Somatic aspects of depressive disorders: pivots of understanding symptoms and improving treatments

Theme
The aim of this symposium is to describe how alterations in somatic systems are related to symptoms of depressive disorders and how they may be normalized by treatment. The first talk will be a meta-analysis of hypothalamic-pituitary-gonadal (HPG) axis functioning in male depressive disorders and will outline how abnormalities along the axis may map onto sexual dysfunctions. The second talk will present the results of an ambulatory assessment study investigating the role of the hypothalamic-pituitary-adrenal (HPA) axis in fatigue as experienced by patients with depressive and somatic symptom disorders. The third talk will illustrate the role of heart rate variability (HRV) in depressive disorders and summarise preliminary results of a trial of cognitive behavioural therapy aiming to improve HRV in depressed patients. The fourth talk will summarise the findings of a metyrapone trial in patients with treatment-resistant depression, and will explore how pre-treatment levels of inflammation may modulate treatment outcomes.

Takeaways
The symposium will deliver three key messages. First, somatic concomitants of depression (e.g., reduced testosterone levels) are relevant because of their involvement in some of the most distressing symptoms experienced by patients (e.g., sexual dysfunctions). Second, they can be changed for the better by means of standard-first line therapies for depressive disorders (e.g., cognitive behavioural therapy). Third, they may ultimately be used to inform the development of new treatments (e.g., metyrapone) that are tailored to the needs of the individual patient.

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Hypothalamic-pituitary-gonadal (HPG) axis functioning in male depressive disorders – systematic review and meta-analysis

Aim
Sexual dysfunctions, such as erectile disorder, are among the most distressing symptoms in men suffering from depressive disorders. Given that the hypothalamic-pituitary-gonadal (HPG) axis is a crucial regulator of sexual function, the question arises whether subtle alterations in HPG function may underlie these problems. To answer this question, a systematic review and meta-analysis of the literature on HPG axis functioning in male depressive disorders was undertaken.

Methods
PubMed and PsycINFO were searched until October 2018. Inclusionary criteria were: 1) case-control study including male patients with a depressive disorder and 2) assessment of follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol, or testosterone. Full-texts are currently being reviewed and standardised mean differences in HPG measures between patients and controls extracted for meta-analysis.

Results
Twenty studies were identified. None observed any differences in FSH between patients with depressive disorders and controls, and only one provided evidence for lowered oestradiol in patients. By contrast, several studies found comparably attenuated levels of LH and testosterone in patients. However, null-findings were equally reported and studies differed greatly in terms of methodological rigour. Full results of the systematic review and meta-analysis will be presented at the meeting.

Conclusion
Preliminary findings suggest that men with depressive disorders may demonstrate diminished levels of LH and testosterone. This is interesting in light of the anatomical links between the HPG and the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis, the latter of which is often found elevated in depressive disorders and thus may suppress HPG axis activity at the pituitary and gonadal level.

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Associations between stress and fatigue in depression and somatic symptom disorder

**Aim**
Fatigue is a very common symptom that has been associated with stress. It is one of the predominant complaints in depression (DEPR, characterized by affective symptoms), and somatic symptom disorder (SSD, characterized by somatic symptoms). We investigated differences between DEPR and SSD concerning a) subjective sensations of fatigue measured on different dimensions, and b) relationships between psychobiological stress measures and fatigue.

**Methods**
29 women with DEPR and 29 with SSD completed the Multidimensional Fatigue Inventory (MFI), and the Trier Inventory for Chronic Stress (subscale SSCS). They reported momentary stress and fatigue, and provided saliva samples (measuring momentary hypothalamic-pituitary-adrenal axis (HPA) axis activity, available for DEPR only) during 14 consecutive days, 5 time points each day. They also provided hair samples (measuring long-term HPA axis activity).

**Results**
DEPR had higher MFI general and mental fatigue (p<.001) than SSD, but comparable physical fatigue (p=.061). SSCS predicted MFI general and mental fatigue (ps≤.005) in SSD, and MFI physical and mental fatigue (ps≤.030) in DEPR. Hair cortisol was associated with momentary fatigue in SSD (p<.001). In both samples, momentary fatigue was associated with same time-point stress (both p<.001), but neither previous time-point stress nor SSCS, nor salivary cortisol (only DEPR) explained additional variance.

**Conclusion**
We found differences in the subjective sensation of fatigue and the relationship between psychobiological stress measures and fatigue between DEPR and SSD patients. Different reference time frames and time-lags between stress and fatigue assessment should be considered to gain more information about the (chronological) nature of their association.

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Response to anti-glucocorticoid augmentation for treatment-resistant depression: potential role for inflammatory proteins

**Aim**
Patients with treatment-resistant depression (TRD) often have elevated inflammatory activity which could predict a poor subsequent response to common treatments. As such, related biological systems provide new pharmacological targets. Metyrapone, an antiglucocorticoid drug, has been trialled for TRD illness but has mixed outcomes indicating that it might be effective for only a sub-population of patients. We hypothesised that levels of inflammatory proteins might predict subsequent clinical improvements after metyrapone treatment.

**Methods**
Patients with TRD enrolled in a double-blind trial were randomised to 3 weeks of metyrapone or placebo augmented to existing serotonergic antidepressant treatment. Inflammatory proteins and depression severity were evaluated at week 0 (pre-treatment) and week 5 (post-treatment) in 129 patients, who were relatively representative of TRD patients (having not been excluded on the basis of anxiety or physical comorbidities, unless metyrapone was contra-indicated).

**Results**
Patients had higher inflammatory protein levels than healthy controls. During metyrapone (but not placebo) treatment, interleukin-6 (IL-6) levels decreased significantly (p=0.002), although this was not associated with change in depression severity. Lower pre-treatment IL-6 preceded a better outcome for patients taking placebo (p=0.029) while lower tumour necrosis factor predicted a better outcome for patients taking metyrapone (p=0.046).

**Conclusion**
Metyrapone treatment reduces IL-6 production which does not appear sufficient to improve depression severity, although patients with elevated levels of inflammatory cytokines before randomisation showed less improvement during the trial. Although statistically significant, these effects were small and likely affected by the short duration of treatment as well as physical health and lifestyle factors.

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Impaired lipid- and glucose metabolism in persons with various functional somatic syndromes points towards a common genesis. The DanFunD study.

Aim
Disturbed lipid- and glucose metabolism has been reported in persons with functional somatic syndromes (FSS), but mostly in small case-control studies with a high risk of selection bias and only involving one FSS at the time. The aim is to analyse associations between various FSS and markers for lipid and glucose metabolism in a large random sample.

Methods
Data derives from the Danish Study of Functional Disorders (DanFunD); a random sample of a Danish population (N=9,656) comprising men and women aged 18-76 years. FSS was classified based on somatic symptoms in two different ways: a) established FSS using international accepted classifications (fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), whiplash associated disorders (WAD), and multiple chemical sensitivity (MCS)); and b) the bodily distress syndrome concept (BDS) both single-organ and multi-organ. Fasting values of glucose, HgbA1c, triglyceride, and total-, HDL-, LDL-, and VLDL-cholesterol were assessed. Associates between lipid- and glucose profiles and the various FSS was analysed using logistic regression analyses taking lifestyle factors into account as confounders.

Results
Persons fulfilling the criteria for FM (N=442), CFS (N=823), single-organ BDS (N=1447), and multi-organ BDS (N=96) compared to persons without symptoms, all showed significantly positive association to triglycerides, VLDL-cholesterol, glucose and HgbA1c, and significant negative association to HDL-cholesterol. Persons fulfilling the criteria for IBS (N=337), WAD (N=157), and MCS (188) did not show this pattern after co-morbid FSS were excluded.

Conclusion
The findings point towards a common genesis related to the metabolic state of the person in various delimitations of FSS

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Reduced heart rate variability in major depression: meta-analytic evidence and responsiveness to psychotherapy

Aim
Major depression (MD) is a risk factor for cardiovascular disease. Reduced heart rate variability (HRV) has been observed in MD and might be one physiological factor that mediates this association. This talk provides up-to-date random-effects meta-analyses of studies which compare resting-state measures of HRV between unmedicated adults with MD and controls. Further, we present the study design (and possibly first preliminary results) of an ongoing randomized controlled trial that examines the impact of cognitive behavioral therapy on HRV in MD.

Methods
Database search considered English and German literature to July 2018. A total of 22 studies including 2267 patients and 1999 controls were extracted.

Results
Significant differences between patients and controls were found for a wide range of frequency and time-domains of HRV, with small to moderate effect sizes. Results from meta-regressions indicated that the study quality did not moderate these effects.

Conclusion
Our findings strengthen evidence for reduced HRV as a potential physiological cardiovascular risk factor in patients with MD. One important question is whether psychological interventions that aim to reduce depressive symptoms can also improve HRV in these patients.

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