with DS (Institut Jérôme Lejeune, Paris) and in a large reference center (University of Chicago, USA). In light of these elements, we attempted to model the resilience of patients with DS exposed to various types of stress in Figure 2. As summarized in a recent review, resilience is a process influenced by numerous factors and based on genetic and environmental features (Basile et al., 2021). Based on the fact that altered synaptic plasticity and increased neuronal senescence decrease individual resilience to developing AD, it has been hypothesized that sub-cellular mechanisms, such as

neuroinflammation, mitochondrial dysfunction, amyloid plaques, and neurofibrillary tangles, decrease such resilience (Hampel et al., 2019). As all of these events are naturally elevated in patients with DS, it can be envisioned that DS is an additional risk factor for poor resilience to the development of AD.

4.4 Impact of stress on the progression Alzheimer's disease in patients with Down syndrome

Low IQ has been reported to be a risk factor for developing post-traumatic stress disorder (PTSD) after a traumatic event (Daud and Rydelius, 2009), putting the DS population at higher risk. Given the fact that patients with DS show poor resilience, it is plausible that they may perceive certain stressful events (a change in caregiver, loss of a parent, verbal or physical assault, etc.) with the same intensity as very harsh events (bombs, gun assaults, abduction, etc.) that induce PTSD in non-DS individuals. Ultimately, these states could be considered as 'PTSD-like' for patients with DS.

Given their endogenous genetic predisposition to develop AD, poor resilience, and increased exogenous exposure to psychological stress, individuals with DS exhibit a very high risk of developing early-onset AD and difficulty in coping with the rapid cognitive decline, as reported in the literature. We can hypothesize that psychological stress in the DS population may overwhelm adaptive capacities and launch an unstoppable cascade of reactions, as illustrated in Figure 3.

5 Discussion

We have presented the neuro-biochemical pathways that could explain why the DS population may be at a higher risk of developing stress-induced AD. However, it will be highly challenging to demonstrate such susceptibility to stress in patients with DS, as there is currently no specific psychometric scale for the DS population. Various subjective or objective methods could be used, such as EEG analysis (Alonso et al., 2015; Al-Shargie et al., 2018; Lobo et al., 2015; Putman et al., 2014), analysis of the galvanic skin response (GSR) (Boucsein, 2012; Romano et al., 2017), or measuring salivary cortisol for acute stress (González-Cabrera et al., 2014; Tavares et al., 2017) or hair cortisol for chronic stress (Lee et al., 2015).

However, we suggest to not wait for such data but rather immediately recommend that individuals with DS be raised and allowed to live in a calm and low-stress environment. Stress at work (when work is possible) or at home should be avoided as much as possible, as stressful events may trigger molecular cascades that are far more deleterious for individuals with DS than those without. Of course, antidepressant medication could also be tried for two reasons. First, it may help to differentiate atypic depressive disorders from dementia. Second, a retrospective study showed that elderly people without cognitive impairment who received SSRIs within the previous five years, for an average of 32 months, had a significantly lower number of plaques, as assessed by PET, than untreated matched patients (no

difference in age, sex, or ApoE status) (Cirrito et al., 2011). This was confirmed by a study in animal models, which showed that amyloidosis and plaque formation were lower after the use of antidepressants (Stagni et al., 2015). The use of antidepressants to prevent AD was emphasized in a recent comprehensive review, although it did not discuss DS individuals (Dafsari and Jessen, 2020). We believe that closely monitored clinical trials should be set up and launched for people with DS to evaluate the effect of antidepressants (such as SSRIs) in preventing or delaying the occurrence of AD.

6 Conclusion

Patients with DS often develop AD. It is thus important to further investigate the cellular and molecular mechanisms that trigger and/or amplify neurodegeneration. Based on the research presented in this review and our experience in clinical practice, we strongly believe that patients with DS are much more sensitive to psychological stress than non-DS individuals, in other words, they show much poorer resilience. This may be very difficult to prove using evidence-based medicine but, as it may have a substantial impact on the care of patients with DS, we advocate research in this field and emphasize the importance of a non-stressful environment for patients with DS.

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Figure legends

Figure 1. Genetic predisposition of patients with Down syndrome to Alzheimer's disease.

Several studies have shown that certain genes carried by Chromosome 21 are involved in the pathophysiology of Alzheimer's disease (AD).

RCAN1 and SYNJ1 are involved in altered endocytosis; RCAN1, APP, and SOD1 in oxidative stress; ETS2, BACE2, DYRK1A, and APP in amyloid plaque formation; DYRK1A and ETS2 in neurofibrillary tangle formation; APP and S100B in neuroinflammation; APP S100B and SOD1 in mitochondrial dysfunction; and DYRK1A SOD1 and ETS2 in neuro-excitotoxicity and neuronal apoptosis.

Figure 2. Theoretical models for the interaction between psychological stress and resilience in non-Down syndrome individuals and those with Down syndrome.

- (A) After acute stress, patients with Down Syndrome (DS) take more time to recover than non-DS individuals. After an intense event, patients with DS may more rapidly pass a critical threshold and thus not recover as well (PTSD) as non-DS individuals.
- (B) After experiencing chronic stress, patients with DS may not return to their baseline state and progressively lose their resilience until they pass a critical threshold and do not recover at all.

Figure 3. Impact of stress on Alzheimer's disease progression in patients with Down syndrome.

The impact of several pathophysiological elements involved in both Alzheimer's Disease (AD) and Down Syndrome (DS) may be increased by psychologically stressful events (brown arrows). Gene triplication plus stress can stimulate amyloid plaque formation, neuroinflammation (1 and 2), induce an imbalance between GABA and glutamate (3), leading to neuronal apoptosis (3 bis), NFT formation (4), and mitochondrial dysfunction (5) and oxidative stress (6), thus increasing amyloid plaque formation (7) and activating a vicious circle (8). Finally, endocytosis is also altered (9).

Figure 1

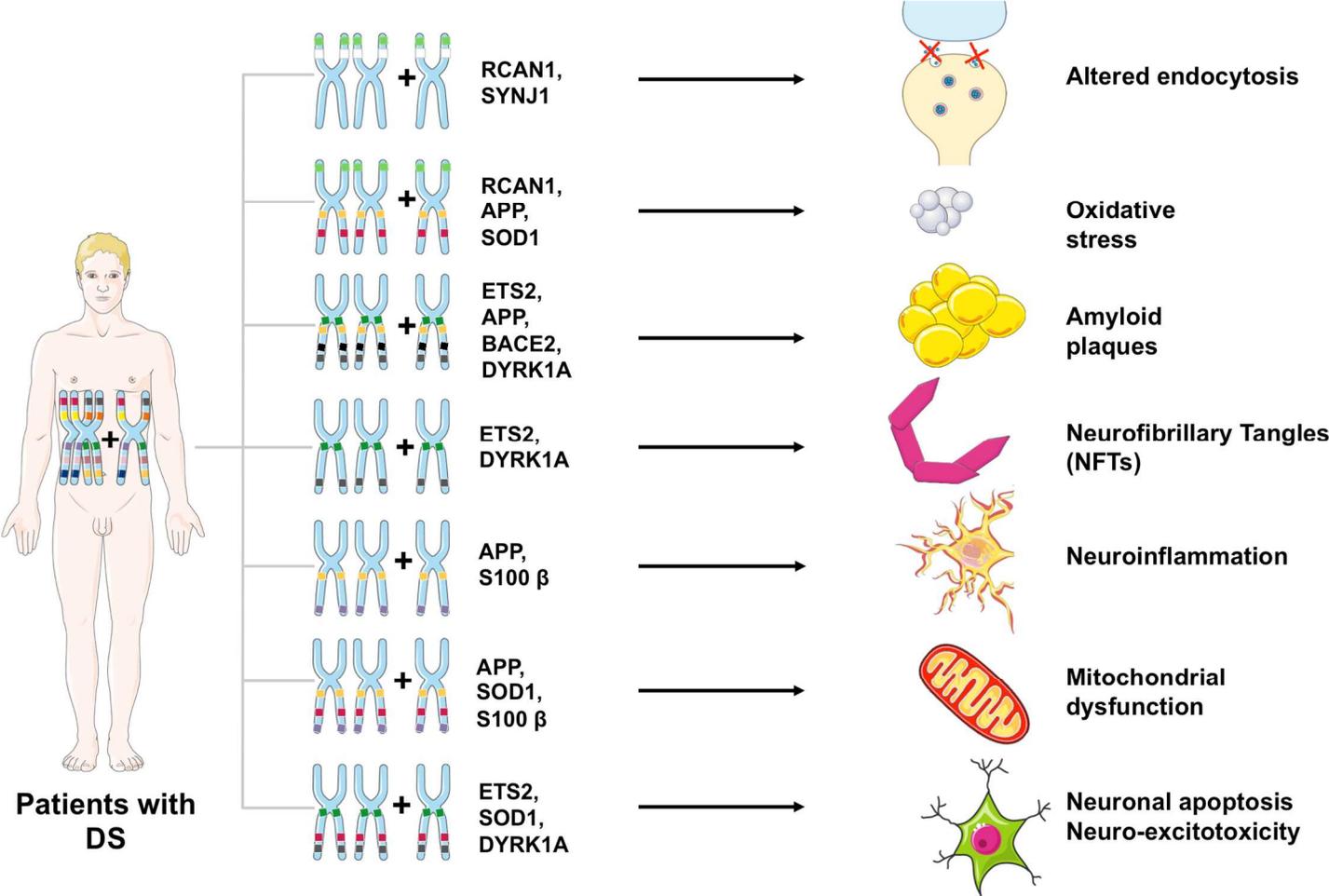
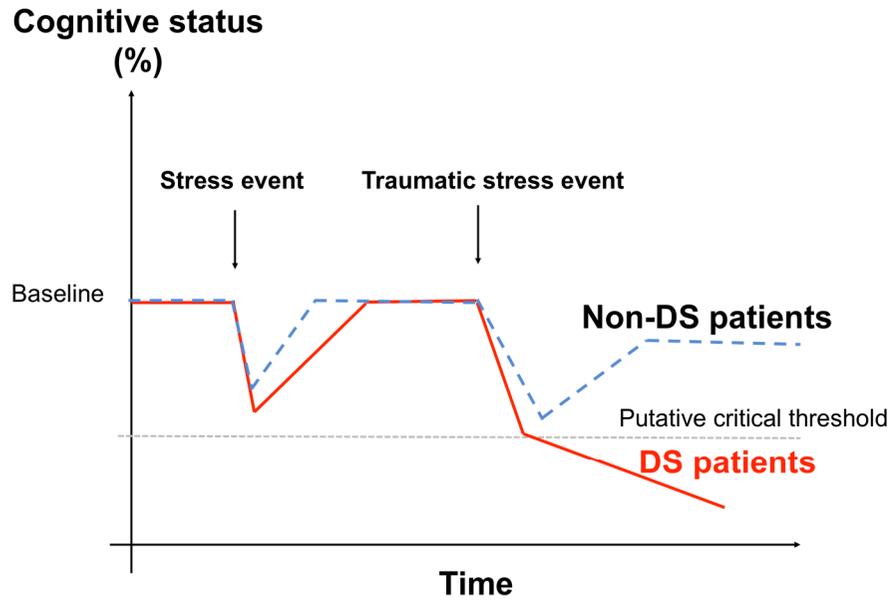
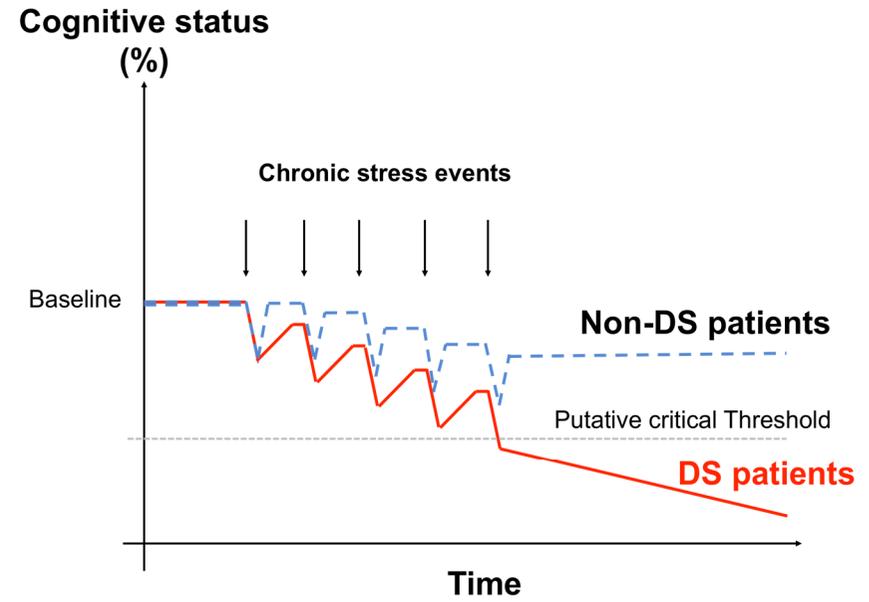


Figure 2

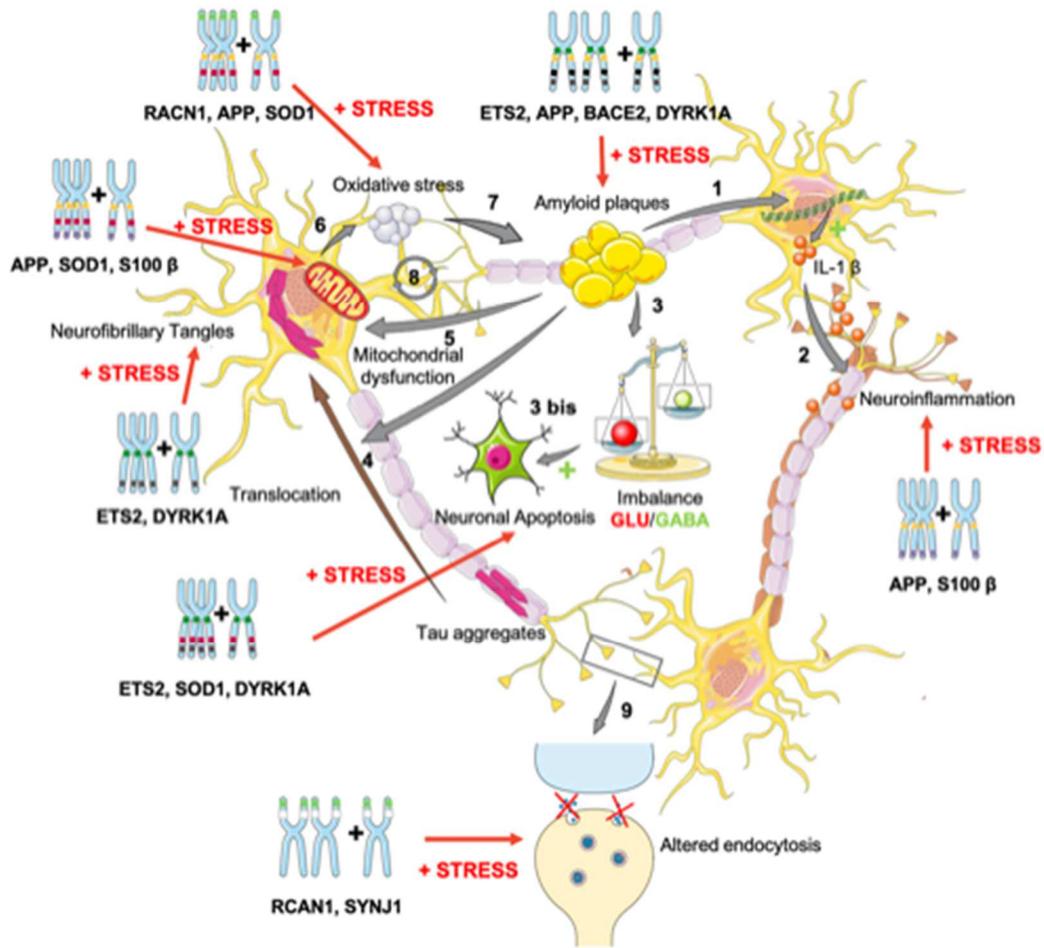


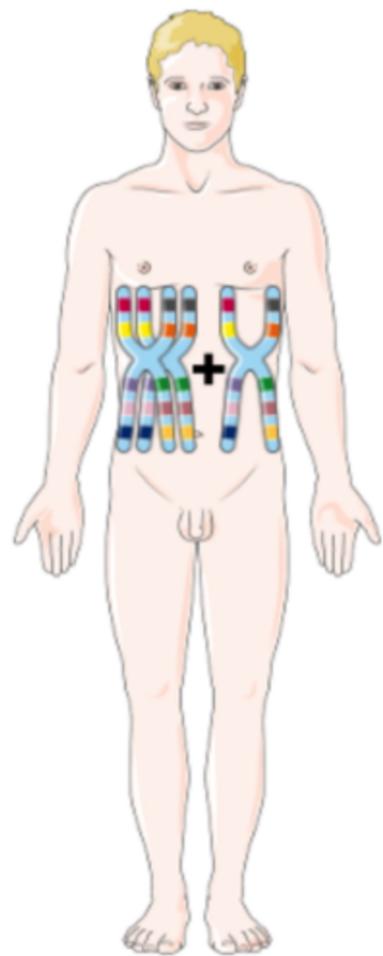
(A) Reaction to acute psychological stress event in DS and non-DS patients.



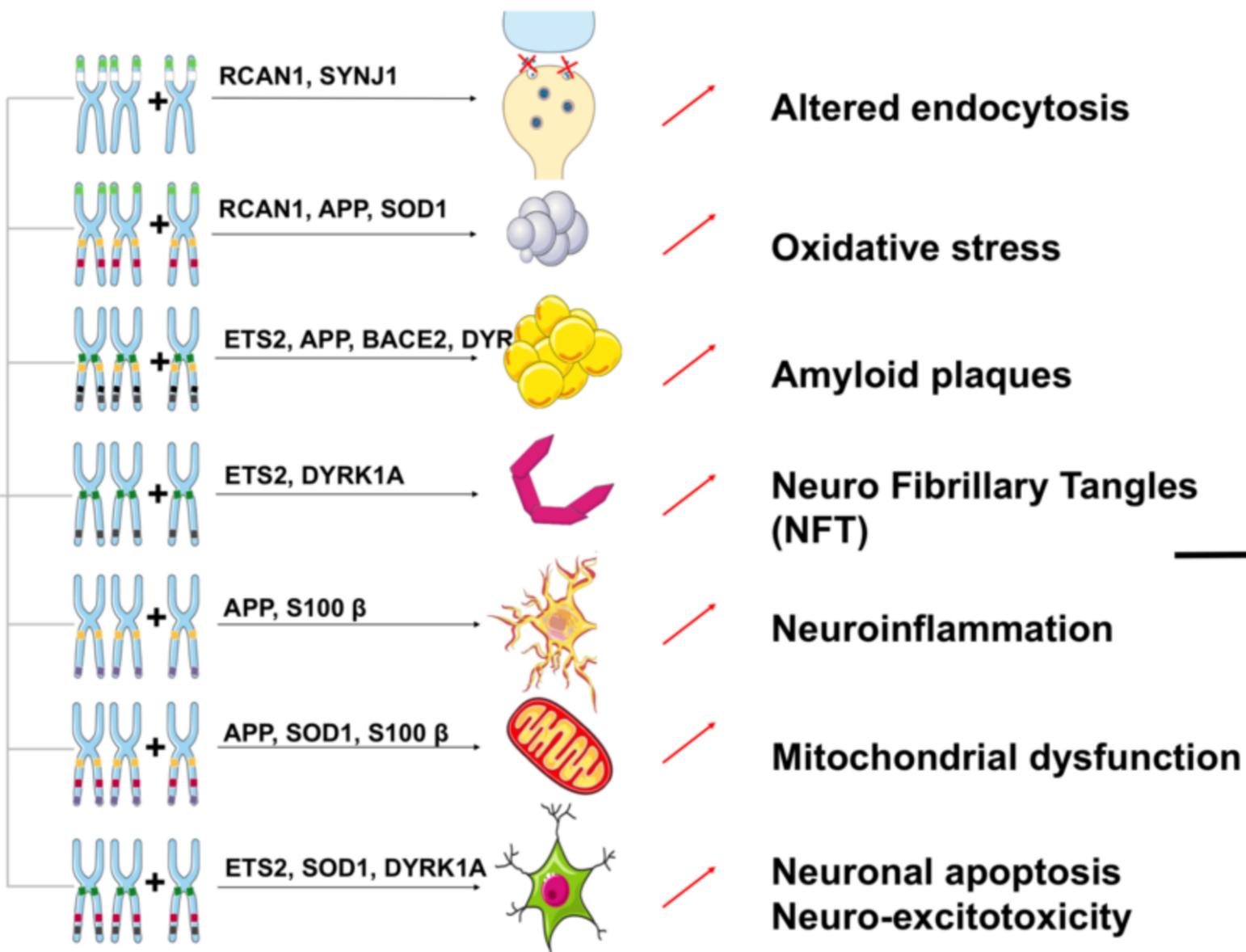
(B) Reaction to chronic psychological stress event in DS and non-DS patients.

Figure 3



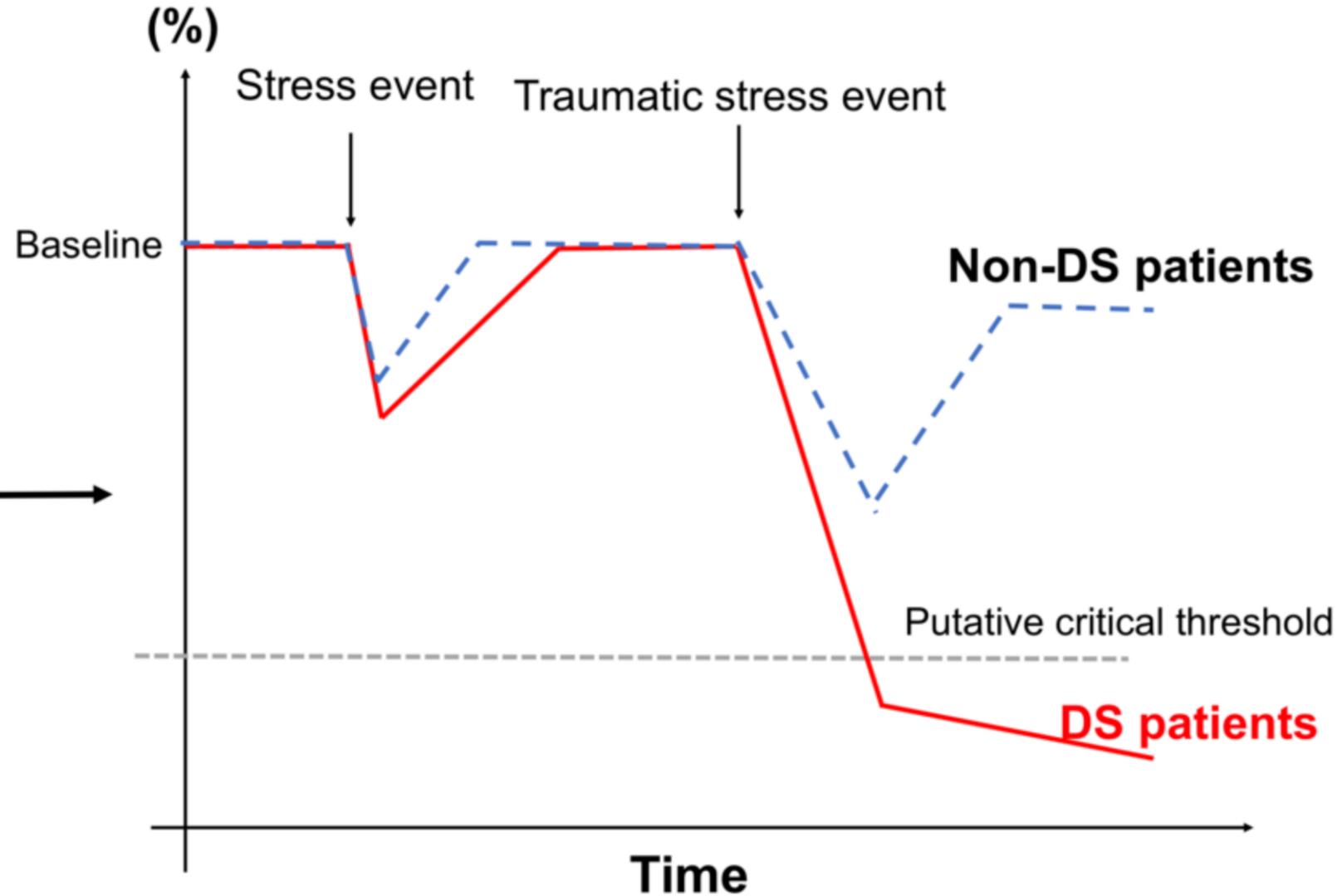


Patients with DS



Molecular and cellular events

Cognitive status (%)



Reaction to acute psychological stress event in DS and non-DS patients