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Co-Morbid Substance Use in Psychotic Disorder: The Role of a Neurocognitive Dysfunction

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Scientific Abstract

Background and aims: Psychotic disorders (PD) are often accompanied by substance (ab)use. Recent studies demonstrated a connection between these conditions through a common neurocognitive dysfunction. This common dysfunction concerns the executive functions (EF). Through this way it affects both cognitive control and mechanisms of motivation/reward. An EF dysfunction is a core feature of both PD and substance (ab)use. Moreover, it is found to be present prior to the onset of both conditions. It is suggested that this common EF dysfunction highlights a vulnerability for co-morbidity. Hence, this study investigated whether a common neurocognitive dysfunction is associated to the co-morbidity of substance (ab)use and PD. Investigating EF in co-morbidity is especially relevant for theories of aetiology, prevention and treatment. First, we examined whether poor EF predicts an increase in substance use in PD patients. Second, we examined whether poor EF, combined with substance use, predicts an increase in substance dependency. **Methods:** This cross-sectional study included 90 patients diagnosed with PD (18-65 years). Data were obtained through self-report questionnaires that measured EF, substance use and -dependency. Three multiple linear regression analyses were calculated to evaluate whether EF scores predicted substance use; three moderated binary logistic regression analyses were calculated to evaluate whether EF scores, moderated by substance use, predicted substance dependency. **Findings:** Results showed that *Initiative* deficits predicted substance use (p=.01). Deficits of *Emotional regulation* (p=.04) and *Working memory* (p=.03), moderated by substance use, predicted a decrease of dependency. **Conclusions:** Our results partially confirmed that poor EF predicted substance use and -dependency in PD. It did not lend sufficient support for the idea that the co-morbidity of substance (ab)use and PD is associated with a common EF dysfunction. Nevertheless, results demonstrated a relation between EF and substance (ab)use, namely that PD patients use substances as a means of self-medication in order to cope with an EF dysfunction. It can be concluded that this self-medicative behaviour promotes the development of co-morbid substance (ab)use in PD. This study offers new insights into the self-medication hypothesis. It demonstrated that, besides psychotic symptoms, an EF dysfunction induces self-medicative substance use in PD. Clinical implications may concern prevention techniques and treatment methods.

Layman's Abstract

Veel patiënten met een psychotische stoornis (PS) vertonen middelenmisbruik en/of verslaving. Recente studies tonen aan dat middelengebruik en -afhankelijkheid en psychose een onderliggende neuropathologie delen, die gerelateerd is aan een verstoorde werking van de executieve functies (EF) in de hersenen. Deze hersenfuncties betreffen hogere cognitieve processen die gedrag, emoties en gedachten reguleren. Zo zijn EF nauw betrokken bij 'cognitieve controle', maar ook bij het beloningssysteem van de hersenen. Een EF-dysfunctie verstoort deze systemen en hindert het dagelijks functioneren. Studies tonen aan dat een dergelijke EF-dysfunctie kenmerkend is voor zowel PS als middelenmisbruik, en dat deze zelfs al in de voorstadia van beide aandoeningen aanwezig is. Dit doet vermoeden dat er sprake is van een gedeelde 'kwetsbaarheid' in het brein, die het veel voorkomende middelenmisbruik in PS-patiënten kan verklaren.

In deze master thesis studie onderzoeken we bovenstaande vermoeden door te kijken of een EF-dysfunctie ten grondslag ligt aan het tegelijkertijd voorkomen (i.e., comorbiditeit) van middelenmisbruik en PS in patiënten. Hierbij is allereerst onderzocht of een EF-dysfunctie, middelengebruik voorspelt in de psychose groep. Vervolgens is onderzocht of een EF-dysfunctie, in combinatie met middelengebruik, een verhoogde middelenafhankelijkheid voorspelt in de psychose groep. Voor dit onderzoek is gerandomiseerd een steekproef genomen, bestaande uit 90 participanten (18-65 jaar) met de hoofddiagnose PS. Bij hen is aan de hand van door hen zelf ingevulde vragenlijsten inzicht verkregen aangaande EF, middelengebruik en middelenafhankelijkheid. Op deze data zijn verschillende analyses uitgevoerd om te testen of 1) EF-problemen middelengebruik voorspellen; en 2) EF-problemen met middelengebruik middelenafhankelijkheid voorspellen.

Uit de studie bleken alleen *Initiatief*-problemen voorspellend voor middelengebruik in de psychosegroep. Dit resultaat was onvoldoende bewijs voor de theorie dat een EF-dysfunctie ten grondslag ligt aan de comorbiditeit van middelenmisbruik en psychose. Wel vonden we dat problemen in *Emotionele Regulatie* en *Werkgeheugen*, in combinatie met verminderd middelengebruik, een verhoogde middelenafhankelijkheid voorspelden. Deze resultaten tonen dat psychotische patiënten geneigd zijn tot middelengebruik ter zelfmedicatie van hun EF-dysfunctie. De studie levert voorzichtig bewijs voor de zelfmedicatietheorie en toont dat, naast psychotische symptomen, ook EF-problemen een stimulans zijn voor zelfmedicatie. Deze bevindingen zijn relevant voor klinische doeleinden, zoals preventie- en behandeling methoden.

Introduction

Psychotic disorder (PD) is a severe mental disorder that affects 10-20% of the general population worldwide. PD is mainly characterised by the presence of psychotic symptoms, including hallucinations, delusions, disorganised thought/speech, disorganised motor behaviour, and negative symptoms, referring to the absence of behaviour (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; American Psychiatric Association, 2013; Heckers et al., 2013; Tan & Van Os, 2014). Many PD patients not only have to cope with these psychotic symptoms but suffer from other conditions as well. PD rarely occurs in pure isolation and co-morbidity is rather common. One co-morbid condition most commonly seen in psychotic patients is substance (ab)use (Regier et al., 1990). This master thesis examines whether the co-morbidity of substance (ab)use and PD is associated with a neurocognitive dysfunction.

Substance (ab)use is generally characterised by a state of dependency and is highly associated to psychotic symptomatology (Brañas et al., 2016; Khokhar, Dwiel, Henricks, Doucette, & Green, 2018). Almost half of PD patients (47%) endures severe problems with substance use during their lifetime, which mainly concerns the use of tobacco, alcohol, cannabis, and cocaine (Regier et al., 1990). The high prevalence of substance (ab)use in PD is remarkable and indicates the presence of an underlying connection. Khokhar et al. (2018) explained this connection by suggesting a shared neuropathology. According to their theory, both PD and substance (ab)use are defined by a dysfunction of the mesocorticolimbic circuitry; a dopaminergic pathway that transmits dopamine from the midbrain to the ventral striatum and prefrontal cortex (PFC). This particular brain circuit is involved in many brain processes. For instance, besides facilitating cognitive control of behaviour, it is involved in the reward system of the brain. Cognitive control and the mechanisms of motivation and reward overlap extensively as they are both facilitated by the executive functions (EF) (Hyman, et al., 2006; Juckel et al., 2006; Malenka, Nestler, & Hyman, 2009).

EF is a cognitive construct, referring to a set of higher-order abilities that facilitate together cognitive, emotional, and behavioural regulation (Otero & Barker, 2014). Researchers agreed upon the existence of nine EFs that can be classified in terms of a two-factor model: 1) *Behavioural Regulation*, which captures the ability to maintain regulatory control of one's own behaviour and emotional responses. It includes functions of Inhibitory Control, Cognitive Flexibility, Emotional Regulation, and Self-Monitoring; and 2) *Metacognition*, which captures the knowledge and regulation of cognition. The latter includes functions of taking Initiative, Working Memory, Planning and Organising, Task Monitoring, and Organisation of Materials. Together, these EFs manage abilities that are essential for everyday functioning, such as cognitive control and goal-oriented behaviour (Gioia, Isquith, Guy, & Kenworthy, 2000; Otero & Barker, 2014).

The relation between goal-oriented behaviour, which is facilitated by EF, and the mesocorticolimbic circuitry is demonstrated by several studies. These studies demonstrated that the

mesocorticolimbic circuitry is central to the reward system of the brain (Hyman, et al., 2006; Juckel et al., 2006; Malenka et al., 2009). An increasing number of researches suggest that a malfunction of this brain circuitry – as seen in PD and substance (ab)use – results in a 'reward deficiency'. It is believed that patients are prone to self-medicate this deficiency through substance use, which leaves them vulnerable for developing a dependency and substance (ab)use (Albanese, 2003; Khantzian, 2013; Iseger & Bossong, 2015). Virtually all substances of abuse seem to have similar (activating) effects on the reward system, despite having different pharmacological properties. This suggests that a common mechanism is involved in the development and maintenance of an addiction. According to recent literature, this common mechanism is closely connected to EF through functions of learning, memory and reasoning. (Khantzian, 2003; Hyman et al., 2006; Iacono et al., 2008; Gould, 2010; Salamone, Yohn, Lopez-Cruz, San Miguel, & Correa, 2016).

As previously described, PD and substance (ab)use are both defined by a malfunction of the mesocorticolimbic circuitry. Hence, a wide variety of EF deficits is demonstrated to be present in both PD (Habets et al., 2008; Sheffield, Karcher, & Barch, 2018) and substance (ab)use (Gupta, Murthy, & Rao, 2018). As a matter of fact, it is suggested that an EF dysfunction is a core feature, rather than a symptom of these conditions. Research illustrated that cognitive deficits are present prior to the onset of psychotic symptoms and substance use behaviour. While psychotic symptoms typically emerge between the ages 18 and 25, an EF dysfunction is observed much earlier on in the lifespan of those who are developing PD (Rapoport, Giedd, & Gogtay, 2012; Sheffield et al., 2018). Likewise, an EF dysfunction is observed in individuals who are at risk for substance (ab)use (Iacono et al., 2008). An EF dysfunction could therefore be seen as a marker of abnormal neurodevelopment for both PD and substance (ab)use.

The question arises whether an EF dysfunction highlights a neurocognitive vulnerability that contributes to the developmental course and risk of co-morbid substance (ab)use in PD. Very little attention has been paid so far to the role of EF in co-morbidity. Increasing literature suggests, however, that an EF dysfunction precedes substance use and dependency. The present master thesis study explored whether an EF dysfunction in PD precedes co-morbid substance (ab)use by investigating the predicting effects of EF on substance use and substance dependency in PD patients. Two hypotheses were developed to visualise the relationship between an EF dysfunction and substance (ab)use in PD. First: Poor EF is related to an increase in substance use in PD patients. Second: Poor EF, when moderated by substance use, is related to an increase in substance dependency.

To understand the underlying mechanisms of co-morbidity, a better understanding of the role of EF is key. Investigating the underlying mechanisms of co-morbidity is particularly relevant as it potentially has implications for theories of aetiology, prevention and treatment. For example, if co-morbidity arises due to a common risk factor (e.g., a shared neurocognitive dysfunction that is reflected in poor EF), addressing this risk factor should reduce the prevalence of these multiple

problems. Paying attention to an EF dysfunction may not only improve treatment outcome in PD patients that suffer from substance (ab)use but contributes to prevention techniques as well (Degenhardt, Hall & Lynskey, 2003).

Methods

Design

The present master thesis study was part of a larger, longitudinal study (*UP'S cohort study* by the Erasmus MC, Rotterdam) that aimed to disentangle time-dependent relationships between — and identify determinants of — personal, symptomatic, functional and societal recovery in people with PD. The UP'S research team gathered data of 1.100 patients with PD as the main diagnosis during a period of 10 years (http://www.upsstudie.nl). The UP'S cohort study was approved by the *Medisch Ethische Toetsings Commissie* of the Erasmus MC (METC number: NL58697.078.17) and the Declaration of Helsiniki was applied.

Being part of the UP'S cohort study, this master thesis study analysed UP'S data to investigate whether a neurocognitive dysfunction is associated to the co-morbidity of substance (ab)use and PD. This cross-sectional study specifically evaluated the effects of EF on both substance use and substance dependency.

Participants

The research sample of this master thesis study consisted of 90 patients with PD as the main diagnosis, including schizophrenia disorder, brief PD, schizophreniform disorder, PD due to substance use, postpartum psychoses, delusional disorder, and PD-NOS. Patients with PD as a secondary diagnosis were not included. The research sample was randomised regarding gender. It operated within the age-range of 18-65 years. Participation was voluntarily. Participants were randomly selected out of the patient pool of several healthcare teams (i.e., Flexible Assertive Community Treatment (FACT) teams and 'Vroege Interventie Psychose' (VIP) teams) that were connected to the UP'S cohort study.

Measures

For the UP'S cohort study, patient data were obtained through interviews, structured diagnostic procedures, and psychometric tools, assessed by trained raters. Two questionnaires measured the variables of interest for this master thesis study:

EF was measured with the Behaviour Rating Inventory of Executive Function-Adult Version (BRIEF-A); a self-report questionnaire designed for adults 18-90 years of age, including those with mental disorders such as PD (Gioia, et al., 2000; Roth, Isquith, & Gioia, 2005; Scholte, & Noens, 2011). It captured views of an adult's EF in his or her everyday environment by assessing nine EFs

(i.e., Inhibitory Control, Cognitive Flexibility, Emotional Control, Self-Monitoring, Initiative, Working Memory, Planning & Organising, Task Monitoring, and Organisation of Materials). Raw scores for each scale were summed and used to interpret the individual's level of EF, for which higher scores indicated worse EF. Additionally, the questionnaire provided an estimation of EF in terms of Behavioural Regulation, Metacognition, and a total score of EF (Global Executive Composite; GEC). Cases in which the difference between the subscale scores of Behavioural Regulation and Metacognition was too large (≥12) – which reflected a disproportion between one's ability to control behaviour/emotions and one's ability to control cognition – were considered as disharmonic cognitive profiles. The GEC total scores of these patients must be carefully interpreted as it may not adequately reflect the overall level of EF. The BRIEF-A was considered valid and reliable. Construct validity was indicated by significant correlations (.63- .67) with the executive dysfunction scale of the Frontal Systems Behavior Scale (FrSBe). The BRIEF-A demonstrated high internal consistency within the separate functions of EF (Cronbach's α = .80-.94) and within the broader constructs of Behavioural Regulation and Metacognition (Cronbach's α = .96-.98). Test-retest correlations ranged between a satisfactory .82 and .94, indicating high reliability (Gioia, et al., 2000; Roth, Isquith, & Gioia, 2005; Scholte, & Noens, 2011).

Substance use and *–dependency* were both measured with the Measurements in the Addictions for Triage and Evaluation (MATE); a structured interview that assessed self-reported substance (ab)use and substance dependency (Schippers, Broekman, & Buchholz, 2011). The substances considered in this master thesis study varied within the categories of 'Depressants' (e.g., alcohol, sedatives, opioids), 'Stimulants' (e.g., nicotine, cocaine, ecstasy), 'Hallucinogens' (e.g., cannabis), and 'Other' (e.g., gambling). *Substance use* was determined by the total amount of usage days regarding all substances that were used within the last 30 days. With regard to *substance dependency*, users were categorised as either 'dependents' or 'non-dependents'. According to DSM-V, patients were considered to be dependent when a score of ≥3 was obtained on the MATE items of dependency (range of 0-7). The MATE is considered a valid and reliable measurement tool with the inter-rater reliability ranging between a satisfactory .75 and .92 (Schippers, Broekman, Buchholz, Koeter, & Van Den Brink, 2010).

Procedure

Participants were interviewed and tested individually during multiple 1-hour appointments. Participants gave prior consent for their participation. Data were collected through 25 self-report questionnaires and neuropsychological tests, including the two questionnaires as described in the Measures section of this master thesis study. The amount of appointments per participant depended on how rapidly they completed the questionnaires and tests. The collected data were processed in OpenClinica; a web-based software program specialised in data collection and –management of

clinical studies. The UP'S research team provided the sample and associated data for the present master thesis study, which were used for statistical analyses.

Statistical Analyses

The sample size of this master thesis study (N=90) was calculated with a power analysis. We analysed the descriptive statistics of the sample to define the participants characteristics regarding age, gender, substance usage days, and dependency. Additionally, an overview was generated to illustrate the types and related quantities of substance (ab)use within this sample. The two hypotheses of this master thesis study were tested as follows:

First, in order to investigate whether poor EF (independent variable) was significantly related to substance use (dependent variable), three multiple linear regression analyses were performed. The first model included the scores from the nine EF subscales of the BRIEF-A as predictors. The second model included the scores from the two subscales Behavioural Regulation and Metacognition of the BRIEF-A as predictors. The third model included the total scores from the GEC subscale of the BRIEF-A as predictor.

Second, in order to determine whether poor EF (independent variable) was significantly related to substance dependency (dependent variable) when moderated by substance use (moderator variable), three moderated binary logistic regression analyses were performed. These analyses included the scores from the nine EF subscales, the scores from the two subscales Behavioural Regulation and Metacognition, and the total scores (GEC) of the BRIEF-A as predictors, respectively.

For all of the statistical analyses described above, the assumptions of multicollinearity, linearity and homoscedasticity were checked and interpreted. Patients that were showing disharmonic cognitive profiles (i.e., difference between scores of Behavioural Regulation and Metacognition ≥12) were omitted as the total scores (GEC) of these patients may not adequately reflect their overall level of EF. All analyses were performed using SPSS Statistics 26 (IBM Business Analytics, NY USA). A *p*-value less than 0.05 was considered to be statistically significant.

Results

The research sample (N=90) consisted of 30 females (33.3%) and 57 males (63.3%), with three missing cases due to incomplete data. Participants were aged between 18 and 65 years old; more specific descriptive statistics could not be calculated as the age data were centred for privacy reasons. Table 1 provides an overview of the raw EF subscale scores as obtained from the BRIEF-A.

Table 1.

Non-standardised EF Subscale Scores from the BRIEF-A (N=87)

EF	Mean	SD	Range
Inhibitory control	13.74	3.09	8-21
Cognitive flexibility	11.45	2.84	6-18
Emotional control	16.55	4.24	10-26
Self-monitoring	9.86	2.52	6-17
Initiative	14.34	3.78	8-24
Working memory	15.52	3.65	8-24
Planning & organising	17.00	4.26	10-29
Task monitoring	10.77	2.32	7-18
Organisation of materials	13.66	3.33	8-24
Behavioural Regulation (BR)	51.60	9.67	33-76
Metacognition (MC)	71.29	14.61	43-112
Total score (GEC)	122.89	22.51	82-188

Substance use within the last month was reported by 72 participants, for whom the total amount of usage days ranged between 0 and 123 days. The average amount of usage days was 32.39 days (SD=25.35), meaning that the average substance user of our sample used multiple substances per day. Table 2 provides an overview of the substance types that participants reported for their use. Substances most commonly reported were alcohol (24.2%), nicotine (24.2%), and cannabis (16.1%). *Hallucinogens* have been used to a lesser degree by this sample of PD patients. With regard to substance dependency, we found 24 dependents (26.7%) and 40 non-dependents (44.4%).

Table 2.

Overview Types of Substance Use

Substance type		Frequency	Percent
DEPRESSANTS	Alcohol	57	24.2%
	Benzodiazepines	12	5.1%
	Opioids	8	3.4%
	Nitrous oxide (laughing gas)	1	0.4%
STIMULANTS	Nicotine	57	24.2%
	Amphetamines	15	6.4%
	MDMA	15	6.4%
	Cocaine	14	5.9%
HALLUCINOGENS	Cannabis	38	16.1%
	Psychedelic mushrooms	3	1.2%
	LSD	1	0.4%
	2C-B	1	0.4%
OTHER	Gambling	14	5.9%

EF and Substance Use

Three regression analyses were calculated to evaluate whether EF subscale scores were predictive of substance use. We first checked the multicollinearity assumption. Results showed that none of the VIF values were below 0.1 and none of the Tolerance values were above 10, hence the assumption of no multicollinearity was met. Furthermore, the scatterplot of standardised residual on standardised predicted value did not funnel out or curve, and thus the assumptions of linearity and homoscedasticity were met as well. No outliers were found within this analysis. We performed three multiple linear regression analyses with substance use as a dependent variable; the respective results are presented in Table 3.

The first model, which included the nine EFs, was not significant ($F(9,62) = 1.33$, p=.24) and did not explain much of the variability in predicting substance use (*Nagelkerke* R^2=.16, *adjusted* R^2*=.04)*. However, a significant effect was found for the Initiative subscale (p=.01), for which an increase in Initiative deficits resulted in an increase in substance usage days (see Figure 1). Results showed no other significant effects (ps > .15).

The second model, which included the subscale scores of Behavioural Regulation and Metacognition, was not significant ($F(2,69) = 1.28$, p=.29). Significant effects were found neither for Behavioural Regulation nor for Metacognition. With a *Nagelkerke* R^2 of .04 and an adjusted R^2 of .01, this model appeared to explain less than the former regression equation.

Finally, the third model, which included the total GEC score of EF, did not show a significant main effect ($F(1,53) = 1.65$, p=.21). With a *Nagelkerke* R^2 of .03 and adjusted R^2 of .01, this model appeared to explain just as little as the former regression equation.

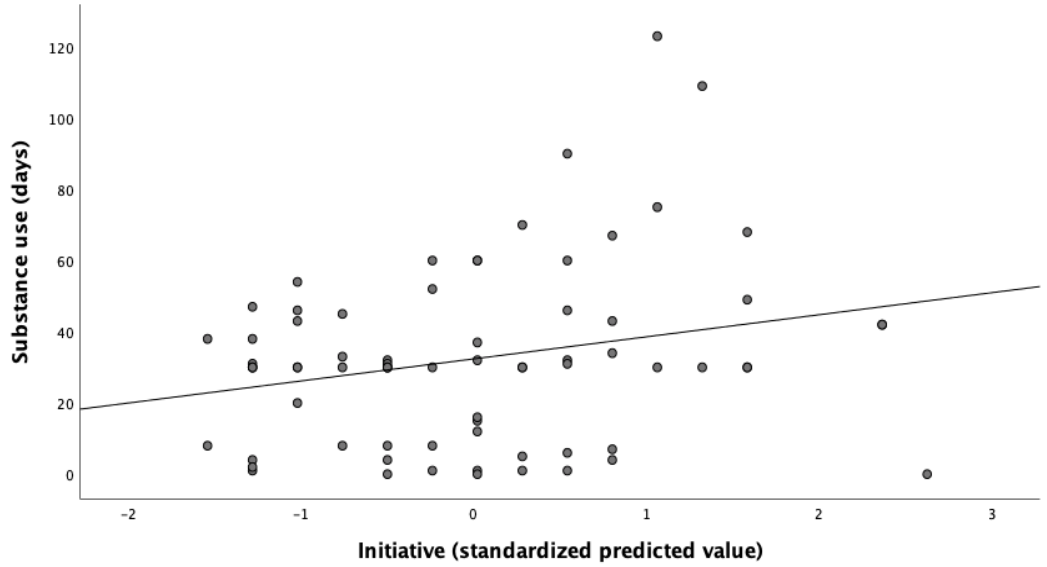
Table 3.

Results of the Linear Regression Analyses of EF Subscales Predicting Substance Use

	Predictor	b_i	S.E.	ß	*p*
MODEL 1	Constant	13.26	17.24		.45
	Inhibition	-1.38	1.44	-.17	.34
	Cognitive Flexibility	.72	1.75	.08	.68
	Emotional Regulation	.96	.90	.16	.29
	Self-Monitoring	1.68	1.74	.17	.34
	Initiative	3.45	1.36	.52	**.01**
	Working Memory	-.95	1.48	-.13	.52
	Planning/Organising	-2.06	1.44	-.34	.16
	Task Monitoring	-1.21	2.14	-.11	.57
	Organisation	.81	1.27	.10	.53
MODEL 2	Constant	7.25	16.80		.67
	Behavioural Regulation	.50	.44	.19	.25
	Metacognition	-.01	.29	-.00	.99
MODEL 3	Constant	8.25	18.33		.66
	GEC	.19	.15	.17	.21

Figure 1.

Changes in Substance Use as a function of Initiative



EF, Substance Use, and Dependency

Three binary moderated logistic regression analyses were calculated to evaluate whether EF subscale scores were predictive of substance dependency, when moderated by substance use. Assumptions were met and no outliers were found. We performed three binary moderated logistic regression analyses with substance dependency as a dependent variable; the respective results are presented in Table 4. In all three analyses, substance use demonstrated a significant positive effect on dependency.

The first model, which included the nine EFs, did not demonstrate a significant main effect on dependency ($\chi^2(9)=12.43$, $p=.19$) and was not fully appropriate to predict the influence of EFs on substance use with a *Nagelkerke* R^2 of .25. No main effects were found for the separate EFs (ps > .10). However, we found that some EFs moderated by substance use predicted substance dependency: Both Emotional Regulation (b=-.02, Wald's $\chi^2(1) = 4.32$, $p<.05$) and Working Memory (b=-.05, Wald's $\chi^2(1) = 4.61$, $p<.05$) showed significant effects. These results demonstrated that deficits of these two EFs combined with substance use decreased the chance of substance dependency. Some similar effects were found for Self-monitoring and Initiative. The predicting effects of these EFs were not significant, but the considerable trend towards significance (p=.06) is worth mentioning. The remaining moderated effects were not significant (ps >.14).

The second model, which included the two subscale scores of Behavioural Regulation and Metacognition, was not significant ($\chi^2(2)=1.54$, $p=.46$). With a *Nagelkerke* R^2 of .03, this model was not appropriate to predict substance dependency. Neither the main effects of Behavioural Regulation and Metacognition nor their interaction effects with substance use were significant.

Finally, the third model, which included the GEC total score of EF, was not significant ($\chi^2(1)=1.53$, $p=.22$), with a *Nagelkerke* R^2 of .03. Hence, there was no effect of the overall level of EF on dependency in case of (high) substance use.

Table 4.

Results of the Binary Moderated Logistic Regression Analyses of Predictors of Substance Dependency

	Predictor	*B*	*S.E.*	*Wald*	*p*	*Odds ratio*
MODEL 1	Constant	-2.18	1.69	1.66	.20	.11
	Inhibition	-.04	.16	.06	.81	.96
	Cognitive Flexibility	-.29	.20	2.08	.15	.75
	Emotion Regulation	.14	.09	2.54	.11	1.16
	Self-Monitoring	-.13	.18	.55	.46	.89
	Initiative	.04	.15	.07	.80	1.04
	Working Memory	.11	.09	.45	.50	1.12
	Planning & Organising	.13	.15	.71	.40	1.14
	Task Monitoring	-.36	.26	1.97	.16	.70
	Organisation	.27	.15	3.16	.08	1.31
	Substance use	.03	.02	4.22	**.04**	1.03
	Inhibition*Substance use	-.02	.02	1.60	.21	.98
	CogFlex*Substance use	.03	.02	1.71	.19	1.03
	EmoRegu*Substance use	-.02	.01	4.32	**.04**	.98
	Self-monitor*Substance use	.04	.02	3.51	.06	1.04
	Initiative*Substance use	.02	.01	3.47	.06	1.02
	WorkMem*Substance use	-.05	.02	4.61	**.03**	.95
	PlanOrganis*Substance use	-.02	.02	1.24	.26	.98
	Taskmonitor*Substance use	.04	.02	2.06	.15	1.04
	Organisation*Substance use	-.00	.01	.03	.86	1.00
MODEL 2	Constant	-2.22	1.45	2.35	.13	.11
	BR	.01	.04	.06	.81	1.01
	MC	.02	.03	.39	.53	1.02
	Substance use	.03	.01	5.35	**.02**	1.03
	BR*Substance use	-.00	.00	3.14	.08	1.00
	MC*Substance use	.00	.00	.32	.57	1.00
MODEL 3	Constant	-2.25	1.44	2.44	.12	.11
	GEC	.01	.01	1.49	.22	1.01
	Substance use	.03	.01	5.36	**.02**	1.03
	GEC*Substance use	-.00	.00	1.45	.23	1.00

Discussion

The present master thesis study aimed to investigate whether the co-morbidity of substance (ab)use and PD is associated with a shared EF dysfunction. Investigating the role of EF in the framework of co-morbidity is particularly relevant as it potentially has implications for theories of aetiology, prevention and treatment of co-morbid substance (ab)use in PD (Degenhardt et al., 2003; Khantzian, 2003; Iacono et al., 2008).

The present study examined the role of an EF dysfunction by specifically investigating the predicting effects of EF on substance use and substance dependency in PD. First, we hypothesised that poor EF is related to an increase in substance use. Second, we hypothesised that poor EF, when moderated by substance use, is related to an increase in substance dependency in PD patients. Our research analysed substance use and substance dependency in general. Studying the specific effects of different substances was beyond the scope of this master thesis study.

We analysed the types and related quantities of substance (ab)use in our sample. Our study confirmed the results of previous studies, namely that alcohol, nicotine, and cannabis were most commonly reported amongst PD patients (Regier et al., 1990; Brañas et al., 2016; Khokhar et al., 2018). Furthermore, the EF subscale scores of our sample corresponded to the results of a study on schizophrenia patients (Bulzacka, Vilain, Schürhoff, Méary, Leboyer, & Szöke, 2013). The studies referred to above assumed a valid representation of the PD population. Since our sample coincides with these results, our sample appears to be a valid representation of the PD population as well.

With regard to the first hypothesis (i.e., poor EF predicting substance use), results demonstrated that Initiative deficits – referring to a disability to spontaneously employ cognitive procedures and strategies – predicted an increase in substance use. Other EFs or expressions of EF (i.e., Behavioural Regulation, Metacognition and GEC) were not predictive of substance use. These results were seemingly in conflict with previous studies that suggested substance use being related to a wide variety of EF deficits (Verdejo-García et al., 2004; Verdejo-García et al., 2006; Iacono et al., 2008; Gupta et al., 2018). One possible explanation could be that this master thesis study investigated the effects on/of substance use in general, whilst effects could possibly differ per type of substance. For instance, other studies that investigated specific types of substance use, demonstrated a relation between EF deficits (i.e., Working Memory, Cognitive Flexibility, and Inhibitory Control) and the use of alcohol, cannabis, cocaine, and MDMA/ecstasy (Verdejo-García et al., 2004; Gupta et al., 2018). Another possible explanation for this contradiction could be that the sample used in this study solely existed of PD patients. Our results could differ from previous studies due to PD (symptomatology) interfering with the relationship of EF and substance use. For instance, the presence of psychotic symptoms, such as hallucinations, could increase substance use as patients feel the urge to suppress these symptoms, which is demonstrated by previous literature (Albanese, 2003; Khantzian, 2013; Iseger & Bossong, 2015; Brañas et al., 2016).

With regard to the second hypothesis (i.e., poor EF and substance use predicting dependency), results demonstrated that EF did not predict of substance dependency. This was in contradiction with previous studies that suggested a relation between poor EF and substance dependency (Verdejo et al., 2006; Iacono et al., 2008; Gould, 2010; Gupta et al., 2018). However, when substance use was added as a moderator, results demonstrated a predictive effect of EF. These results indicated that substance use in an EF dysfunction (i.e., deficits of Emotional Regulation and Working Memory) decreased the chance of substance dependency. This was seemingly in conflict with our former result, demonstrating that substance use on itself enlarged the chance of dependency, and in conflict with the theories of tolerance and withdrawal (Khantzian, 2003; Hyman et al., 2006; Iacono et al., 2008; Gould, 2010). A possible explanation for this apparent contradiction is that, although substance use is generally considered to be maladaptive behaviour, it can be debated that substance use could actually have adaptive effects. There is an old basic psychodynamic assumption that every psychological problem represents a solution (Khantzian, 2003). Building on this assumption, one could say that substance use could have adaptive effects as well, for instance by serving as a coping mechanism. Substance use as a manner of self-medication helps to alleviate psychotic symptoms and reduce cognitive deficits. For example, patients who are not able to regulate their emotions due to an EF dysfunction could be prone to use substances to cope with these emotions. Although the self-medication hypothesis is controversial and a much-disputed theory within the field of mental disorders, there is increasing evidence for the adaptive effects of substance use with respect to a patient's mental state (Albanese et al., 1994; Albanese, 2003; Khantzian, 2013; Iseger & Bossong, 2015).

In summary, this study demonstrated that a few EF deficits – being a core feature of PD – predict substance use and substance dependency in psychotic patients. Our results partially confirmed those of previous studies (Verdejo-García et al., 2004; Verdejo-García et al., 2006; Gupta et al., 2018) and carefully suggest that a relationship between an EF dysfunction and substance (ab)use generalises (in part) to the PD population as well. However, this study does not lend sufficient support for the theory that a common neurocognitive dysfunction is associated to the co-morbidity of substance (ab)use and PD since we found only a few predicting effects of EF. Nonetheless, results demonstrated a relation between EF and substance (ab)use, suggesting that PD patients use substances as a means of self-medication, in order to cope with an EF dysfunction. In accordance with the self-medication hypothesis, this study supports the idea that co-morbid substance (ab)use in PD is related to self-medicative behaviour (Albanese, 2003; Khantzian, 2003).

Strengths of this research included the cross-sectional design and the transdiagnostic approach pursued. This approach provided in our view a new and more global perspective on aetiology and development of co-morbid disorders in PD. By examining relationships across conditions, the high prevalence of co-morbidity can be explained (McHugh, Murray & Barlow, 2009).

However, it should be noted that a limitation of this study is that data is obtained through self-report questionnaires only, which implies the risk of a reporting bias or social desirability bias

affecting the results. As PD is associated with anomalous attribution judgment, it is plausible to assume that patients may either underreport or overreport due to an impaired introspective ability and/or a tendency to give socially desirable answers (Bulzacka et al., 2013; Hur, Kwon, Lee, & Park, 2014). Future research is advised to overcome this limitation by using additional performance-based testing (besides self-report methods) for the purpose of objective results. A second potential limitation of this study concerns a sampling bias. The sample used in this study may not be equally balanced or objectively represented, as unstable functioning patients (e.g., experiencing acute severe psychotic symptoms) were likely unable to participate. Due to this unintentional exclusion and selective drop out, the sample might not truthfully represent the PD population (Jørgensen, Munk-Jørgensen, Lysaker, Buck, Hansson, & Zoffmann, 2014). Future research could overcome this sampling bias by deliberately including the less stable functioning PD patients. Their participation could be facilitated, for instance, by collecting data through telephone conversations.

The two limitations described above have implications for the validity and interpretation of the data and therefore, the results should be treated with some caution. For instance, it is not clear whether results will differ according to the type and/or severity of PD symptoms applied. Likewise, it is yet unclear whether the results generalise to patients with PD as a secondary diagnosis. Future research is recommended to address these additional questions through a (larger) confirmatory study, that evaluates the effects of PD symptomatology as well. Additionally, one could wonder whether the reported effects will be similar for different types of substance use. Hence, future studies are advised to elaborate on the effects of different substances as well, as their biochemical impact might affect the relationship described.

Overall, the present study showed no sufficient effects to support the theory that suggests a shared neurocognitive dysfunction to be associated to the co-morbidity of substance (ab)use and PD. Our study indicates that substance (ab)use in PD patients is in fact related to self-medicative behaviour. Former studies mainly discussed psychotic symptoms, such as hallucinations, delusions, disorganised thought/speech, disorganised motor behaviour, to be the subject of self-medicative behaviour (Albanese et al., 1994; Iseger & Bossong, 2015; Brañas et al., 2016). The present study concludes that an EF dysfunction is a subject of self-medication as well. It offers new insights into self-medicative behaviour in PD and contributes thus to the self-medication hypothesis. This conclusion could have clinical implications in terms of prevention techniques and treatment methods. It highlights the relevance of treating an EF dysfunction for it could reduce not only the prevalence of existing substance (ab)use in PD patients but the risk of a developing substance dependency as well.

References

Albanese, M. (2003). The self-medication hypothesis. *Psychiatric Times, 20*(3), 42-42.

Albanese, M. J., Khantzian, E. J., Murphy, S. L., & Green, A. I. (1994). Decreased substance use in chronically psychotic patients treated with clozapine. *The American Journal of Psychiatry, 151*(5), 780-781.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th edition)*. Washington, DC: American Psychiatric Association Publishing.

Brañas, A., Barrigón, M. L., Garrido-Torres, N., Perona-Garcelán, S., Rodriguez-Testal, J. F., Lahera, G., & Ruiz-Veguilla, M. (2016). U-shaped curve of psychosis according to cannabis use: New evidence from a snowball sample. *Journal of Psychopharmacology, 30*(12), 1331-1338.

Bulzacka, E., Vilain, J., Schürhoff, F., Méary, A., Leboyer, M., & Szöke, A. (2013). A self-administered executive functions ecological questionnaire (the Behavior Rating Inventory of Executive Function-Adult Version) shows impaired scores in a sample of patients with schizophrenia. *Mental Ilness*, *5*(4), 14-16.

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Chapter 2: What is comorbidity and why does it occur?. In M. Teesson (Ed.), *Comorbid Mental Disorders and Substance Use Disorders: Epidemiology, Prevention and Treatment* (pp. 10-38). Sydney, Australia: National Drug and Alcohol Research Centre, University of New South Wales.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *BRIEF: Behavior Rating Inventory of Executive Function*. Lutz, Florida: Psychological Assessment Resources.

Gould, T. J. (2010). Addiction and cognition. *Addiction Science & Clinical Practice*, *5*(2), 4-14.

Gupta, A., Murthy, P., & Rao, S. (2018). Brief screening for cognitive impairment in addictive disorders. *Indian Journal of Psychiatry, 60*(4), 451-456.

Habets, P., Krabbendam, L., Hofman, P., Suckling, J., Oderwald, F., Bullmore, E., Woodruff, P., Van Os, J., & Marcelis, M. (2008). Cognitive performance and grey matter density in psychosis: Functional relevance of a structural endophenotype. *Neuropsychobiology*, *58*(3-4), 128-137.

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D, Owen, M. J., Schultz, S., Tandon, R., Tsuang, M., Carpenter, W., & Van Os, J. (2013). Structure of the Psychotic Disorders classification in DSM-5. *Schizophrenia Research, 150*(1), 11-14.

Hur, J. W., Kwon, J. S., Lee, T. Y., & Park, S. (2014). The crisis of minimal self-awareness in schizophrenia: A meta-analytic review. *Schizophrenia Research, 152*(1), 58-64.

Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: The role of reward-related learning and memory. *Annual Review of Neuroscience, 29*, 565-598.

Iacono, W. G., Malone, S. M., & McGue, M. (2008). Behavioral disinhibition and the development of early-onset addiction: Common and specific influences. *Annual Review of Clinical Psychology, 4*, 325-348.

Iseger, T. A., & Bossong, M. G. (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research, 162*(1-3), 153-161.

Jørgensen, R., Munk-Jørgensen, P., Lysaker, P. H., Buck, K. D., Hansson, L., & Zoffmann, V. (2014). Overcoming recruitment barriers revealed high readiness to participate and low dropout rate among people with schizophrenia in a randomized controlled trial testing the effect of a Guided Self-Determination intervention. *BMC Psychiatry, 14*(1), 28-38.

Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., & Heinz, A. (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage, 29*(2), 409-416.

Khantzian, E. J. (2003). The self-medication hypothesis revisited: The dually diagnosed patient. *Primary Psychiatry, 10*(9), 47-54.

Khokhar, J. Y., Dwiel, L. L., Henricks, A. M., Doucette, W. T., & Green, A. I. (2018). The link between schizophrenia and substance use disorder: A unifying hypothesis. *Schizophrenia Research, 194,* 78-85.

Malenka, R. C., Nestler, E. J., & Hyman, S. E. (2009). Chapter 6: Widely projecting systems: Monoamines, Acetylcholine, and Orexin. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (pp. 147-157). New York, NY: McGraw-Hill Education / Medical.

McHugh, R. K., Murray, H. W., & Barlow, D. H. (2009). Balancing fidelity and adaptation in the dissemination of empirically-supported treatments: The promise of transdiagnostic interventions. *Behaviour Research and Therapy, 47*(11), 946-953.

Otero, T. M., & Barker, L. A. (2014). The frontal lobes and executive functioning. *Handbook of Executive Functioning* (pp. 29-44). New York, NY: Springer.

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: Update 2012. *Molecular Psychiatry, 17*(12), 1228–1238.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) study. *Jama, 264*(19), 2511-2518.

Roth, R. M., Isquith, P. K., & Gioia, G. A. (2005). *BRIEF-A: Behavior Rating Inventory of Executive Function--Adult version: Professional Manual.* Lutz, Florida: Psychological Assessment Resources.

Salamone, J. D., Yohn, S. E., Lopez-Cruz, L., San Miguel, N., & Correa, M. (2016). Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. *Brain, 139*(5), 1325-1347.

Sheffield, J. M., Karcher, N. R., & Barch, D. M. (2018). Cognitive deficits in Psychotic Disorders: A lifespan perspective. *Neuropsychology Review*, *28*(4), 509-533.

Schippers, G. M., Broekman, T. G., Buchholz, A., Koeter, M. W., & Van Den Brink, W. (2010). Measurements in the Addictions for Triage and Evaluation (MATE): An instrument based on the World Health Organization family of international classifications. *Addiction, 105*(5), 862-871.

Schippers, G. M., Broekman, T. G., & Buchholz, A. (2011). *MATE 2.1. Handleiding en protocol. Nederlandse bewerking: G. M. Schippers & T. G. Broekman*. Nijmegen, Nederland: Bêta Boeken.

Scholte. E., & Noens, I. (2011). *BRIEF-A Handleiding: Vragenlijst executieve functies voor volwassenen*. Amsterdam, Nederland: Hogrefe.

Tan, N., & Van Os, J. (2014). Schizofreniespectrum en andere psychotische stoornissen in de DSM-5. *Tijdschrift voor Psychiatrie, 56*(3), 167-72.

Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine, 39*(2), 179-195.

Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, A. L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research, 25*(1), 21-31.

Verdejo-García, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: An examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society: JINS, 12*(3), 405-415.

Verdejo-García, A., López-Torrecillas, F., Giménez, C. O., & Pérez-García, M. (2004). Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. *Neuropsychology Review, 14*(1), 1-41.