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Working memory and postpartum depression

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AKADEMISKA SJUKHUSET

Abstract

Background

Postpartum depression (PPD) is a common disorder among new mothers. Previous studies have reported that depressed patients suffer from cognitive difficulties. It is possible that cognitive deficits appear before postpartum depression is fully developed.

Aim

The study sought to determine whether working memory deficits during the last trimester of pregnancy are associated with depressive symptoms at the same timepoint, or/and with the development depressive symptoms six weeks postpartum.

Methods

The study was conducted within the BASIC project, a population based cohort of delivering women in Uppsala, Sweden, investigating correlates of postpartum depression. Between September 2009 and September 2011, 135 women participated in a sub-study and answered the Edinburgh Postnatal Depression Scale (EPDS) at pregnancy weeks 17, 32, as well as 6 weeks and 6 months postpartum. Women were also tested with the MINI psychiatric interview and the Digit Span test as a measure of working memory in weeks 36-40.

Result

Ten among 135 women were diagnosed with some form of depression at week 36-40 based on the MINI interview. 25% and 12,5% of women were screened positive for depressive symptoms using the EPDS at pregnancy week 32 and 6 weeks postpartum, respectively. There were no statistically significant differences in the mean DST scores between those who screened positive at weeks 32 or 6 weeks postpartum, or between depressed patients and controls based on the MINI interview. On the other hand, statistically significant associations could be demonstrated between scoring 6 points or less on the DST and depression as diagnosed with MINI interview at the same visit (OR 5,25, 95% CIs 1,39 – 19,82) as well as presence of depressive symptoms 6 weeks postpartum (OR 3,08, 95% CIs 1,01 – 9,45).

Conclusion

Women with a low score on the DST at the last trimester of pregnancy are at higher risk for depression at the same timepoint, but also at higher risk for developing depressive symptoms postpartum. The DST could, together with other tests, prove a useful instrument for the early detection of individuals at high risk for developing PPD.

Introduction

Postpartum depression (PPD) is a common disorder affecting approximately 13-20% of al newly delivered women (O'Hara & Swain 1996; Josefsson et al., 2001). Of these, the majority of women are diagnosed within the first three months postpartum (Cooper & Murray 1998). PPD has shown to have a major impact on the child's development, both emotional and mental and on the important process of attachment between the mother and child (Cicchetti mfl. 1998; Murray & Cooper 1998). The symptoms manifest in lower mood, feeling of emptiness, appetite and sleep disorders, fatigue and lack of energy and guilt feelings of being a bad mother (Brown & Harris 1978). These symptoms and PPD in general do not differ from an "ordinary" depression (Whiffen 1992; Cooper & Murray 1998). PPD patients are usually separated into two groups, those where the PPD is primarily based on the child and parenting situation, and the second group that is unrelated with those circumstances. Women belonging to the first group possess an higher risk of developping PPD also when giving birth to a second child, while group two women are more likely of falling into an depression later in life without any link to partus (Cooper & Murray 1995).

Risk factors

A woman with a biological, psychological or sociological vulnerability before partus has a greater risk of PPD. The risk factors identified are primarily of sociological and psychological character. Examples are; lacking support from her partner, friends and family, economical struggle, low self esteem, being a single parent and interfered sleep. To illustrate how conclusive and major the sociological aspects are, we can distinguish the difference in PPD rate around the world. In Japan, where being married and having kids gives a high status to women, the incidence of PPD is lower than elsewhere (Cox & Holden 2003). In Capetown in South Africa, the prevalence rises to 1/3 of all mothers, possibly due to the difficult socioeconomical situation (Cooper m.fl. 1999).

Depression earlier in life or during the pregnancy is associated with a higher risk of PPD, as experience of a traumatic episode also is (Harris 1994**;** O'Hara & Swain 1996; Beck 2001). PPD has a seasonal variation, with higher risk if delivery takes place within the three last months of the year (Sylvén 2011). Regarding biological factors, our knowledge is much more

limited and despite much research the mechanisms underlying PPD remains elusive. Hypothyreoidism is associated with higher risk (Sylven 2011, manuscript) while higher levels of leptin, seem to have an protective effect on PPD (Skalkidou 2009).

Another major risk factor for PPD is the development of postpartum blues (PPB). PPB is a condition in the first few days postpartum, which strikes as much as 50-80% of all newly delivered mothers in the form of emotional disturbance. This is due to the major estrogen drop and the exhaustion from giving birth. If this condition persists, it often develops into a PPD (Henshaw et al 2004). Because PPB is a relative common condition generally accepted as normal by health workers and the woman's family, many women are not correctly assessed and missed.

Depression and the brain

Several brain regions regulate our emotions, but a complete understanding of which site of pathology is responsible for a depression is unclear. Human brain imaging studies and postmortem analysis of depressive patients has reported abnormalities in the prefrontal and cingulated cortex, hippocampus, striatum and amygdala (Nestler & Berton 2006). Hippocampus has received most attention among these structures, mostly due to its responsibility of cognition and memory performance. A functional hippocampus is needed for specific cognition processes and surgical removal or volumetric loss is correlated with deficits in declarative memory in humans (Brown et. al. 1999).

Cognitive impairment occurs in many depressive patients, as indicated by concentration difficulties, memory problems and reduced stress tolerance. These cognitive deficits are associated with a dysfunction of the hypothalamus-pituitary-adrenal-axis (HPA-axis) (Brown et. al. 1999) and brain-derived neurotrophic factor (BDNF) (Gonul 2003).

The HPA-axis is controlling the glucocorticoid release from the adrenal cortex. The final product of the secretory pathway is cortisol, which is initiated by the release of cotrophine-releasing hormone (CRH) from the hypothalamus. CRH stimulates secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn stimulates

the adrenal cortisol secretion. During depressive states hyperactivation of the axis usually occurs, which results in an excess of the cortisol level. Hinkelman et al. (2011) have recently shown that the cognitive deficits are related to these elevated cortisol levels and that some cognitive parameters also improve with decreasing cortisol secretion. The working memory dysfunction is reported in severe and moderate depression. Zobel and her research team have also demonstrate how specifically the working memory improvement is correlated with decrease in cortisol levels (Zobel et. al. 2003).

It has also been reported that one of the most important neurotrophins, brain-derived neurotrophic factor (BDNF), have a reduced expression in depressed patients compared with healthy controls. A hypothesis is then that BDNF might play a critical role in the pathophysiology, the cellular mechanism of learning and memory, due to its regulatory role in neurogenesis and synaptic plasticity. Gonuls et al. demonstrated this when depressed patients BDNFs levels increased significantly after 8 weeks of antidepressant treatment (Gonul et al 2004; Dwivedi 2003). It has also been shown that women in the last three moths of pregnancy and in the first two months postpartum have remarkably decreased serum BDNF levels, suggesting a crucial role in the development of mood disorders postpartum period (Lommatzch et al 2006).

During pregnancy HPA-axis hormones alter in concentration. The woman's cortisol levels rise continuously and peak just before partus, with levels twice the normal values (Pawluski et al 2009). This is due to the placenta that's generating CRH and releasing it into the blood stream. CRH being released from both hypothalamus and placenta, but more cortisol is secreted from the adrenal cortex among pregnant patients. The cortisol levels drop postpartum, although it can take a week until they reach normal values again (Kammerer et. al. 2006).

Memory division

One of the most important cognitive functions is memory. Encoding, storage and retrieval of learned information are a way to define the term memory. Memory can be divided into two sections: Qualitative and Temporal. The quantitative part can general be described of what

is remembered and how we possess the memories, if they are available to consciousness or not. Declarative memory refers to memories brought to consciousness and can be expressed by language, e.g. remembering a phone number, thus referring to facts and knowledge. The ability to dial the telephone number is an example of non-declarative memory and involves skills and associations.

The temporal categorization is according to the time over which it is effective, and has three subgroups. Immediate memory is the ability to hold ongoing experiences in mind for fractions of seconds. Within the category working memory the ability to hold, control and manipulate information is for seconds to minutes and is in order to use it to do a complex task or behavioural goal. A way of testing this is through repeating a random order of digits (described below in detail) and in this test the normal "digit span" is only 7-9 numbers. Thus, this capacity can be dramatically increased through practicing. The last category is long-term memory where information can be retained in a more permanent form for days, weeks or for a lifetime (Neuroscience 4th 2008).

Working memory can be measured by the Digit span test. Through this test data can be gathered on the patients working memory, with depressed patients scoring usually lower. We hypothesize that mechanisms that lead eventually to depression (eg high cortisol levels, low BDNF levels) first affect brain structure and function, working memory included. Women with low working memory would then be at higher risk for developing depression.

Aim

The main objective of this study was to determine whether working memory deficits during the last trimester of pregnancy are associated with depressive symptoms at the same timepoint, or/and with the development depressive symptoms six weeks postpartum.

Material and Methods

This study was undertaken as a part of the BASIC project, a population-based cohort study in the county Uppsala Sweden, investigating multiple correlates of postpartum depression. The study was conducted at the department of Obstetrics and Gynaecology at Uppsala University hospital. The University Hospital is responsible for all delivering women within the county, as well as the high-risk pregnancies from nearby counties.

Study population

From 2009 all women undergoing the routine ultrasound examination in week 16-17 are asked to participate in the longitudinal study of maternal well-being. Both written and oral information is given and the becoming mothers provide written consent. The study subjects then receive a self-administered web-based structured questionnaire in pregnancy weeks 17 and 32, six weeks postpartum and six months postpartum. These questionnaires contain inter alia the Edinburgh Postnatal Depression Scale (EPDS), as a screening instrument for depressive symptoms. A random selection of the women participating in the study were invited to attend additional tests in the research department of the Obstetrics and Gynaecology Clinic in Uppsala in week 36-40 into the pregnancy.

The Digit Span Test (DST)

The Digit Span test (DST) is an analysis instrument measuring cognitive ability, more specifically the verbal working memory. The test leader presents digits orally in a specific order and the patients are asked to repeat the digits in the same order. Secondly the patients are required to relate the digits in reversed order. The first stage is two digits, but subsequently the number of digits increases step-by-step until 9 digits in the forward and 8 in the backward part. The test leader continues until the patient has failed two consecutive trials at the same level. The scores on the various parts are combined into an overall score, a total score. The final DST-score is calculated based on the total score and taking into account the patients age (Wechsler 2003).

Outcome measures

The outcome measures comprised of the Swedish version of the EPDS and the MINI psychiatric interview. The EPDS is a self-rating scale which functions as a screening instrument for postpartum depression. The test is designed of 10 statements, which the women mark the closest to how she felt during the past seven days. Every statement marks with 0-3 points, where 3 are equivalent to the most depressive and 0 to the "normal" state. Total score is 30 with a cut-off of 12 points for being at high risk of postpartum depression. (Wikberg 1996). The structured psychiatric interview MINI (Mini International Neuropsychiatric Interview) is a well studied psychiatric instrument for the diagnosis of several psychiatric disorders. For this study, women were interviewed in order to diagnose mild depression, major depression or dysthymia.

Statistic analyses

SPSS version 18.00 was used for statistical analyses. Statistical significance was set at a p-value of 0,05. Differences in the distribution of the variables among the different patient groups were assessed with the Mann-Whitney U-test.

The final DST-score was dichotomised with a cut-off at 6 points (where a score of 6 or below was considered low, while a score of 7 and above was considered normal) and cross-tabulations were performed between the dichotomised final DST-score and depression status based on the EPDS or MINI at week 32, 6 weeks postpartum. Odds Ratios (OR) and 95% Confidence Intervals (95% CIs) were calculated using the Mantal-Haenzel chi-quare test.

Results

Table 1 shows the prevalence of study subjects who screened positive or negative on the EPDS (with a cut-off of 12 points), over the various time-points in the study (pregnancy week 17, week 32, 6 weeks and 6 months postpartum) as well as the mean, median and standard deviation of the EPDS scores at the same time-points. The highest prevalence of depressive symptoms (25%) is recorded at pregnancy week 32, and this is because subjects are called to this visit based on a case-control sub-study recruitment protocol and therefore does not represent the prevalence of depressive symptoms for the whole study population.

Table 1 – Prevalence of depressive symptoms based on the EPDS and mean, median and standard deviation of the EPDS scores at various time-points.

	EPDS w17	**EPDS w32**	**EPDS 6w pp**	**EPDS 6m pp**
Total	130	133	130	93
Screened Negative	112 (82,4%)	99 (72,8%)	113 (83,1%)	79 (58,1%)
Screened Positive	18 (13,2%)	34 (25%)	17 (12,5%)	14 (10,3%)
Mean	6,26	7,77	6,35	6,33
Median	5,00	7,00	6,00	5,00
Std. Deviation	4,671	5,016	5,068	4,830

Table 2 presents the distribution of subjects with a clinical diagnosis of depression (major depression, minor depression or dythymia) or without one, based on the MINI interview. Ten subjects (7,4%) suffered from some form of depression at the time of the interview.

Tabel 2 – Distribution of patients according to psychiatric diagnosis based on the MINI interview.

	Frequency	**Percent (%)**
Healthy	125	91,9
Depressed (minor, major, dystymi)	10	7,4
Total	135	99,3
Missing	1	0,7

Figure 1 shows a histogram over the final DST scores. The maximum number of points achieved by the study subjects was 16 points and lowest was 4. Eight and 9 points represent the most common score achieved. By setting the cut-off at ≤6 points, approximately one fourth of the study population is represented among those achieving a low score.

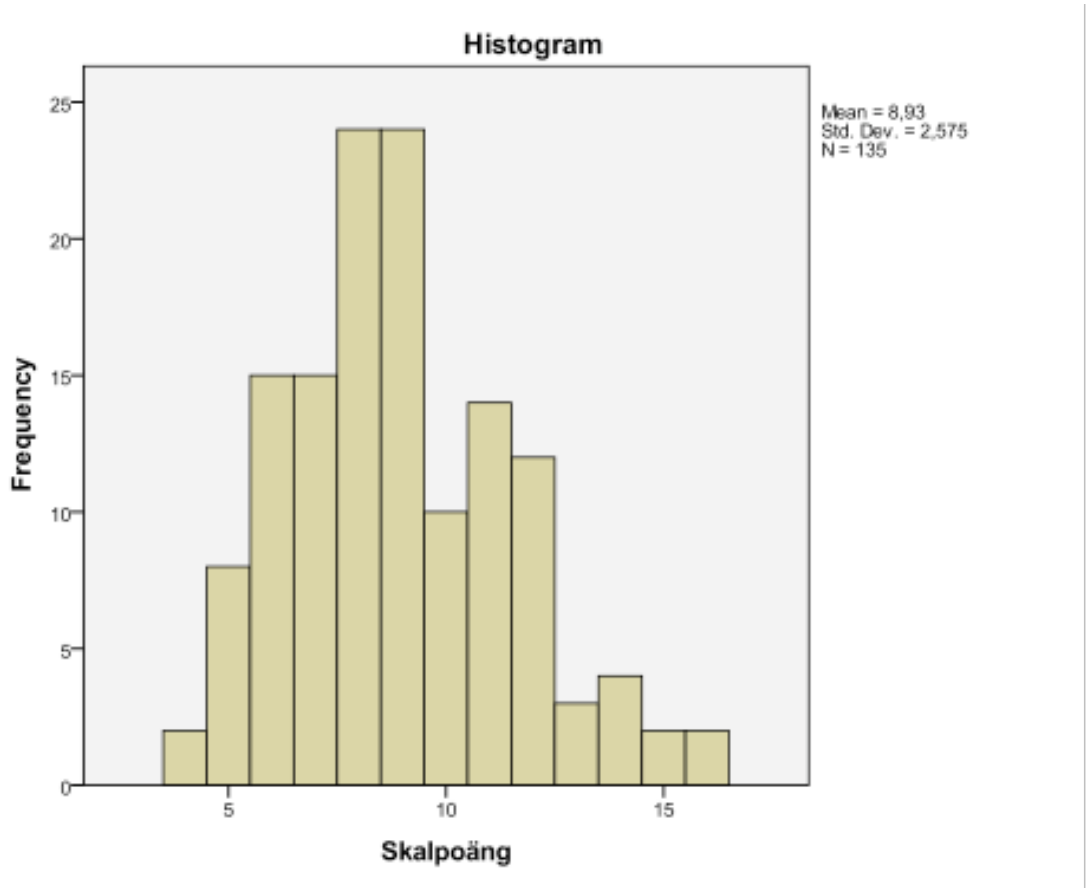

Figure 1 – Histogram over the final DST-scores.

Tables 3a,3b and 3c show the mean, median, standard deviation, minimum and maximum of the final DST-score according to depression status based on the EPDS in pregnancy week 32, the EPDS 6 weeks postpartum and the MINI interview at pregnancy week 38 respectively. Using the Mann-Whitney U test, no statistically significant differences could be identified.

Table 3a - The final DST-score by depression status based on the EPDS in pregnancy week32.

	Cases	**Controls**
Mean	8,91	9,00
Median	8,00	9,00
Std. Deviation	3,147	2,356
Minimum	4	5
Maximum	16	14

Table 3b - The final DST-score by depression status based on the EPDS 6 weeks postpartum.

	Cases	**Controls**
Mean	8,59	9,03
Median	9,00	9,00
Std. Deviation	2,959	2,530
Minimum	5	4
Maximum	15	16

Table 3c - The final DST-score by depression diagnosis based on the MINI interview in pregnancy week 38.

	Cases	**Controls**
Mean	8,20	8,99
Median	6,50	9,00
Std. Deviation	3,521	2,494
Minimum	5	4
Maximum	16	16

Figure 2 represents a steam and leaf plot over the final DST-score by depression status.

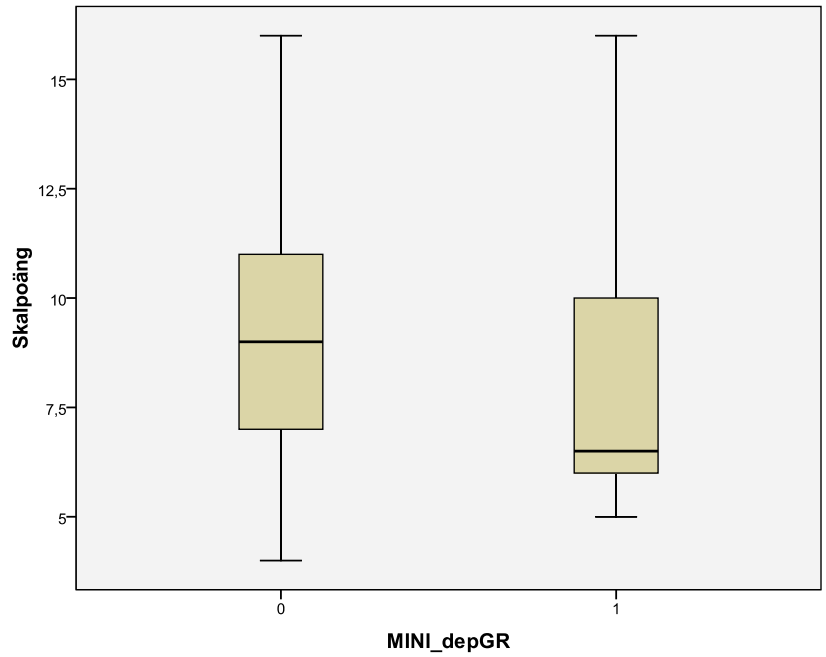

Figure 2 – Steam and leaf plot over the final DST-score by MINI-assessed depression status.

Table 4 shows crosstabulations of low/normal final DST-score and depression status at pregnancy week 32 (EPDS based), week 38 (based on the MINI interview) and 6 weeks postpartum (EPDS based), as well as Mantel-Haenzel chi-square test derived ORs and 95% CIs. Subjects scoring low in the DST test at pregnancy week 38 were more likely to be depressed at the same time-point (OR 5,25, CIs 1,39-19-82), but also more likely to have depressive symptoms postpartum (OR 3,08, CIs 1,01-9,45).

Table 4 – Crosstabulations of low/normal final DST-score and depression status at pregnancy week 32 (EPDS based), week 38 (based on the MINI interview) and 6 weeks postpartum (EPDS based), as well as Mantel-Haenzel chi-square test derived ORs and 95% CIs.

		Final DST-test		OR	CI
		LOW	**NORMAL**		
Dep. v32	**NO**	15 (65,2%)	84 (76,4%)	-	-
	YES	8 (34,8%)	26 (23,6%)	1,72	0,66-4,52
MINI	**NO**	20 (80%)	105 (95,5%)	-	-
	YES	5 (20%)	5 (4,5%)	5,25	1,39 – 19,82
Dep. v6 pp	**NO**	17 (73,9%)	96 (89,7%)	-	-
	YES	6 (26,1%)	11 (10,3%)	3,08	1,01 – 9,45

Discussion

In this study, an association between scoring low on the DST at the last trimester of pregnancy and depression status at the same time-point and as well as depressive symptoms 6 weeks postpartum was demonstrated. On the other hand, no statistically significant differences could be demonstrated in the mean DST scores between those who screened positive for depressive symptoms at pregnancy week 32 or 6 weeks postpartum, or among depressed patients and controls based on the MINI interview.

These results strengthen the hypothesis that cognitive impairment is involved in the patophysiology of depression, both during pregnancy and postpartum, but the understanding of the exact mechanisms involved are still to be revealed.

Scientists have previously shown that high cortisol levels are associated with cognitive deficits in depression and that lowering high cortisol levels reduces cognitive impairments (Hinkelman et al 2011; Zobel et al 2003). During pregnancy plasma levels of cortisol rise, due to the placentas CRH secretion and reach twice normal levels (Kammerer et al 2006). Cortisol binding protein levels also rise in an attempt to bind cortisol. How these changes affect cognitive functions during pregnancy is debated. "Placenta-brain" or "baby-brain" are two "conditions" indicating that the memory and cognition are poor during and maybe because of the pregnancy. Even if these have been supported by some studies, a large study for its kind determined that there were no significant differences in cognitive changes as a result of pregnancy (Christensen 2010). Christensen et al claim that the previous findings might be a result of biased sampling.

It is, on the other hand, plausible to speculate that cortisol levels might play a role in cognitive processes and risk for development of depression during and after pregnancy. One has to consider interpersonal variations in the rising of cortisol levels, as well as individual sensitivity or even adjustment time for all changes described.

A genetic predisposition for the development of PPD has also been suggested. The neurotrophic factor BDNFs levels are decreased in the last three moths of the pregnancy and

in the first two moths postpartum. This may lead to an increased risk for development of mood disorders postpartum (Lommatzch et al 2006). Studies on patients with depression have namely also shown that patients have a reduced expression of the BDNF compared with healthy controls. Researchers demonstrated that the BDNF levels increased significantly after 8 weeks of antidepressant treatment (Gonul et al 2004; Dwivedi 2003). In addition, the decreased BDNF levels may also have a considerable role in the reduced capacity of cellular mechanisms for learning and memory, due to BDNFs participation in neural plasticity. These studies do not contribute with detailed information about the cognition and memory performance. But they do indicate that there may be a link between neurotrophic factors and long-term changes in synaptic strength, effects that may contribute to learning and memory (Dwivedi 2003).

In summation, more research is needed in order to comprehend the pathophysiology behind memory deficits and depression. One must take into account that both depression and cognition are multifactorial processes and the association between them, if any, could be modified by the presence of third factors.

The present study has many strengths. It is a longitudinal, population based study, therefore the possibility of selection bias is minimal. The response rate is also quite good for a study of this kind, with a 25% participation rate among all pregnant women in Uppsala county. The responses gathered in the web-based survey are of good quality, since women in general answer all the questions. The answers are automatically transferred to a data file for analyses, so mistakes due to computerization of data do not exist. The neuropsychiatric interview MINI was performed by a small number of well instructed researchers, which limits the possibility for interpersonal interpretation and assessment of study subjects.

Limitations of the study include the total number of patients recruited thus far in order to increase power, and the use solely of the EPDS for depressive symptom assessment in many time-points. The EPDS has a high sensitivity but quite low specificity. The addition of the MINI interview in those time-points would rightly identify depressed patients.

The associations described in the current study might be confounded by factors that influence both performance on the DST as well as depression risk, e.g. education, socio-economic status, sleep, breast-feeding, age, etc. These factors could be controlled for in a larger patient sample. Another improvement in the study design might involve performing the DST in the beginning of the pregnancy, so that each woman would serve as her own control.

Another limitation refers to the method used in order to measure cognition. Cognition is a huge concept and measuring the working memory describes just a limited aspect of the complete picture. Cognition is influenced by numerous factors such as education and background. Because depression affects specific brain regions (hippocampus, prefrontala cortex, cingulated cortex, striatum & amygdala) that are responsible for the function of the declarative memory, investigating the association between performance in a test measuring the declarative memory instead for the working memory and risk for depressive symptoms would be also very interesting. The working memory is still interesting to measure, because despite the fact that it is primarily controlled by locus frontalis and locus parietalis, which are not really affected in depression, there is evidence that the prefrontala cortex, abnormal during depression, interact with locus parietalis.

Because a PPD affects both the child, the partner as well as the women in many troublesome ways with prolonged consequences, development of a prediction model for the identification of individuals at risk would be of great importance. The results of this study would hopefully be of help for the development of such a model in the future. Cognition can be used, together with other markers, as a screening instrument. A big advantage of the DST test is that it is a fast and easy way to determine part of our cognition. Therefore it would prove a useful in a prediction of individuals at high risk for development of PPD in a health care environment. The early identification of women with PPD is of paramount importance, and the development of a screening method with high sensitivity and specificity would have important clinical implications.

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